



Queensland University of Technology  
Brisbane Australia

## ***Final Report***

# **LITERATURE REVIEW ON THUNDERSTORM ASTHMA AND ITS IMPLICATIONS FOR PUBLIC HEALTH ADVICE**

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## DECLARATIONS OF CONFLICTS OF INTEREST

Associate Professor Janet Davies current research on pollen allergy is supported by NHMRC Partnership Project (GNT 1116107) for the AusPollen Partnership including matching cash and in kind co-sponsorship from six organisations (see Appendix I), the ARC Discovery (DP170101630 Appendix II) and QUT Catapult Grant. She has recently received grant funding from the NHMRC, National Foundation for Medical Research Innovation, the Allergy and Immunology Foundation of Australasia, Asthma Australia, The University of Queensland and contracted research grants from Stallergenes (France). The NHMRC Development Grant (2011-2013) was supported by in kind provision of materials from ThermoFisher (Sweden) and Sullivan Nicolaides Pathology (QLD). She is an inventor on a patent assigned to QUT granted in Australia and three applications pending examination in Australia, USA and Europe relating to development of new tests and treatments for subtropical grass pollen allergy. Assoc. Prof. Davies's institute has received Honorarium payments and refunds for travel expenses for education session and conference presentations from Stallergenes Australia, GlaxoSmithKliene, and Meda Pharmaceuticals.

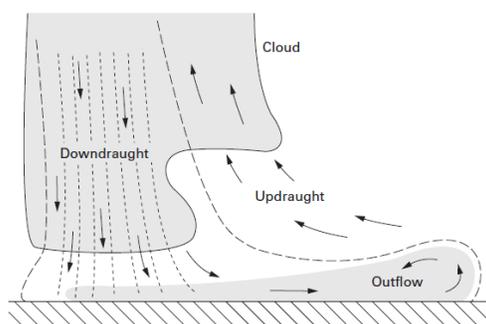
Other contributors declare no conflicts of interest.

## EXECUTIVE SUMMARY

This report, written for the Victorian Department of Health and Human Services explores and details published reports on thunderstorm asthma (TA). It will inform part of the Victorian Government’s response to an outbreak of TA that occurred on November 21, 2016. This review and evaluation of literature is designed to help better understand the factors leading to TA, highlight knowledge gaps that need to be filled to better predict and prevent the impact of future episodes.

In December 2016, the State Coroner announced that there would be coronial investigation into the circumstances of each epidemic TA related death. We are aware of nine deaths that have been referred to the Coroner. However, at the time of writing the coronial investigation had yet to be completed. Ambulance and emergency departments endured unprecedented and unpredicted demand, some hospitals were placed on “Code Brown” alert and the community expressed significant concern at this poorly understood public health threat

This outbreak was linked to the weather conditions of that day. The highest temperatures since March (35°C) were reached in the middle of the day and a line of otherwise unremarkable thunderstorms from the north-west moved quickly across metropolitan Melbourne at about 5pm.



**FIGURE 1: DEPICTION OF THE PROPOSED MECHANISM BY WHICH THUNDERSTORM OUTFLOWS COLLECT ALLERGEN PARTICLES (E.G. POLLEN GRAINS OR MOULD SPORES) IN THE AIR NEAR THE GROUND.**

An updraft lifts the pollen grains into the clouds where humidity and electrical activity breaks open grains and releases small breathable allergen-containing granules. The shaded area near ground level represents starch granules released by rain from grass pollen grains at or near ground level which are then transported ahead of the rainfall by the preceding outflow winds (Marks et al. 2001).

The unprecedented surge in number of people seeking emergency medical assistance for respiratory distress began within the first hour of the thunderstorm and continued into the next day. The epidemic of breathing difficulties was attributed to TA. A proposed mechanism for this phenomenon is illustrated (see Figure 1).

Whilst TA is an infrequent seasonal occurrence there have been six earlier reports in Melbourne. All have occurred in November, the peak of the grass pollen season and the beginning of the summer storm season. Analyses of published literature reveals 22 outbreaks of TA internationally since 1983; 10 of them in Australia (see Figure 2). Others occurred in the United Kingdom, Italy, Iran and Canada. No previous TA event in Australia or elsewhere has occurred on the scale of the 2016 episode. International comparisons reveal some common elements in outbreaks of TA. Some, but not necessarily all, are present in each outbreak.

Marks and Bush (2007) propose four common conditions necessary for generation of TA outbreaks. These conditions are: (1) presence of biological allergens on a large scale, precisely grass pollen and/or certain fungal spores; (2) presence of a thunderstorm with outflows that pick up allergens and concentrates them close to ground level; (3) the formation of small breathable particulate matter from the rupturing of pollen grains (or fungal spores), and; (4) exposure of people predisposed to symptoms of asthma who know they suffer from hayfever and in many cases asthma.

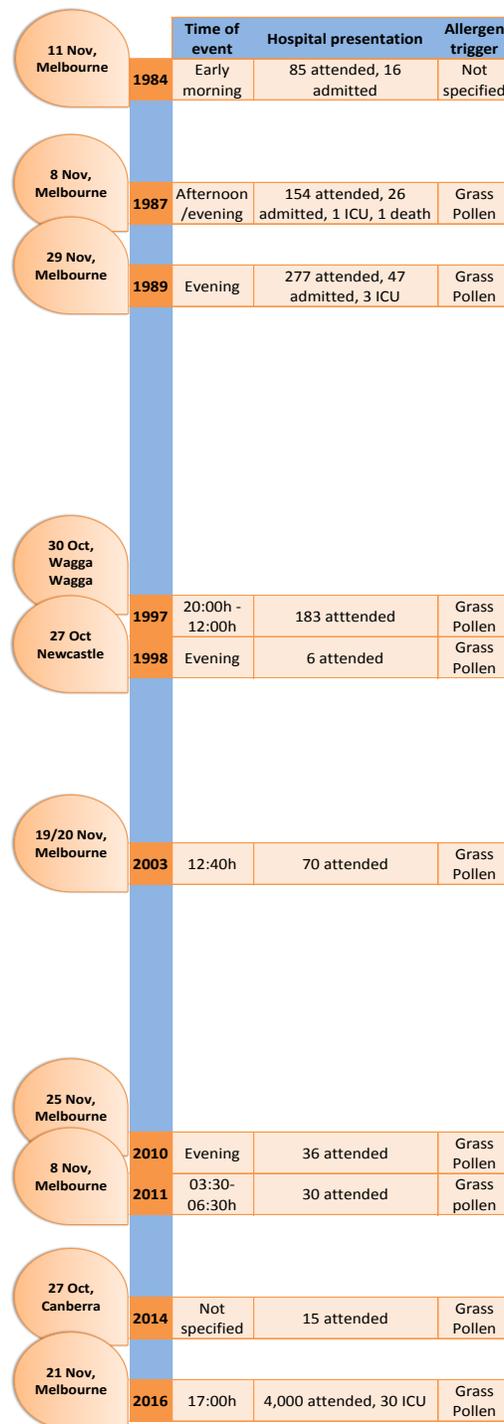


FIGURE 2: NATIONAL TIMELINE FOR THUNDERSTORM ASTHMA EPIDEMICS

The group led by D'Amato (D'Amato et al. 2016), the allergy physician who managed care of patients during several episodes in Italy, outlined evidence that indicates TA epidemics only occur during pollen and outdoor mould seasons. Two groups of people are at higher risk; those not receiving anti-asthma treatment and those with allergic rhinitis. Those who are not allergic to the triggering allergen source and those who stay indoors with windows closed appear to be insulated from risk (D'Amato et al., 2016). A high level of airborne outdoor allergen (pollen grains or mould spores) coincides with the occurrence of TA.

In the context of previous reports and proposed explanations for TA, this review focuses on three areas:

1. Current international and national knowledge of TA;
2. Evidence that supports identified risk factors or conditions that may be associated with an event, including the strength and weight of this evidence base, and;
3. Gaps in knowledge or other evidence associated with other reported possible risk factors.

These three areas are addressed in a series of 14 questions focusing on the individual, climatic and aeroallergen factors at play in TA. The report examines the variabilities such as the irregularity of outbreaks, the differing sensitivities of affected patients, the allergenic makeup of pollens and fungal spores, the models for predicting potential events and the means to warn the public of their likelihood.

The review team draws on an array of specific expertise to review, analyze and combine the available published material weighing up the level of evidence in a framework that considers the contributions of multiple contributing factors. Each of the 14 questions is answered in the body of the report. For the purposes of this report, we break the issues into the three themes illustrated in Figure 3 which our review of the current body of evidence suggests need to co-exist for an incident of TA to occur. Knowledge gaps were identified within the review as specific aspects where there was insufficient evidence in the literature.

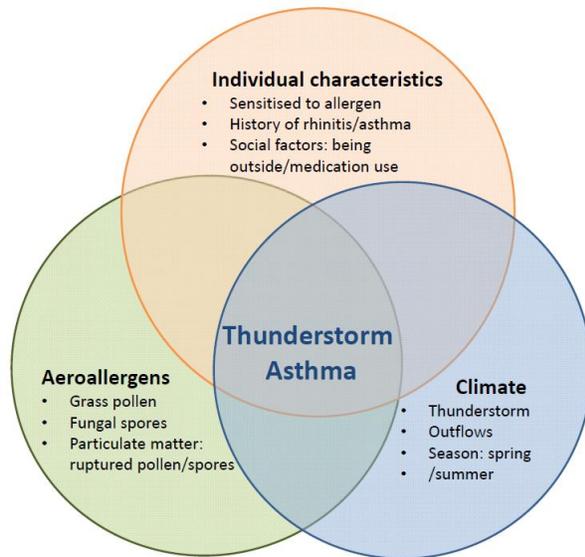
### Individual characteristics; allergic sensitivity and disease status

**Explanation:** To be vulnerable to a TA outbreak, an individual has to have at least one (but not all) of these characteristics:

1. To be sensitised to the triggering allergen;
2. To suffer from allergic rhinitis (hayfever) with or without asthma;
3. Being exposed to open air and not taking preventative medication for asthma.

**Understanding:** Sensitisation to the triggering outdoor airborne allergen appears to be essential for TA-affected patients but there is no clear common allergen identified globally. Allergic sensitisation to ryegrass, however, appears to be universal in Australia (Question 1).

Whilst being asthmatic is an indicator, it isn't sufficient by itself. In many reported TA episodes here and overseas, close to 40% of patients presenting with respiratory difficulties had not previously experienced asthma attacks. However, almost all (90-100%) of those acutely affected with breathing difficulties had a history of hayfever. This same pattern has been observed internationally (Question 1).



**FIGURE 3: THREE TYPES OF CONTRIBUTING CONDITIONS FOR CAUSATION OF THUNDERSTORM ASTHMA.**

The conditions contributing to the development of thunderstorm asthma epidemics have been identified through this review process and grouped into related factors; individual characters conferring vulnerability to TA, weather factors grouped under Climate, and environmental exposure to airborne allergen triggers (aeroallergens).

Direct exposure to a thunderstorm also increases the risk of vulnerable patients enduring an asthma attack. The review identifies a pattern of characteristics of storms with the greatest impact occurring at a time of day when people are likely to be outside. The Melbourne storm, like many other TA epidemics, occurred at a peak afternoon commuting time and patients started to call for help in the evening and throughout the night.

Another key factor is that individuals affected by asthma symptoms during thunderstorm epidemics (whether they had known asthma or hayfever only) were not using asthma preventer medications. Hayfever patients would not be recommended use of asthma inhalers, but patients who knew they had previously had asthma, could reasonably have been expected to have and to use inhalers. Good control of asthma through proper use of asthma preventers may protect asthmatic individuals from experiencing asthma symptoms during TA events.

**Prediction:** A history of hayfever with or without known asthma and sensitivity to the triggering outdoor allergen source may have some use for identifying individuals at risk of TA but the population prevalence of grass pollen allergy in Australia is as much as two thirds of the 15% of Australians with allergic diseases.

**Prevention:** Maintaining proper use of prescribed asthma preventer medications to maintain good asthma control may reduce risk of TA. Adequate control of hayfever is likely to be beneficial in reducing risk of TA. This relies on knowing which hayfever sufferers may have undiagnosed asthma or be at risk of asthma during spring time thunderstorms. Staying indoors with windows closed may provide some protection from exposure to high levels of outdoor aeroallergen triggers of asthma during thunderstorms. However, this relies on prediction of the likelihood of a TA outbreak. Specific public health messages targeted to separate patients groups would be useful; for those with asthma, education on correct use of medications; for those with hayfever, awareness of symptom escalation (e.g. wheeze) during the pollen season and recommendation to seek medical attention.

**Knowledge Gaps:**

- (1) Knowledge of which patients with hayfever are at risk of TA including the demographic characteristics (age and gender), immunological and genetic biomarkers that are associated with highest risk of TA.
- (2) Knowledge of the patterns and levels of allergic sensitivities to key allergens within grass pollen grains that are associated with progression from hayfever to asthma during thunderstorms.
- (3) Knowledge of whether treatment of at-risk hayfever patients with asthma medication and/or allergen immunotherapy for grass pollen allergy would prevent escalation of their disease to asthma.

**Climate and Environment factors**

**Explanation:** Thunderstorm activity is at the basis of TA outbreaks and many meteorological factors associated with thunderstorms including wind, rainfall, lightning, relative humidity and changes in these factors as well as cold fronts and outflows have been proposed to be responsible for initiating asthma outbreaks, independently of the role of aeroallergen factors (Question 3).

**Understanding:** The most frequent explanation – that high speed wind gusts (or outflows) of cold air can sweep up pollen grains and/or fungal spores and concentrate them in the air near ground level – has been properly investigated in only one study from Wagga Wagga, NSW (Marks et al. 2001). That study indicated that thunderstorm outflows, rather than a cold front, lightning, thunder or rain alone, were important contributors to asthma epidemics. A number of overseas studies show association with lightning.

Importantly, while thunderstorm activity can increase incidents of asthma, high levels of airborne allergens have to co-exist to create the extreme outbreaks of TA. There is no clear evidence about why outbreaks occur in some years and not others and what factors could influence that pattern. In Victoria, winter rainfall has been shown to be moderately well correlated with high grass pollen seasons in Melbourne. Many, but not all TA events in Melbourne follow wet winters that lead to high grass land productivity.

**Prediction:** Capacity to accurately predict thunderstorms with the particular set of conditions associated with TA events would underpin an operational public health warning and alert system when integrated with broad regional information on grassland pollen production and airborne pollen levels.

**Prevention:** Extreme weather events are predicted to worsen in future and thunderstorms may be difficult to avoid. However, integration of a capacity to predict thunderstorm activity with the forecasting of relevant bioaerosol levels may be used to develop a system to predict days with increased risk of TA. Some evidence suggests that minimisation of exposure of at risk-individuals to thunderstorms by remaining indoors before, during and for several hours afterwards may provide a protective benefit, although this has not been proven conclusively.

**Knowledge Gaps:**

- (1) Validity of the most accepted hypothesis (Marks and Bush 2007); contribution of thunderstorm outflows and lightning activity during TA events, particularly the recent 2016 TA event.
- (2) Full understanding of the influence of rapid changes in weather conditions on likelihood of TA; systematic long-term study of recent TA events in Australia to detect consistent weather patterns that repeatedly associate with TA episodes.
- (3) Understanding of the drivers for year-to-year variations in weather patterns associated with TA.
- (4) Modelling of long-term trends in thunderstorm activity with climate change and their influence on storm frequency and severity.

**Aeroallergen Exposure**

**Explanation:** Strong and consistent evidence indicates that high levels of aeroallergen in the air is associated with TA episodes here and overseas. The Melbourne events and one in New South Wales all occurred on days with high or extreme concentrations of grass pollens. (Question 8) Aeroallergens coming either from grass pollens or fungal spores and their effect depends on the allergy status of the individual breathing in the allergens.

**Understanding:** Ryegrass is the most abundantly planted fodder crop in Victoria. The peak of its pollen release in November coincides with incidence of TA. Grass pollen grains have been shown experimentally to be capable of rupturing in the presence of water to release large numbers of tiny (sub-micronic) starch granule particles loaded with allergen. Such ruptured grass pollen grains were also present in the air on separate TA events in Melbourne and Wagga Wagga (NSW) asthma epidemics. Ryegrass pollen starch granules can induce asthma-like symptoms during breathing challenge tests of volunteer subjects. Patients who experienced asthma during thunderstorms in Melbourne and Wagga Wagga show higher levels of allergic sensitivity to ruptured ryegrass pollen starch granules. Elsewhere in the world, fungal spores have been associated with epidemics. This may be due to wheat harvesting, particularly because farmers accelerate their harvest to avoid the threat of bad weather (Question 10). Notably, as well as sensitisation to ryegrass pollen, Australian patients who experience asthma during TA epidemics can also be allergic to some mould spores suggesting this could be a contributing factor for some individuals.

**Prediction:** Best aided by a sophisticated and broad reaching pollen monitoring system as well as remote sensing of grassland greenness and grass pollen production, working in tandem with accurate weather forecasts of thunderstorm activity.

**Prevention:** Accurate short-term models predicting the onset, severity and peak of grass pollen production as well as daily levels of grass pollen exposure in urban areas, in tandem with weather prediction, will better alert hospital and health services, ambulance services and individuals with hayfever at risk of TA.

**Knowledge Gaps:**

- (1) Widespread pollen and mould spore monitoring and forecasting;
- (2) Connection between agricultural activity, aeroallergen release and wind transport to urban areas;
- (3) Utility of satellite sensing of grassland cover, greenness and grass flowering cycles;
- (4) Long-term changes in land use practices and grassland production and trends in distributions of different types of allergenic pollens (e.g. spread of subtropical grasses and invasive weed species like ragweed).

## Other Factors potentially contributing to causation of thunderstorm asthma

**Air pollution:** Several studies show associations with ozone and thunderstorms and other gaseous pollutants can be elevated during thunderstorms but there is no clear evidence these conditions are associated with asthma admissions within the context of TA events.

**Agricultural activity:** Harvesting practices may release high levels of fragmented *Alternaria* or *Cladospodium* spores prior to the onset of thunderstorms. In general, modern agricultural practices lead to synchronised planting of monoculture pastures that give rise to high levels of grass pollen from fodder and grain crops in spring time which provide a source of high aeroallergen loads.

### Further points for considerations:

- Not everyone with hayfever triggered by grass pollen allergy is at risk of asthma during TA epidemics.
- No consideration has been given to the influence of ethnicity or genetic factors on susceptibility.
- Asthma epidemics can occur without thunderstorms; for instance with very high levels of grass pollen (e.g. in California) or due to soybean husk exposure near processing plants in Barcelona and Italy.
- Respiratory viruses like the common cold are major triggers for asthma outside of spring.
- Pollen and mould spores can also be associated with asthma outside of thunderstorms.
- A wide range of ages can be affected but the peak age for TA seems to be the twenties and thirties.
- The age group who fill the fewest number of scripts for asthma preventers in Australia are in their teens coinciding with the rise in frequency of allergic sensitivity to grass pollen allergens.
- Many studies nationally and internationally observe that TA episodes are initiated by afternoon thunderstorms with presentations peaking in the evening and continuing overnight.
- Some studies (but not all) observed women are more commonly affected than men.
- Relatively few reports from USA mention TA.

**Alert systems:** TA alert systems have been considered elsewhere but not implemented, most likely due to challenges with integrating multiple information sources into an operational predictive model for TA, and the consequences of unacceptable levels of likely false alarms.

**Public health messaging:** Foundations (Asthma Australia, National Asthma Council) and peak professional bodies (Australasian Society for Allergy and Clinical Immunology) provide advice on risks and prevention of TA consistent with the reported contributing factors. Except for Wagga Wagga NSW, Australia does not have a public health messaging strategy for reducing the impact of TA.

## Considerations arising from this review

Provide a model of **integrated care by respiratory physicians and clinical immunologist** for patients with grass pollen allergy who have asthma or severe hayfever with symptoms consistent with seasonal asthma; control hayfever by medication and allergen immunotherapy for individuals at risk of TA (identified by biomarkers).

Provide **targeted health education** on risks and management of TA to emergency medicine, ambulance services, allergy and respiratory specialists, general practitioners, pharmacists, and at risk groups of patients.

Improve capacity and distribution of **standardized and validated pollen monitoring** services.

Develop, implement and evaluate **evidenced-based pollen and TA forecasting systems** to enable timely and targeted delivery of **public health warnings and alerts** to emergency services, health care providers and patients.

## ACRONYMS AND ABBREVIATIONS

AR	Allergic rhinitis
CI	confidence interval
CO	carbon monoxide
Dec	December
ED	emergency department
EDSS	Emergency Department Syndromic Surveillance system
ESTA	Emergency Services Telecommunications Authority
Exacerbation	incident with asthma symptoms worsen or “flare-up”
Feb	February
GP	general practice
h	hour
ICS	Inhaled corticosteroids
Jan	January
Jul	July
Jun	June
m	meters
Max	maximum
Min	minimum
NA	not applicable
NO	nitric oxide
NO <sub>2</sub>	nitrogen dioxide
Nov	November
O <sub>3</sub>	ozone
Oct	October
OR	odds ratio
PM	particulate matter
PM <sub>10</sub>	fine particles with diameter of 10 µm or less
PM <sub>2.5</sub>	fine particles with diameter of 2.5 µm or less
RH	relative humidity
RHA	regional health authority
RHS	UK regional health authority
RR	relative risk
Sep	September
SO <sub>2</sub>	sulphur dioxide
SO <sub>4</sub> <sup>-</sup>	sulphate
SPT	skin prick test
TA	thunderstorm asthma
Temp	temperature
TS	thunderstorm
WD	wind direction
WS	wind speed

## CONTEXT AND DEFINITIONS

Whilst pollen exposure has been reported to be associated with a wide variety of adverse inflammatory health conditions (including respiratory e.g. COPD, cardiovascular and mental health conditions), this review will focus on respiratory conditions and in particular asthma.

Relevant studies on children and adults will be considered being mindful of any effects of age on susceptibility to thunderstorm effects or capacity to detect cases of TA.

The review focuses on the literature published in the last 10 years but the search period was extended to include earlier relevant publications.

The breadth of the literature on causative factors for asthma in general within the three chosen themes is vast. In addition to a systematic search for all literature specifically on TA the most salient and relevant papers were included to enable a comprehensive response to each question.

Given the interdisciplinary and transdisciplinary nature of this topic and the rarity of reported TA episodes, many primary research publications employed varied approaches with diverse research designs. The diversity of types of studies prevented adherence to prescriptive criteria by which the relevance and quality of studies could be judged systematically.

**TABLE 1: TERMS AND DEFINITIONS**

Term	Definition
<b>Allergic asthma</b>	Chronic lower airways disease characterized by shortness of breath, wheeze, cough, excessive mucus production with airway hyper-reactivity with underlying allergic (e.g. eosinophilic) inflammation and structural airway changes (collagen deposition, smooth muscle thickening).
<b>Thunderstorm asthma</b>	An episode of symptoms of breathlessness, breathing difficulties or other symptoms consistent with asthma experienced by a patient on a day with a thunderstorm occurring in the vicinity.
<b>Thunderstorm asthma epidemic</b>	A reported epidemic of presentations or admissions of patients with symptoms consistent with asthma at rates significantly above expected rates for that time and location occurring on a day with a thunderstorm in the vicinity.
<b>Allergic rhinitis</b>	Allergic respiratory disease of the upper airway characterized by nasal inflammation, mast cell influx, watery rhinorrhea, sneezing, itchy nose, throat and eyes. Seasonal or intermittent allergic rhinitis known as hayfever is associated with allergic sensitisation to outdoor aeroallergens frequently pollen of grasses, trees and weeds.

## INTRODUCTION

On the evening of Monday 21st November, 2016, and throughout the night, Melbourne experienced an epidemic of asthma following a severe thunderstorm. This resulted in increased emergency department presentations and other health service usage. Emergency services were overwhelmed and this event led to emergency coordinators activating code brown (a nationally recognised code used by health services and facilities to plan, prepare, respond and recover from an external emergency) within several hospitals located in the north western parts of Melbourne. Preliminary data indicates that approximately 9,900 people experienced asthma and/or respiratory in total presented at hospital emergency departments across metropolitan Melbourne and Geelong areas over 21 and 22 November, compared to a three-year average of around 6,260. We are aware that nine deaths have been referred to the Victorian State Coroner. These deaths occurred both on the day of the event and in subsequent weeks and following this episode of thunderstorm asthma (TA). Although the scale of the event was unprecedented at least five earlier TA events in Melbourne have been reported in scientific literature (Egan 1985; Howden et al. 2011; Erbas et al. 2012). The phenomenon of TA has also been reported elsewhere including rural NSW, Australia and overseas (Girgis et al. 2000; Packe et al. 1985).

Current literature on TA epidemics has used a general definition of an outbreak (occurrence of disease in excess of what would normally be expected in a defined community, geographical area or season (Samet et al. 2009). In context of TA, outbreaks of asthma epidemics are generally done by establishing a background rate of the disease (Bellomo et al. 1992; Marks et al. 2001; Venables et al. 1997). The usual rate of asthma presentations for the time period of interest, are taken from a particular healthcare setting such as an ED or GP clinic. An average attendance rate is then calculated, for the time period of interest. In instances where presentation of asthma are considered “in excess of normal” this has been defined as an outbreak or epidemic of asthma. However, “excess of normal” has rarely been quantified and remains very unclear throughout the literature. In the context of this review considerations of how a TA epidemic is defined has an obvious impact on the capacity to clearly identify and evaluate the contribution and mechanism of interaction of component causes of TA.

Two of the many reviews on TA led by key opinion leaders in TA research, have summarised the available evidence and proposed components of the causation of TA. D’Amato and colleagues have identified a number of common characteristics among described outbreaks of thunderstorm-associated asthma (Box1, D’Amato et al 2016). Marks and Bush have also suggested that the evidence points to a common set of circumstances that underlie reported thunderstorm-related epidemics (Box 2, Marks and Bush, 2007). In this report we evaluate the strength of evidence to support each of the proposed component causative factors for TA in these models using the framework of Rothman for the causation of disease in which the component causative factors are either considered contributing and necessary or sufficient to lead to TA.

### Proposed component causes for thunderstorm asthma identified by D'Amato et al. (2016)

1. There is a close temporal association between the start of the thunderstorm and the onset of asthma epidemics.
2. Asthma epidemics related to thunderstorms are limited to pollen (and outdoor mould) seasons.
3. There are not high levels of gaseous and particulate components of air pollution during thunderstorm-related asthma outbreaks.
4. Subjects with pollen allergy who stay indoors with the window closed during thunderstorms are not involved.
5. There is a major risk for subjects who are not receiving antiasthma treatment but subjects with allergic rhinitis and without previous asthma can experience severe bronchoconstriction.
6. Non-allergic subjects are not involved in thunderstorm-related asthma.

### Component causes of thunderstorm asthma epidemics proposed by Marks and Bush (2007)

1. A key hypothesis is that thunderstorms occurring during the spring/summer growing season, concentrate pollen grains at ground level which rupture due to osmotic shock and release fine (i.e. respirable) allergenic particles or aeroallergens into the atmosphere.
2. During the first 20 to 30 minutes of a spring/summer thunderstorm, people with diagnosed asthma and those who have not previously experienced asthma symptoms but have a history of hayfever (i.e. allergic rhinitis) and atopy can experience asthma symptoms.
3. These susceptible groups inhale allergenic materials such as fine starch particles from ryegrass pollen, other micronic pollen fragments or starch granules, or other aeroallergens that are small enough to bypass the nose and throat, and penetrate into the lungs and induce irritation and an allergic inflammation with asthma symptoms that are often severe.
4. Epidemic thunderstorm asthma events described in Melbourne have almost always occurred in November (peak of spring).

#### About this review

This literature search will provide an in-depth and broad review of the available literature that reports and focuses on TA events. The literature search broadly covered multiple disciplines to provide insights into the mechanisms contributing to TA epidemics.

Medical and scientific publications that provide insights to evidence and knowledge gaps on TA will be grouped into three themes:

- 1) the susceptibility of individual patients who experience asthma during thunderstorm epidemics
- 2) exposure to bioaerosol triggers and
- 3) climate, meteorological and environmental factors.

## REQUIRED SCOPE

This literature review has been commissioned to inform the work of the Department of Health and Human Services on TA, particularly in understanding:

1. The current international and national knowledge on TA.
2. The evidence that supports identified risk factors or conditions that may be associated with an epidemic TA event, including the strength and weight of this evidence base.
3. Of any gaps in knowledge or evidence associated with other reported possible risk factors.

Risk factors may include but should not be limited to respirable pollen fragments, fungal spores, other aeroallergens, ambient ozone levels, ambient fine dust particles, temperature, air pollution and temperature changes, relative humidity and pressure changes.

The following questions were addressed in the literature review:

1. Describe the epidemiology of TA, including TA epidemics including:
  - a. Who is susceptible to TA?
  - b. What is the spectrum of likely or documented health effects?
  - c. What were the clinical outcomes for those affected i.e. number hospitalised, admitted to intensive care?
  - d. How many deaths have been attributed to epidemic TA events?
2. What aetiological factors are thought to contribute to TA and particularly an epidemic TA event?
3. What spring or summer meteorological conditions (e.g. temperature, wind speed or direction, relative humidity, rainfall, thunderstorm electric or lightening activity etc.) are thought to contribute to conditions associated with an epidemic TA event?
4. What evidence explains why epidemic TA events do not occur every spring or summer?
  - a. What background environmental factors (e.g. air quality – fine particles, ozone etc.) may contribute to conditions associated with an epidemic TA event?
  - b. What seasonal factors (e.g. wet winter or spring; vegetation index) may be associated with an epidemic TA event?
  - c. What trends in agricultural harvesting (e.g. timing of hay bailing etc) may be associated with an epidemic TA event?
5. Describe the environmental and meteorological factors that can result in exacerbations or first onset of asthma in general.
6. Summarise the evidence that metrological conditions (other than thunderstorms such as temp change, humidity change, high winds, other) or specific environmental conditions (high mould, pollution, pollen, other) have been shown to cause (or are associated with) a smaller rise in asthma exacerbations across the community rather than an epidemic TA events.
7. What is the evidence that thunder-storms cause a small increase asthma exacerbation's and what is the proposed mechanism (ie is the mechanism different to osmotic shock of pollen leading to allergic fragments being inhaled during thunder-storm outflows)?
8. What are the proposed factors (environmental, meteorological, social) that may turn a small increase in exacerbations of asthma into an epidemic increase. Is there a threshold or combination of factors that have been proposed.

9. What are the major aeroallergens in ryegrass pollen? What other pollen types are associated with spring/summer hayfever or asthma?
10. What are the major aeroallergens in fungal spores? Which fungal spores have been associated with epidemic TA?
11. Do the same allergenic materials trigger the allergic response in diagnosed asthmatics experiencing TA compared to spring/summer hayfever sufferers experiencing TA symptoms? Is the severity of response different and why?
12. What long-term model or algorithms are documented for predicting potential epidemic TA events? What data inputs (i.e. key risk factors) have been used?
13. What early warning (or alert) systems have been developed (and by whom) that are specific to potential epidemic TA events?
14. What public health messaging specific to TA has been used in the past? Was the messaging evaluated?

## REVIEW METHODOLOGY

### Thematic literature search strategies

Databases searched include CINAHL (via EBSCOhost), PubMed, EMBASE (including Medline), Web of Science and SCOPUS.

**Search strategy 1:** The initial searches of literature published between 2007-2017 were designed to broadly cover multiple disciplines in sufficient depth to inform the key aspects of TA necessary for responses to each of the specific questions raised by the Department. The terms that were used in each of the databases had included the key terms related to each of the themes (Immunology and disease status; public health and epidemiology; and Meteorology and environment). Outcomes of these initial literature searches were too extensive to allow meaningful review and analysis of evidence addressing each of the specific questions raised (see “Search strategy 1” and “Search strategy outcomes” in Appendix VI).

### Targeted literature search: “thunderstorm” and “asthma”

**Search strategy 2:** A second focused search strategy without date restrictions was undertaken to identify relevant academic literature published for each of the three themes using only the specific terms “thunderstorm” and “asthma”. Outcomes of this search for each database are shown listed in Figure 4 and Table 21; 386 articles were identified. Abstracts extracted from all databases were exported to an Endnote library and duplicates were deleted. Each of the remaining 173 articles for the secondary search were considered and evaluated for strengths and weaknesses. These abstracts are included as citations (with abstracts when available) in the appendices to enable further review and evaluation of relevant publications in future if required (Appendix XI). After screening for relevance by title, 165 papers were retained. Each of these abstracts was reviewed and those not relevant to the scope of this review were excluded leaving 142 articles. Publications not written in English were excluded. After detailed reviewing of the full text articles, 60 were found to be primary studies with original research, 10 letters and replies to the editor, 6 conference abstracts, 2 books, 2 reports, 1 news article and 42 review publications. Data on conditions contributing to TA from primary research publications were extracted and synthesized descriptively in Table 2 (5 Australian events) and Table 4 (20 international primary articles). Secondary sources including review articles were excluded from full evaluation unless new information on additional episodes of TA not captured in primary research articles was tabulated or described. Information provided in secondary research articles (Letters, books, Editorials, conference abstracts etc.) were included as secondary types of evidence in Table 3 (Australia) and Table 5 (international).

Additionally, based on prior knowledge of the relevant fields of research, specific searches and citation tracking, further papers determined to be appropriate and relevant primary studies, were reviewed to inform response to specific questions are included in the response to questions and discussion.

Medical and scientific publications that provide insights to evidence and knowledge gaps on TA risk, prediction and prevention were grouped into three content-related themes. Responses to several questions raised by the Department draw upon literature from within more than one of these themes. All relevant studies globally were included in the review but geographical influences on study outcomes, applicability of local factors and their relevance to Australia are considered.

Grey literature searches covered broad search terms of “Thunderstorm and asthma” to identify unpublished reports of TA incidences and epidemics globally as well as any government policies or public health responses to TA.

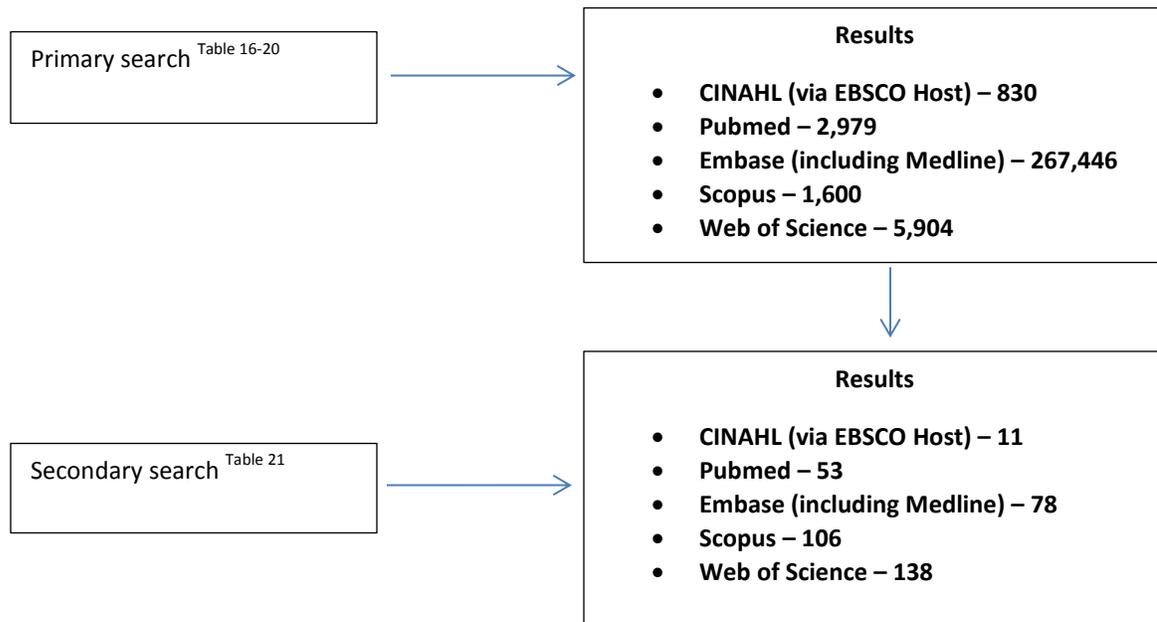


FIGURE 4: SEARCH STRATEGY OUTCOMES

### Search and review considerations

A broad range of study types; for instance epidemiological studies, case-control studies, descriptive case series reports, short communications, letters to editors and meteorological modeling studies, were considered for inclusion in the literature review and evaluation.

The need to source and assimilate information from a broad range of article types that assess different factors contributing to the occurrence of TA epidemics, was addressed by a multidisciplinary team of researchers with diverse backgrounds relevant to key themes who have capacity to understand research on TA from different disciplines.

It was anticipated that given the multidisciplinary nature of TA research and the sporadic timing of TA episodes that diverse study designs would be used. This situation and the time constraints, prevent a prescriptive systemic approach to evaluation of findings, strength and weight of evidence in each study. Each study focused on TA was evaluated on its merit taking into account the design type and methods employed. For instance, case-control studies were evaluated for the number of subjects included and demographics of each group whilst ecological studies were evaluated for the type and quality of environmental conditions included and the number of centres involved.

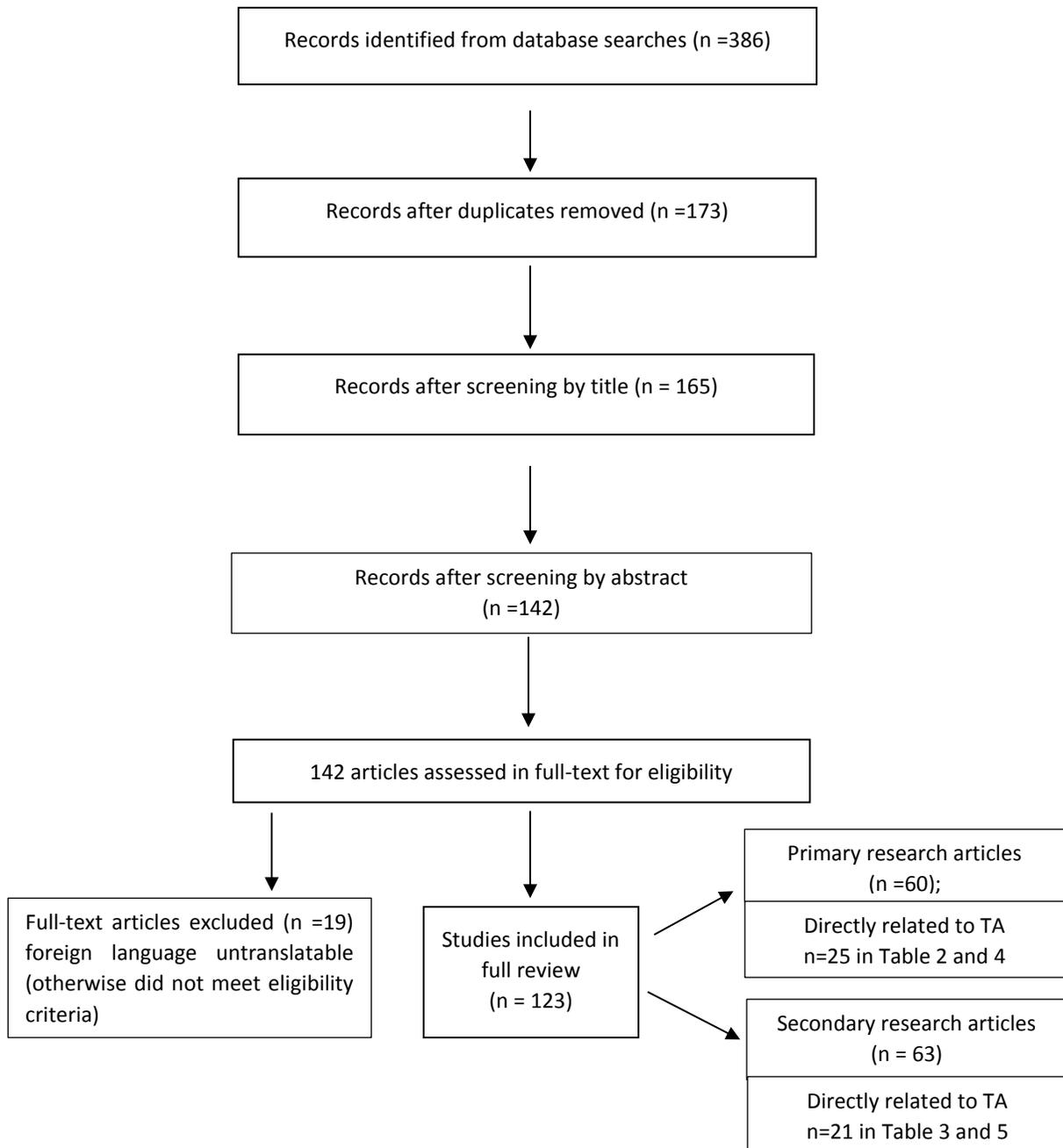


FIGURE 5: SECOND SEARCH STRATEGY OUTCOMES

## THUNDERSTORM AND ASTHMA SEARCH OUTCOMES FROM PRIMARY ACADEMIC LITERATURE SOURCES

TA has been observed in only eight countries (Australia, Canada, Greece, Iran, Italy, Saudi Arabia, USA and the UK). In five of these countries, reports of epidemic TA events have been recorded (Australia, Canada, Italy, Iran and the UK). Seventeen of 22 reported epidemic TA events, come from Australia and the UK alone.

### Summary of key features of Australian thunderstorm asthma episodes

Ten TA episodes have occurred in Australia since 1984, seven of them in Melbourne (Tables 2 and 3). The other three were in central and southern NSW or the ACT (Newcastle, Wagga Wagga and Canberra). Table 2 summarises the key features from primary studies of the episodes. Notable factors are:

- All Australian TA events occurred in spring; November in Victoria and October in NSW or ACT (Tables 2 and 3).
- Thunderstorm outflows were detected on 33% of epidemic days and only 3% of control days in one longitudinal case-control study of six NSW towns (Marks et al. 2001). Moreover, on days when epidemics of asthma were observed, if there was a thunderstorm within 80km then only 15% of the thunderstorms did not have these outflows.
- Grass pollen aeroallergens appears to be a necessary factor for TA in Australia evidenced by; i) high airborne exposure precedes and/or coincides with all Australian TA episodes (when measured) and ii) almost universal prevalence of sensitisation to Ryegrass in affected patients (see Questions 4 and 8).
- In each Australian TA event for which clinical data was reported, nearly all affected patients had hayfever e.g. (Bellomo et al. 1992; Girgis et al. 2000; Wark et al. 2002).
- As well as grass pollen, mould spores have been implicated in TA episodes (Girgis et al. 2000).
- Attendance at Melbourne ED for asthma-related symptoms increased up to 10-fold during the 1989 TA epidemic and the condition named in this report “November Asthma” was more common in case ( $p < 0.05$ ) than controls (Bellomo et al. 1992).
- During all known TA events (Tables 2 and 3) in Australia ten deaths have been reported, all occurring in Melbourne, one in 1987 (Bellomo et al. 1992) and nine attributed to the 2016 event which at the time of writing was being investigated by the State Coroner (Inspector-General for Emergency Management 2017).
- Both (Bellomo et al. 1992) and (Girgis et al. 2000) found no significant effect of gender or age on risk of TA, however in the Newcastle study of TA, being a female was a predictor of presenting with asthma following the thunderstorm, RR 2.0 (95%CI: 1.2 to 3.4; Wark et al. 2002).
- During the 1987 and 1989 Melbourne events ozone, sulphur dioxide and nitrogen dioxide levels were lower than usual for November (Bellomo et al. 1992) indicating that airborne pollutants was not an important contributing factors. However, the influence of pollutants on TA in Australia has not been well investigated.

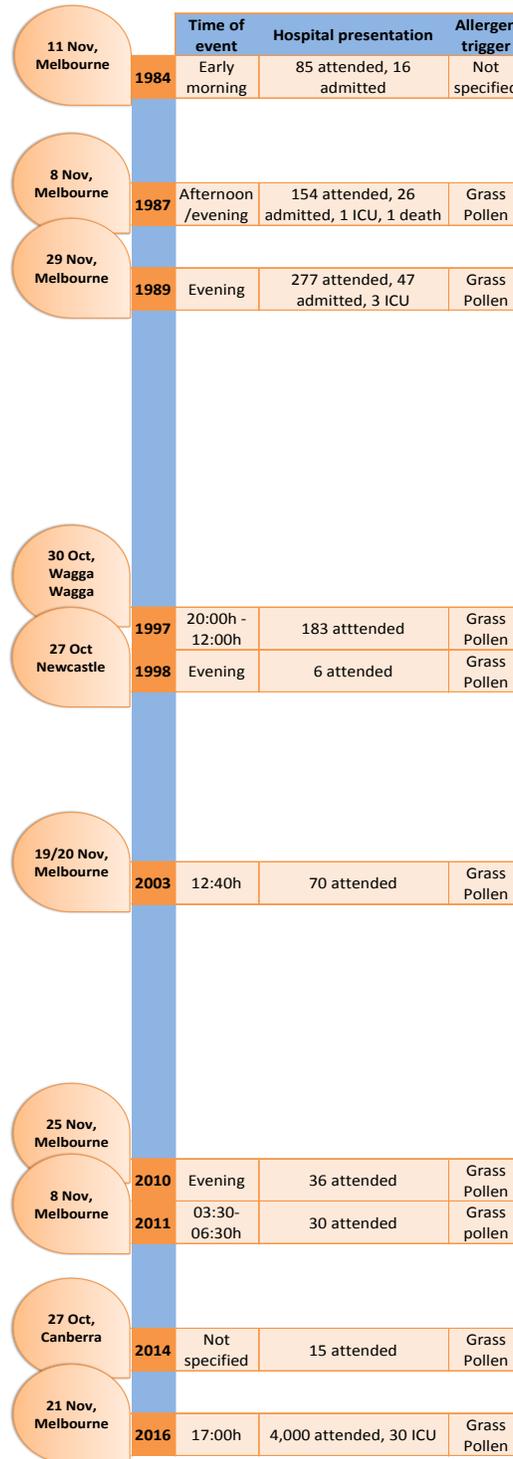


FIGURE 6 REPEATED: NATIONAL TIMELINE FOR THUNDERSTORM ASTHMA EPIDEMICS

**TABLE 2: PRIMARY STUDIES EXAMINING THUNDERSTORM ASTHMA EVENTS (AUSTRALIA)**

Location and date	Methods and participants	Objective	Key climatic measures	Key aeroallergen count measures	Patient characteristics	Results	Quality of evidence
<p><b>Melbourne EDs, Australia. 1987 and 1989.</b></p> <p><b>(Bellomo et al. 1992)</b></p>	<p><u>Ecological and Case control study.</u></p> <p>Storm affected asthmatic patients from 1989 = cases (n=12).</p> <p>Asthmatics not affected by storm from 1989 = controls (n=16).</p>	<p>Document clinical impact and identify meteorological and environmental circumstances surrounding two epidemics of TA in Melbourne and to find a possible aetiology for these events.</p>	<p>Hourly concentration of NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub> and PM.</p> <p>Pressure systems, TS, temp, rainfall, wind, humidity and cold front.</p>	<p>NA</p>	<p>SPT; Ryegrass &amp; tree pollen, starch granules.</p> <p>Questionnaire, medical interview, pulmonary function test.</p>	<p>1987; 157 asthma presentations, 26 ED admissions, 1 death.</p> <p>1989; 277 asthma presentations, 47 ED admissions.</p> <p>5- to 10- fold increase in asthma attendance. In 1989 TA event, patients were more likely to suffer hayfever (p&lt;0.05), show sensitivity to ryegrass pollen (p&lt;0.05) and ryegrass starch granules (p&lt;0.025).</p>	<p>A small number of cases and controls.</p> <p>Asthma assessed as mild, moderate or severe.</p> <p>No pollen counts performed.</p> <p>Number of EDs not specified.</p>
<p><b>Six inland NSW town EDs, Australia.</b></p> <p><b>Jan 1995 to Dec 1998.</b></p> <p><b>(Marks et al. 2001)</b></p>	<p><u>Case control study.</u></p> <p>Case/Epidemic days (n=48); Observed number of ED attendances was greater than four standard deviations in excess of the expected number.</p> <p>Control days (n=191); observed ED attendances was within one standard deviation of the expected number.</p> <p>“control days” randomly sampled from non-epidemic days over same period.</p>	<p>Establish contribution of TS outflows to hospital asthma attendance in region where severe TS related epidemics have been reported. The relative importance of TS, TS outflows, and cold fronts in predicting TA events also investigated.</p>	<p>Days in which TS were reported within 80 km of a cold front or TS outflow was identified by sudden increases in wind speed, pressure and RH, decreases in temp, and changes in wind direction and rainfall. Wind direction and speed recorded each minute.</p>	<p>Pollen grains collected using Burkard seven day volumetric spore trap. Grass pollen grains classified either as intact grains or ruptured, spraying or empty pollen grains. Data expressed as average number/m<sup>3</sup> air for each 1 hour</p>	<p>NA</p>	<p>TS outflows were detected on 33% of epidemic days and only 3% of control days (OR 15.0, 95% CI; 6.0 to 37.6).</p> <p>Detailed examination of one severe epidemic showed that its onset coincided with the arrival of the TS outflow and a 4–12 fold increase in the ambient concentration of grass pollen grains.</p>	<p>Low specificity of meteorological prediction of TS producing outflows.</p> <p>Study analysed data over four year period.</p> <p>No reporting of patient attendance.</p> <p>No modelling performed.</p> <p>Pollen trap located at Charles Sturt but they investigated many towns that may be located further from the trap than is reasonably expected.</p>

<p><b>Wagga Wagga ED, Australia. Jul to Oct 1997.</b></p> <p><b>(Girgis et al. 2000)</b></p>	<p><u>Case control study.</u></p> <p>People aged 7-60 attending ED 01/07/97-31/10/97 with diagnosis of asthma (ICD9 code 493).</p> <p>Cases (n= 183); attending between 12pm 30/10-12am 31/10.</p> <p>Controls (n= 121); attending at other times.</p> <p>Logistic regression modelling.</p>	<p>Characterize patients at risk of asthma exacerbation during spring TS and identify potential measures to ameliorate the impact of those events.</p>	<p>TS</p>	<p>NA</p>	<p>SPT; <i>Alternaria alternata</i> (fungi), wheat grain, ryegrass pollen, <i>Cladosporium</i> (fungi), cotton, cat dander, mixed grains, and house dust mite.</p> <p>Questionnaire; sociodemographic, location during storm, symptoms.</p>	<p>One hundred and thirty-eight (95%) cases who attended ED during the TS gave a history of hayfever prior to the event, compared to 66 (74%) controls attending at other times (OR, 6.01, 95% CI; 2.55±14.15).</p> <p>111 (96%) cases were allergic to ryegrass pollen compared to 47 (64%) controls (OR, 23.6, 95% CI; 6.6±84.3).</p>	<p>Children aged &lt;7 yrs (11 cases and 78 controls) were excluded. Wide age grouping with no age stratification.</p> <p>Only one ED studied.</p> <p>Adjusted results reported in text.</p> <p>No pollen data not shown but discussed.</p>
<p><b>Newcastle ED, Australia. 27 Jun, Sep, Oct 1998.</b></p> <p><b>(Wark et al. 2002)</b></p>	<p><u>Case control study.</u></p> <p>Patients presenting with acute asthma, atopic with confirmed asthma seen with 4h of presentation. Cases (n=6); presented 27/10/98.</p> <p>First control (n=12); atopic asthmatics presented Jun-Sep 1998, with acute exacerbation of asthma. Second control group (n=6); atopic asthmatics, naïve to inhaled corticosteroids, presented with acute asthma over a 12-month period.</p>	<p>Characterize airway inflammation in TA and to compare them to a group of atopic asthmatics.</p>	<p>TS</p>	<p>NA</p>	<p>SPT; <i>Aspergillus fumigatus</i>, <i>Aspergillus</i> mix, <i>Penicillium</i>, <i>Alternaria tenuis</i>, <i>Dermatophagoides pteronyssinus</i>, <i>D. farina</i>, cockroach, peanut, hazelnut, wild oats, plantain, timothy, bent grass, blue grass, ryegrass, cat hair, dog hair, feather mix and horse dander, and controls (histamine and saline).</p>	<p>Thunderstorm cases were more likely to have a history of hayfever and grass pollen allergy and less likely to be on inhaled corticosteroids prior to presentation. Cases had elevated sputum eosinophils and higher sputum eosinophil cationic protein compared to controls. Cases had more cells positive for IL-5 compared to controls. Cases and control groups had a similar degree of moderate to severe acute airway obstruction.</p>	<p>Only one ED studied.</p> <p>Broad age group; 16-67.</p> <p>Very small number of cases n=6.</p> <p>No data on environmental factors in the modelling or in the results section.</p> <p>No aeroallergen counts.</p>

<p><b>Melbourne EDs, Australia.</b></p>	<p><u>Ecological time series analysis.</u></p>	<p>Examine association between grass pollen levels and asthma ED presentations in children. To determine whether associations only after a thunderstorm, or whether grass pollen levels have a consistent influence on childhood asthma ED visits during the season.</p>	<p>Average daily concentrations of the Airborne Particle Index and max daily 4-h average concentrations of NO<sub>2</sub> and O<sub>3</sub>. Daily max temp, rainfall and average daily RH. thunderstorm activity.</p>	<p>Airborne grass pollen levels recorded daily. Low grass pollen days (&lt; 20 grains/m<sup>3</sup>), moderate grass pollen days (20–49 grains/m<sup>3</sup>), high grass pollen days (50–99 grains/m<sup>3</sup>) and extreme grass pollen days (&gt; 100 grains/m<sup>3</sup>).</p>	<p>NA</p>	<p>Spike of extreme level grass pollen on 15, 18 and 19 Nov; preceded a large spike in asthma ED attendances on 20 Nov 2003.</p> <p>When grass pollen increased to about 19 grains/ m<sup>3</sup>, same-day risk of childhood ED presentations increased linearly (P &lt; 0.001). Wind speed was greater than 90 km/h on 15 and 17 Nov. During thunderstorm days, ED attendance peaked at 70 for asthma.</p>	<p>Investigated dose-response associations.</p> <p>Only people less than 15 years of age; no sensitisation data.</p> <p>Association between thunderstorm and pollen together on asthma admissions not assessed.</p>
<p><b>2003 (Erbas et al. 2012)</b></p>	<p>A total of 2,559 children attended an ED due to asthma during the study period.</p> <p>Thunderstorms observed during study period; 19/20 Nov 2003.</p> <p>Childhood asthma diagnosis (ICD10-AM, J45 and J46).</p>						

**Abbreviations;** Temp; temperature, Max; maximum, O<sub>3</sub>; Ozone, NO<sub>2</sub>; Nitrogen Dioxide, SO<sub>2</sub>; Sulphur Dioxide, PM; Particulate Matter, SPT; Skin Prick Test, NA; Not applicable, TS; Thunderstorm, TA; Thunderstorm Asthma, OR; Odds Ratio, CI; Confidence Interval, m; Meters, RH; Relative Humidity, ED; Emergency Department. Jun; June, Jul; July, Sep; September, Oct; October, Jan; January, Dec; December, Nov; November. \*Emergency room and the accident and emergency department, are both referred to as the emergency department.

**TABLE 3: LETTERS TO EDITORS, REPORTS AND THUNDERSTORM ASTHMA EVENTS CITED IN NEWS OR AGENCY SOURCES (AUSTRALIA).**

Location and date	Type	Description of thunderstorm event	Study findings
<b>Melbourne ED, Australia.</b> <b>11 Nov 1984</b> (Egan 1985)	Letter to the editor	Asthma epidemic of 85 patients following TS. 16 patients admitted, 25% smokers, 15/16 patients female (2 pregnant) Atopy (95%), family history of asthma (30%), previous attacks (85%)	Steady rise in temp over the preceding week, change in wind speed and direction, abrupt rise in relative humidity. No pollen count data available.
<b>Melbourne, Australia.</b> <b>25 Nov 2010</b> (Howden et al. 2011)	Letter to the editor	Melbourne ED asthma presentations on the day of the TS were above 35°C, of which the majority were children. All other days recorded in the month had less than 10 visits.	Pollen counts in extreme range (>100 grains/ m <sup>3</sup> ) days before storm, but moderate levels on day of the storm.
<b>Canberra, Australia.</b> <b>27 Oct 2014</b> (Colley 2014)	Newspaper	The string of high pollen days began on Sunday October 26 Professor Haberle (CanberraPollen; ANU) said, coinciding with a spike in emergency department presentations for asthma at Canberra Hospital – where 15 people sought treatment compared to a more average day of just four.	"We've had at least 10 days of high to extreme pollen in the atmosphere... and that's quite unusual." October's spike in asthma cases at the hospital was blamed on TSs in Canberra.
<b>Melbourne, 8 Nov 2011</b> (Erbas et al. 2015; Murnane 2011)	Letter to the editor	Initial news report 30 people (50% increase on previous two days); peak in childhood asthma presentations (Murnane 2011). Grass pollen; extreme Nov 5-11, peaking at 727 grains/m <sup>3</sup> Nov 7 (Pers Comm, Ed Newbiggin, MelbournePollen at Uni of Melb, Feb 17, 2017)	Rate of sensitisation to grass pollen was 47% in boys and 37% in girls. Presence of grass pollen in the atmosphere was significantly associated with an increased risk of admission in an adjusted model (OR 5 1.11; 95% CI, 1.003-1.22) .
<b>Melbourne ED, Australia.</b> <b>21/22 Nov 2016</b> (Inspector-General for Emergency Management 2017)	Preliminary report	Following hottest day since March, a TS passed through Melbourne on Nov 21. Between 3.00pm on 21 Nov and 6.00am on 22 Nov 2016, ESTA processed 2666 emergency and non-emergency ambulance events, of which 962 related to breathing problems. By 7.00pm on 21 Nov, EDs experienced an unprecedented level of demand, estimated by some hospitals to be at least 50 per cent greater than for the same period in the previous week.	Approximately 9,900 people presented at hospitals in metropolitan Melbourne and Geelong. Of these approximately 4,000 were respiratory related cases. Thirty patients were admitted to ICU. Nine deaths were reportedly attributed to this event and Victoria's State Coroner is investigating those circumstances.

**Abbreviations;** Temp; Temperature, NA; Not applicable, TS; Thunderstorm, OR; Odds Ratio, CI; Confidence Interval, ESTA; Emergency Services Telecommunications Authority, ED; Emergency Department, Nov; November.

\*Emergency room and the accident and emergency department, are both referred to as the emergency department.

Five further TA events occurred in Australia that are not reported in primary studies are described in Table 3. Notable factors from descriptions in editorials, reports, news or agency sources are:

- Rapid change in weather conditions in Melbourne in Nov 11, 1984 episode (Egan 1985).
- Multiple days of extreme levels of grass pollen precede Melbourne episodes 2010 and 2011 (Howden et al. 2011; Murnane 2011) and 2014 Canberra episode (Colley 2014).
- Grass pollen sensitisation 47% in boys and 37% in girls in Melbourne study after 2011 episode (Erbas et al. 2015).

Approximately 4000 people presented at hospitals for respiratory related problems in Melbourne in Geelong on Nov 21/22 2016. Nine deaths attributed to the 21 November 2016 event have been referred to the Victorian Coroner to investigate (Inspector-General for Emergency Management 2017).

## Summary of observations of International thunderstorm asthma episodes

Twenty-four studies examine international TA episodes, summarised in tables 4 and 5 below.

**They include seven in the United Kingdom. Notable features are:**

- All 7 recorded epidemics of TA in the UK took place in early summer (June to July); 1983 (Packe et al., 1985) 1984; (Alderman et al., 1985); 1989 (Allitt et al., 1997); 1994 (Higham et al., 1994); 2002 (Pulimood et al. 2007); 2005 (Levy et al., 2007) and 2013 (Elliot et al., 2014).
- During the 1994 TA episode, 24% of calls to 29 GP clinics were related to asthma, compared to 7% on control nights (Higham et al. 1997), demonstrating the importance of the primary healthcare sector in responding to TA epidemics.
- In South-Central England, 4/8 Regional Health Authorities (RHAs) witnessed above six fold increase in attendance with asthma/wheeze during the epidemic night of 1994 (1 death), compared to the previous week. Presenting cases were mostly in their 20s and 30s, reporting hayfever (40%) and asthma (38%) (Venable et al., 1994).
- The risk of asthma in thunderstorm affected areas compared with control areas was significant (OR 6.36; 95% CI: 4.97 to 8.32) (Higham et al. 1997).
- Particulate matter (PM) was observed to be in the 90<sup>th</sup> percentile on the 24<sup>th</sup> June, with both grass and nettle pollen levels being extremely high three days prior to the TA event of 1994 (Hajat et al., 1997).
- Multiple studies report increases in asthma attendance following this 1994 TA event in hospitals (Celenza et al. 1996; Davidson et al. 1996) and GP (Higham 1994; Murray et al. 1994; Venables et al. 1996).
- The consultation for asthma associated with increased levels of grass pollen (100 grains/ m<sup>3</sup> unit increase) was calculated to be 6.65 (95% CI: 4.55 to 9.72, p= <0.0001) for all the age groups combined (Hajat et al., 1997). Twelve of 16 examined patients had very high IgE to grass pollen (Venables et al. 1997).
- Lightning strikes, increase in rainfall, fall in temperature and rise in air pressure and humidity were significantly associated in an increase of asthma presentations six hours following the thunderstorm but when levels of pollen peaked, asthma attendance rapidly increase (Celenza et al. 1996).
- A history of hayfever was observed in 63%-90% of patients and 32-44% reported never having an asthma attack before the 1996 TA event. Affected people were mainly young atopic adults (mean 32 years; Davidson et al. 1996; Venables et al. 1996).
- "Difficulty breathing" calls on telephone advice lines increased 400% after a June 4, 2005 event in South-East England (Levy et al. 2007) and a statistically significant rise was noted in London after a July 22 2013 event (Elliot et al. 2014). All surveyed 18 cases from a Birmingham 1983 event had a history of hayfever (Alderman et al. 1986).
- Median age of presenting patients after Birmingham event of 1983 was 24 (Packe et al. 1986). Similar age group was affected in Leicester after 1989 event (Allitt et al. 1997).

**There have been two reports out of southern Italy on TA events; Naples (2004) and Barletta (2010). Notable factors are:**

- Seven patients with severe bronchial asthma presented to hospital during the Naples event (D'Amato et al. 2008) and 20 during the Barletta event (Losappio et al. 2011).
- Four Naples patients had a history of asthma and two had allergic rhinitis; six Barletta patients had a history of asthma and two of allergic rhinitis. All the Naples patients reported being outdoors in the storm.
- Sensitisation testing showed all seven Naples patients to be sensitized to *Parietaria* species pollen, which was found to be high a day before the TA event (D'Amato et al. 2008). All 20 Barletta patients were sensitized to olive tree pollen (*Olea europaea*). No patients were found to be sensitized to *Alternaria* (Losappio et al. 2011).

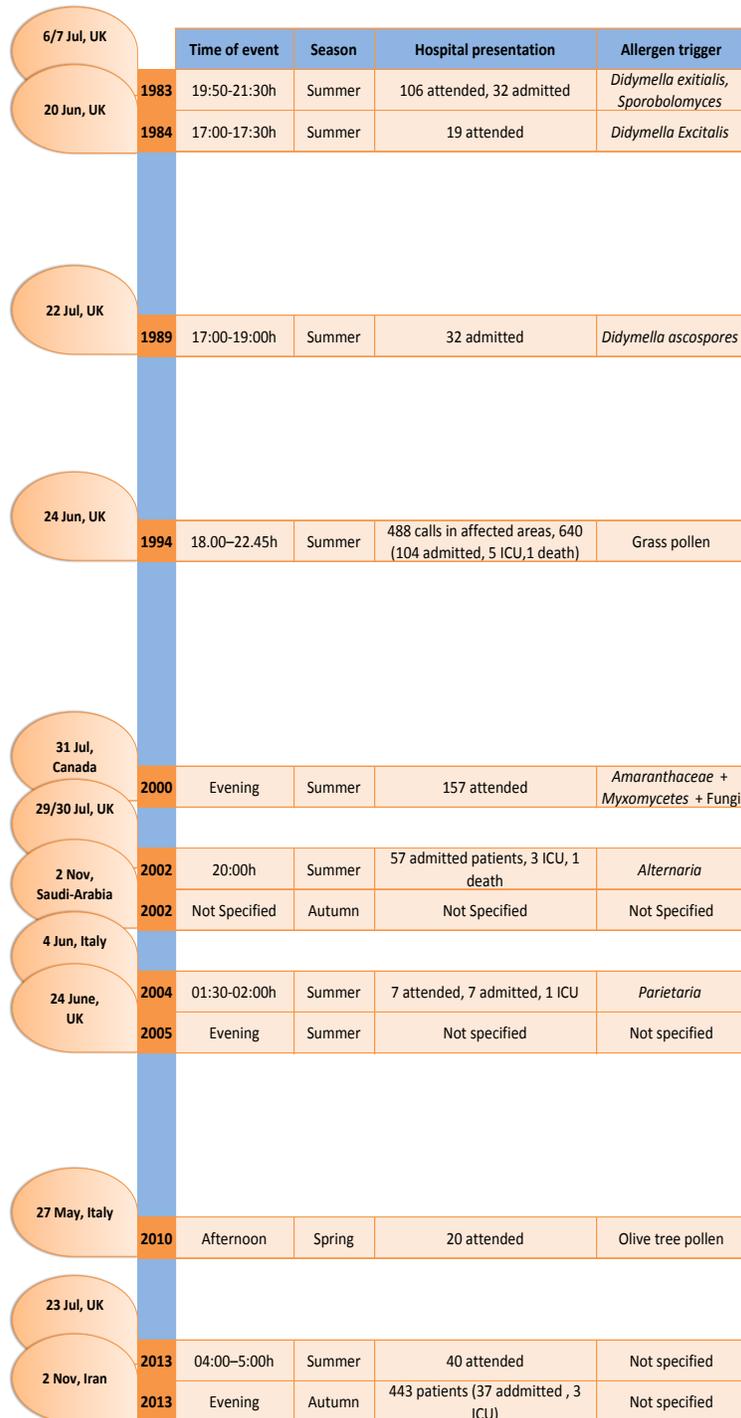


FIGURE 7: TIMELINE FIGURE SHOWING INTERNATIONAL SEQUENCE AND TIMING OF EVENTS

**In the Middle East:** Two TA epidemic events were reported; one in Saudi Arabia, November 2002 and one in Iran, November 2013 (Al-Rubaish 2007; Shoushtari et al. 2016). Both studies limited to insightful description of the events.

**In North America:** There have been few reports of TA in Canada and USA. On July 31<sup>st</sup> to August 1<sup>st</sup> 2002, 157 people presented (17 cases expected) to three EDs across Calgary for asthma or shortness of breath, following a thunderstorm (Wardman et al. 2002). From 46 patients interviewed, 59% were outside during the storm, 78% had a history of asthma, hayfever or allergies, while 46% had a family history of one of the three. The median age of the interviewed cases was 31 (range 17 to 87 years). There was significant increase in bioaerosols a day before the TA event.

Two additional studies in Ottawa Canada, found thunderstorms to be associated with asthma ED presentations. Dales et al. (2003 longitudinal study (1993-1997), which observed an estimated 4,000 yearly asthma hospital admissions found that on thunderstorm days (n=151) compared to non-thunderstorm days (n=919), daily asthma visits significantly increased from 8.6 to 10 ( $p < 0.05$ ), while air concentrations of fungal spores was doubled (from 1,512 to 2,749/ m<sup>3</sup>). The other Canadian longitudinal study (1992-2000) observed summertime thunderstorm activity, had an OR of 1.35 (95% CI=1.02 to 1.77) relative to summer period with no thunderstorm activity, for asthma visits (total study period asthma visits: 18,970; Villeneuve et al. 2005). While no TA event has been noted in the USA, a longitudinal study (1993-2004) was conducted in Atlanta which produced significant results. Grundstein et al. (2008) found an association between daily asthma presentations to the ED and thunderstorm occurrences ( $p, 0.001$ ). Asthma visits (total study period asthma visits: 215,832) were found to be 3% higher on thunderstorm days.

**TABLE 4: PRIMARY STUDIES EXAMINING THUNDERSTORM ASTHMA EVENTS (INTERNATIONAL).**

Location and date	Methods and participants	Objective	Key climatic measures	Key aeroallergen count measures	Patient characteristics	Results	Quality of evidence
<p><b>Birmingham, UK.</b>  <b>Jun and Jul 1983.</b></p> <p>(Packe et al. 1985)</p>	<p><u>Descriptive study.</u>            Patients presenting with acute asthma to 8 EDs. Asthma; acute onset wheeze and breathlessness, if chest auscultation revealed diffuse expiratory wheezes, and if no history of chronic bronchitis/emphysema.</p>	<p>Presentation of data on extent of TA on Jul 6 and 7, 1983 in Birmingham and investigation of causal environmental factors.</p>	<p>Meteorological data (daily); mean temp, RH, rainfall, mean pressure. TA activity. Air pollutants; (daily) smoke and SO<sub>2</sub> levels.</p>	<p>Pollen and fungal spore (<i>Cladosporium</i>, <i>Didymella</i>, <i>Sporobolomyces</i>) counts; 2 sites with volumetric slit sampler (a modified Hirst design); 12 m and 15 m above the ground.</p>	<p>NA</p>	<p>At the 8 Birmingham hospitals attendances for most of Jun and Jul ranged between 2 and 20 per day; on Jul 6 and 7, however, there were 36 and 70 attendances, respectively. Sudden increase in fungal spores (especially <i>Cladosporium</i>, <i>Didymella</i>) at the outbreak was probably one of the contributors for the onset of asthma.</p>	<p>GP visits were mentioned but data not provided. Describes collection of pollen and position. No modelling or patient characteristics or sensitisation reported. Indicates fungi as allergen trigger.</p>
<p><b>UK, 14 RHAs. 1987 to 1994.</b></p> <p>(Newson et al. 1998)</p>	<p><u>Ecological study.</u>            Epidemic defined: asthma admissions count exceeding the predicted count by at least four coefficients of variation. Two control days for each epidemic were selected in the week before and after the epidemic. Asthma admissions for 14 National Health Service RHAs from Hospital Episodes System.</p>	<p>Identifying what risk factors predicting asthma epidemics.</p>	<p>Data was provided by the UK Meteorological Office on sferics (sferics per 100 square kilometres per day), temp (mean between the daily max and min temps in degrees Celsius), rainfall (daily total in millimetres), pressure, humidity and wind speed.</p>	<p>Daily mean birch, oak, grass and nettle pollen counts, measured in grains per cubic metre per day (Gr-m-3-day-1).</p>	<p>NA</p>	<p>Fifty six asthma epidemics were identified. The mean density of sferics, temp and rainfall on epidemic days were greater than those on control days. Two thirds of epidemics were not preceded by TS. Most epidemics not associated with TS or unusual weather conditions, and most TS, even following high grass pollen levels, do not precede epidemics.</p>	<p>Not every RHA had a pollen station. Sferic density was only available in RHAs from 1990.</p>
<p><b>Cardiff/Newport ED, UK.</b>  <b>Jan 1990 to Dec 1996.</b></p> <p>(Anderson et al. 2001)</p>	<p><u>Case control study.</u>            Cases; 32 days with lightning strikes. Controls; same 64 non lightning strike days from different year. Poisson regression; effects on daily asthma admissions (ICD9 493) on case and control days.</p>	<p>Association between TS and asthma admissions and investigate role of pollen, fungal spores counts rainfall, temp and O<sub>3</sub>.</p>	<p>Mean daily conc. O<sub>3</sub>, min/max temp and total rainfall.</p>	<p>Total pollen count, total fungal spore count.</p>	<p>NA</p>	<p>More admissions on TS days (p= 0.04); asthma admissions correlated with increasing [O<sub>3</sub>] in summer (p= 0.02); no significant Spearman's correlations between either pollen or fungal spore counts and asthma admissions (r= -0.07 and r= -0.09).</p>	<p>Study covered data for seven year period but did not report how pollen and fungi were collected. Only one centre studied.</p>

<p><b>UK, 14 RHAs. Jan 1990- Feb 1994.</b>  (Newson et al. 1997)</p>	<p><u>Ecological study.</u> Asthma admissions for each of the 14 National Health Service RHAs in England, on each day, were taken from the Hospital Episodes System. Used log linear autoregression to fit a model of asthma admissions.</p>	<p>To quantify the rise in incidence of asthma which typically follows a TS in England and investigate whether this rise is greater after periods of high counts of grass pollen.</p>	<p>Sferics, measured in sferics per 100 square kilometres per day (Sf/100 km<sup>2</sup>/day).</p>	<p>Daily mean grass pollen counts, measured in grains per cubic metre of air sampled per day (Grains/ m<sup>3</sup>).</p>	<p>NA</p>	<p>Very large sferic densities associated with moderate rises in hospital admissions for acute asthma. However, typical TS days are not associated with spectacular asthma epidemics of the scale previously reported. TS associated excesses are amplified after a run of high pollen counts.</p>	<p>Study looked at data covering four year period. Two age groups 0-14 and 15 and older analysed. Age stratification of 15plus may not be consistent with what is described in the literature. Also 0-2 age group not good to be grouped with 0-14. Extensive reporting of pollen counting.</p>
<p><b>London 45-47 GP practices, UK. Jan 1992 to Dec 1994.</b>  (Hajat S 1997)</p>	<p><u>Ecological study.</u> People presenting with asthma (ICD code 493) to GP clinic over the 3 years. Grouped into children (0-14 years), adults (15-64), and the elderly (65+).  24/06/94 TA epidemic occurred.  Multivariate model used following Poisson regression.</p>	<p>Determine if TA related morbidities increase in the primary care setting similarly to the ED.</p>	<p>NO<sub>2</sub> and CO (averaged over three sites around London), SO<sub>2</sub> and black smoke (averaged over five sites), and O<sub>3</sub> (averaged over two sites); one site provided information on PM (less than 10 micron diameter). Meteorological data obtained from the meteorological office.</p>	<p>24-hour average aeroallergen levels from the National Pollen Monitoring Network.</p>	<p>NA</p>	<p>The consultation rate on 24/06/94 (Saturday) was about six times higher than the average rate for asthma on Saturdays between 1992 and 1994. PM<sub>10</sub> was high on 24 Jun, with both the daily max and daily average values in the 90th percentile, grass and nettle pollen levels were both extremely high on the Wednesday before the TS. Asthma consultations and increased GP visits for all age groups was significant RR 6.65 (95% CI; 4.55, 9.72, p=&lt;0.0001).</p>	<p>Study covered data for three year period. A large number of GP clinics involved. Event occurred at night, GP clinics usually close at night. Quality analysis with appropriate age stratification. Odd addition of "dummy variable" into the models to represent the unusual asthma peak for the TS.</p>
<p><b>Derby EDs, UK. 1993-96.</b>  (Lewis et al. 2000)</p>	<p><u>Ecological study.</u> Daily asthma (ICD 9 493) attendance at two EDs in Derby, from January 1993 to Dec 1996.  Primary analysis between variables using Log linear auto regression.</p>	<p>Investigate the joint effects of aeroallergens, rainfall, TS and outdoor air pollutant levels on measures of acute asthma morbidity in the local community.</p>	<p>Min and max temp, RH, rainfall, wind direction, speed and TS. O<sub>3</sub>, NO<sub>2</sub>, and black smoke.</p>	<p>Grass and birch pollen hyaline <i>basidiospores</i> and coloured <i>basidiospores</i>, <i>Didymella</i>, <i>Alternaria</i> and <i>Cladosporium</i> Volumetric pollen/spore trap with daily slide or 7-day drum traps analysed by standard methods.</p>	<p>NA</p>	<p>Significant interaction between effects of grass pollen and weather conditions upon ED attendance; increase with grass pollen count was most marked on days of light rainfall (adjusted rate ratio for ≥50 vs &lt; 10 grains/m<sup>3</sup> at lag 2 days = 2.1, 95% CI 1.4, 3.3). Asthma admissions increased with <i>Cladosporium</i> count.</p>	<p>Study covered four year period. Only data for the 14 and over age group were included in analyses. No effect modification by patient characteristics done.</p>
<p><b>Isle of Wight, Oxford, Leicester, Derby, Addlestone, Nth London,</b></p>	<p><u>Descriptive study.</u></p>	<p>Investigation of fungal air spore across different sites affected by the TA event.</p>	<p>Informal notes on the time of rainfall in Cambridge; hourly detailed weather records (inc. wind) available for London, but not other</p>	<p>Burkard Volumetric Spore Traps traces were examined and counted from nine selected sites where the storms had occurred.</p>	<p>NA</p>	<p>In London, Addlestone and Leicester (and to lesser extent in Cambridge); very marked transient peaks of smut ustilospores particularly those of <i>Ustilago segetum</i> (Bull.) Roussel. At many sites there were transient peaks</p>	<p>Only investigated fungal air spores reported. No patient related information.</p>

<p><b>Cambridge &amp; Norwich, UK.</b> 24 Jun 1994. (Allitt 2000)</p>		sites.				of <i>Cladosporium conidia</i> . Most other sites except London showed high conc. ascospores after rain.	
<p><b>London ED, UK.</b> Jun – Jul 1994.  (Celenza et al. 1996)</p>	<p><u>Ecological study.</u> 148 patients presenting to ED with asthma between 1 Jun and 31 Jul 1994. 40/148 presented 24 hours after the storm (24/25 Jun). Poisson regression used for environmental factors associated with outbreaks of asthma.</p>	<p>Determine associations between Meteorological factors, concentrations of air pollutants or pollen, and asthma epidemic which occurred in London on 24/25 Jun 1994 after a TS.</p>	<p>Three hourly measurements of rainfall, ambient temp, barometric pressure, and humidity. Hourly measurements of ground lightning strikes. Hourly max concentrations of the air pollutants NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>.</p>	<p>Daily grass pollen counts with two hourly measurements for 24 and 25 Jun were obtained.</p>	<p>NA</p>	<p>Epidemic asthma significantly associated with a drop in air temp six hours previously and a high grass pollen concentration nine hours previously. Non-epidemic asthma significantly associated with lightning strikes, increase in humidity or [SO<sub>2</sub>], a drop in temp or high rainfall the previous day, and a decrease in max air pressure.</p>	<p>Modelling is adequate although they did model the “epidemic” separately.  No mention of pollen trap and location. Only one ED analysed. No sensitisation data available  Only people aged over 16 were included.</p>
<p><b>England, Scotland and Wales, UK.</b> 24/25 Jun 1994.  (Higham et al. 1997)</p>	<p><u>Case control study.</u> Case night; 24/25 Jun Cases were defined as complaints of; "asthma", "difficulty in breathing", "hayfever with difficulty in breathing", "short of breath", or "wheeze". Control night; 17/18 Jun there were 1,951 calls to the GP clinics.</p>	<p>Explore temporal and spatial relationship between TS and associated cases of asthma.  Modelling number of asthma on TS night (case) and non-TS night (control). Unclear how peak lightning was used in models.</p>	<p>TS activity (arrival time difference, lightning flashes.</p>	<p>NA</p>	<p>NA</p>	<p>Risk of asthma in TS affected areas compared with control night was 6.36 OR (95% CI; 4.97, 8.32) compared with a value of 1.01 OR (95% CI; 0.80, 1.27) for those not exposed. 488 patients affected; mostly in their 20's and 30's. There were 2,228 calls to 29 GP clinics of which 536 were for asthma. Of the 17 offices in affected area 488 of 1491 (33%) compared to 48 of 737 (7%) from unaffected areas were calls for asthma.</p>	<p>Broad inclusion criteria used for asthma.  No aeroallergen or patient characteristic data.  17/29 clinics affected by storm. Don't report how adjustments were made in the models. GP attendance outside of normal hours.</p>
<p><b>Southern/ Central England EDs and GP clinics, UK.</b> 24/25 Jun 1994.  (Venables et al. 1997)</p>	<p><u>Descriptive study.</u> 37 known EDs affected, 16 subjects tested for allergens. GP clinics received about 1600 calls for acute asthma. Reviewed records from Medical Deputising Service and 37 hospitals.</p>	<p>Describe the TA epidemic which occurred across south and central England, including the meteorological, aerobiological and air pollution factors and information about affected individuals.</p>	<p>Collection of meteorological (WS, WD, rainfall, temp, RH) and air pollution data (O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, PM<sub>10</sub>)</p>	<p>Pollen counts (grass, lime, dock, sweet chestnut, elder and Nettle). Fungal spores; <i>Cladosporium</i> and the <i>cereal smut Ustilago avenae</i>.</p>	<p>Blood test from 16 affected patients presenting to London ED. Tested specific IgE antibodies measured by ImmunoCAP (Pharmacia) to a grass pollen mix (gx1) and a mould mix (mx1).</p>	<p>Max grass pollen count of 1994, few days before TA epidemics (e.g. 258 grains per m<sup>3</sup> in London, highest over the 6 last years). 4/8 RHAs had six fold greater attendance with asthma/ wheeze on the epidemic night than on the following week and twofold increase in the other regions. One associated death reported. Strong TS outflow, sudden increase in the WS, decrease in temp (5°C), &gt;30% of RH increase preceded TS. 12/16 very high levels of IgE to pollen (classes 4-6),</p>	<p>Just 16 patients tested for allergens. Description of patient characteristics minimal and no formal testing conducted.  This is a descriptive study of each factor and its role during the 1994 asthma epidemic.</p>

						three of whom had a low or moderate IgE level to mould (class 1-2); 2/16 had a negative IgE response to pollen and 13/16 negative to mould.	
<p><b>London 12 ED departments, UK.</b>  <b>24 Jun 1994.</b>          (Davidson et al. 1996)</p>	<p><u>Observational descriptive study.</u>          Epidemic defined; 18:00 24 Jun to 24:00 25 Jun. Observed numbers of patients during epidemic compared with expected number of patients, from six other Fridays and Saturdays in Jun and Jul. Patients presenting with asthma, wheeze, or hayfever or allergy with wheeze or difficulty in breathing and all patients requesting an inhaler or asthma treatment.</p>	<p>Investigate the time course of an epidemic of asthma after TS, characteristics of patients affected, and the demand on emergency medical resources.</p>	<p>NA</p>	<p>Information about aeroallergens obtained from the Pollen Research Unit. Air samples were taken by a volumetric spore trap on the roof of the five storey building of the University of North London.</p>	<p>NA</p>	<p>During the epidemic 640 patients attended the ED compared with an expected number of 66 (P=0.003). A history of hayfever recorded for 403 patients; for 283 patients this was first known asthma episode. History of chronic obstructive airways disease was recorded in 12. People affected were young atopic adults (mean age of 32 years) who either are not known to have previously had asthma or are asthmatic but possibly do not have steroid inhaler prophylaxis.</p>	<p>The records of ~57 patients could not be found.</p> <p>Data about previous treatment of known asthmatics were available from 7/12 EDs</p> <p>No modelling at all.</p>
<p><b>Cambridge and Derby, UK.</b>  <b>29 Jul 2002.</b>          (Pulimood et al. 2007)</p>	<p><u>Case control study.</u>          Cases (n=26); Patients presenting to Cambridge University Hospital ED with acute asthma after the TS. Control (n=31); Patients with seasonal asthma during the grass pollen season attending asthma and allergy clinic at same hospital. Poisson regression modelling.</p>	<p>Study the cause of epidemics of asthma associated with TS. At this time, fungal spores increase rapidly to peak levels. Hypothesis: reported sudden and severe increase in asthma morbidity was due to fungal spore exposure in susceptible allergic asthmatic subjects.</p>	<p>Conc. O<sub>3</sub>, lightning strikes (strikes per hour per square kilometre). Daily data for temp, rainfall, wind speed and direction, max gust speed, and RH.</p>	<p>Average daily concentrations per cubic meter of air for fungal spores and grass pollen.</p>	<p>Questionnaire with 23 domains; demographic details, asthma history and previous TS related asthma symptoms. SPT and specific IgE to mixed grass pollen, tree pollen, <i>Alternaria alternata</i>, <i>Cladosporium cladosporioides</i>, <i>Aspergillus fumigatus</i>, and house dust mite.</p>	<p>23/ 26 cases had specific IgE to <i>Alternaria</i>. 11/ 31 controls had history of asthma exacerbation during TS. 10/11 controls sensitive to <i>Alternaria</i> by SPT, but <i>Alternaria</i> sensitivity was only in 4/20 controls did not report TS-related asthma. The OR of epidemic TA if sensitive to <i>Alternaria</i> species was 9.31 (95% CI, 2.305-37.601; P = .0008) and 63.966 (95% CI, 3.577-1143.9; P &lt;.0001) if sensitive to <i>Alternaria</i> species, <i>Cladosporium</i> species, or both. Mean age 38.6.</p>	<p>From 57 reported cases 26 participated in study and 31 controls were used.</p> <p>Controls were all over 16 years of age          Additional harvesting data provided.          Grass pollen is significant in the Poisson modelling of all admissions but they don't mention the case/control study.</p>
<p><b>London, UK.</b>  <b>23 Jun, 2013.</b>          (Elliot et al. 2014)</p>	<p><u>Ecological study.</u>          Patients presenting to one of 35 EDs across UK. Extracting data from the EDSSS.</p>	<p>Investigating the use of ED attendance data, to monitor the impact of TA.</p>	<p>Lightning strikes across the UK, 23 Jul 2013.</p>	<p>NA</p>	<p>NA</p>	<p>Significant increase in 'asthma/wheeze/difficulty breathing' attendances in London detected in several London EDs. Attendance peaked to 40 visits during the TS. Patients mostly 15-44 years.</p>	<p>Nothing on other weather, pollution or pollen. Nothing in methods of patient characteristics.</p>
<p><b>Athens ED,</b></p>	<p><u>Ecological study.</u></p>	<p>To obtain data on TS</p>	<p>Average daily levels of</p>	<p>NA</p>	<p>NA</p>	<p>No significant difference between TS</p>	<p>People aged 15 to 44.</p>

<p><b>Greece. Jan 1985 to Dec 1992.</b>  (Ilias et al. 1998)</p>	<p>Cases (n= 91); ED attendance for asthma on 74 recorded TS days. Controls (n= 107); ED attendance for asthma on matching control days.</p>	<p>in the region of Athens, data on the number of ED attendances for asthma during these storms and compare to control days.</p>	<p>SO<sub>2</sub>, NO<sub>2</sub> and O<sub>3</sub>, temp and humidity.</p>		<p>and control day pairs was observed (p = 0.39).</p>	<p>Single centre study looked at data covering eight year period. No allergen measures performed. No patient characteristics or modelling.</p>
<p><b>2-7 Nov, 2013. Location blinded for Peer Review. (Iran)</b>  (Feli et al. 2015)</p>	<p><u>Cross sectional, descriptive study.</u>  443 patients with acute bronchospasm (dyspnea, wheezing and cough) attended the ED in the study period.</p>	<p>Determine role of ED medicine in management of TS asthma. Multiple Casualty Incident (MCI), and to give an overview of affected patient characteristics.</p>	<p>TS</p>	<p>NA</p>	<p>NA</p>	<p>Average attendance for the same time period from Oct was 44 patients, compared to 443 in study period. 63% aged 20-40. The majority of patients (45.8%) presented to the ED during the evening until midnight. Previous medical history of asthma in 385 of the patients was recorded.</p> <p>No climatic aeroallergen or patient characteristic measures.</p> <p>Single centre study.</p> <p>Intervention study; "MCI management plan" is implemented, awaiting results.</p>
<p><b>Ahvaz, Iran. 2-20 Nov 2013.</b>  (Forouzan et al. 2014)</p>	<p><u>Descriptive analytical study.</u>  Nine hospital EDs; 2000 patients presenting with acute bronchospasm attacks invited for interview at the ED.  TS event on 2 Nov.</p>	<p>To report the characteristics and treatment management of patients admitted to the ED with bronchospasm attack following the TS event.</p>	<p>TS with rain</p>	<p>NA</p>	<p>2000 patients interviewed at the ED with initial questionnaire. 800 returned to do a supplementary questionnaire.</p>	<p>From initial 2000 patients; 55% female. Confirmed past asthma diagnosis in 22.7%. 39.2% mentioned respiratory diseases such as allergies previously. More than 78.2% had no comorbidity or underlying disease. From 800 recalled patients; most had symptoms following TS event; 60% were outdoor at that time. Previous history of similar symptoms related to the TS in 16% patients.</p> <p>No climatic, aeroallergen or sensitisation data available. Recall bias.</p>
<p><b>Ottawa ED, Canada. Jan 1992 to Dec 2000.</b>  (Villeneuve et al. 2005)</p>	<p><u>Case-crossover study.</u>  18,970 asthma ED visits in the study period  Asthma diagnosed as; ICD 493.</p>	<p>Evaluate associations between meteorological conditions and ED visits for asthma in a children's hospital in Ottawa.  Weather as primary exposure.</p>	<p>Measured on the hour; RH, dry bulb temp, wind speed, cloud opacity and precipitation measures (fog, liquid and freezing precipitation, snow, and TS).</p>	<p>NA</p>	<p>NA</p>	<p>More than half of all visits (56.2%) occurred between ages 2 and 5. The occurrence of fog or liquid precipitation was associated with an increased number of asthma visits, while snow was associated with a reduced number (P&lt;0.05). Summertime TS activity was associated with OR of 1.35 (95% CI; 1.02–1.77) relative to summer period with no activity.</p> <p>Data obtained from children's hospital, study population (2 to 15 years of age)</p> <p>Data obtained from only one centre.</p> <p>No pollen data but very extensive analysis of weather conditions.</p>
<p><b>Ottawa ED, Canada. 1993-1997.</b></p>	<p><u>Ecological daily time series analysis.</u>  All patients presenting to the ED between 1993 and</p>	<p>relationship between TS, air pollutants, aeroallergens, and asthma admissions to</p>	<p>Daily max and min temp, av. barometric pressure, dew point, and RH.; daily max O<sub>3</sub>, daily</p>	<p>Pollen grains and fungal spores collected using rotational implication sampling (Rotarod) at</p>	<p>NA</p>	<p>During TS days (n=151) compared to days with no TS (n= 919), daily asthma visits increased from 8.6 to 10 (p &lt; 0.05), and air concentrations of fungal</p> <p>Study included data covering six year period.</p> <p>Only in children and ED setting.</p>

<p>(Dales et al. 2003)</p>	<p>1997 with a principal diagnosis of asthma ICD9 code 493.</p>	<p>a children’s hospital ED over 6-yr The primary aim of this paper is not pollen but “fungi”.</p>	<p>av. NO<sub>2</sub> and SO<sub>2</sub>. The coefficient of haze, and 24-h averaged SO<sub>4</sub><sup>2-</sup>, measured every sixth day. TS activity.</p>	<p>2,400 rpm collecting 1 min from every 10-min/24 hr. Analysed particles adhering to silicon - coated rods. Sampler eight feet above ground level at the Ottawa Airport, ~4 miles from CHEO.</p>		<p>spores doubled (from 1,512 to 2,749/m<sup>3</sup>), with relatively smaller changes in pollens and air pollutants. Daily time-series analyses over 6 yrs., irrespective of the presence or absence of TS, demonstrated that increased total spores, equivalent to the seasonal mean, was associated with a 2.2% (0.9% SE) increase in asthma visits.</p>	<p>Good description of fungi, pollen collection methods.  Don’t present findings on pollen and ED because they state that they didn’t find an association in the discussion.</p>
<p><b>Atlanta 41 EDs, USA 1993-2004.</b>  (Grundstein et al. 2008)</p>	<p><u>Short report.</u> 215,832 asthma ED visits (ICD9 code 493) during the study period; 24,350 visits occurred on days following TS. Poisson generalised linear models for asthma visits and climatic variables.</p>	<p>Investigate the association between TS activity and asthma morbidity.</p>	<p>Total daily rainfall and max 5 s wind gust data, TS activity.</p>	<p>NA</p>	<p>NA</p>	<p>Association of TS activity with asthma exacerbation; preliminary evidence in support of rainfall and wind gusts playing important roles in this association. Overall, asthma visits were 3% higher on days following TS.</p>	<p>Used only one weather station to represent broad region.  No data on exposure to pollen and air pollutants and/or patient related characteristics.</p>
<p><b>Calgary ED, Canada. Jul 31, 2000.</b>  (Wardman et al. 2002)</p>	<p><u>Ecological study.</u> On 31/07/00 to 01/08/00, 157 individuals presented to three EDs in Calgary, for asthma or shortness of breath. 46 patients interviewed.</p>	<p>Investigate outbreak of asthma or shortness of breath symptoms after TS. Analyse individual symptoms/history of relevant conditions, air quality data, bio aerosol counts and weather conditions.</p>	<p>Atmospheric pressure and wind speed; levels of O<sub>3</sub>, hydrocarbons, NO, nitrogen oxides, NO<sub>2</sub>, and PM (10 µm or less) and PM (2.5 µm or less) collected.</p>	<p>pollen grains or spores counts/ m<sup>3</sup> collected at a suburban monitoring station. The sampler, positioned 2.44 m above ground, operating cycle of 1 min on and 9 min off over 24h, and used rotation impaction technology.</p>	<p>An interview with 46 patients seeking symptoms, personal and family history of relevant conditions, medications used and the patient’s environmental scan.</p>	<p>157 cases observed, 17 expected. interviewed patients(46); Median age of 31, 65% female, 59% outside during storm, 20% taking regular medication, 78% history of asthma, hayfever or allergies, 46% family history of one of the three. recorded increase in bio aerosols and The atmospheric pressure dropped steadily and dramatically during the TS.</p>	<p>Measured airborne algae concentration. Pollen collection described. Median duration of symptoms was 5 hours. Cases were adults. No modelling or formal analysis. Tables do not specifically present the case data.</p>

**Abbreviations;** Temp, temperature; Min, minimum; Max, maximum; Ozone, O<sub>3</sub>; NO<sub>2</sub>, Nitrogen Dioxide; SO<sub>2</sub>, Sulphur Dioxide; PM, Particulate Matter; SPT, Skin Prick Test; NA, Not applicable; Sulphate, SO<sub>4</sub><sup>2-</sup>; TS, thunderstorm; Emergency Department Syndromic surveillance system, EDSSS; TA, Thunderstorm Asthma; OR, Odds Ratio; CI, Confidence Interval; CO, Carbon Monoxide; RHA, Regional Health Authority; m, Meters; RR, Relative Risk; RH, Relative Humidity; NO, Nitric Oxide; GP; General Practice, ED; Emergency Department, Jul; July, Jun; June, Dec; December, Jan; January, Feb; February, h; Hour.

\*Emergency room and the accident and emergency department, are both referred to as the emergency department.

**TABLE 5: LETTERS, EDITORIALS, SUPPLEMENTARY MATERIAL, CASE REPORTS, BOOK CHAPTERS, ABSTRACTS AND THUNDERSTORM ASTHMA EVENTS CITED IN REVIEWS (INTERNATIONAL).**

Location and date	Type of article	Description of thunderstorm event	Study findings
<b>Birmingham EDs, UK. Jul 1983</b> (Packe et al. 1986)	Letter to the editor  Case control	Following a TS, 36 patients presented with acute asthma.  Cases (n=18); presenting patients consenting to further investigation.  Controls (n=18); patients who were asthmatics attending hospital clinics for other issues.	All 18 cases had a history of hayfever and 17 gave a clear history of asthma.  All patients said that their hayfever had been troublesome in the weeks before the TS, and that symptoms had become suddenly worse over the evening and night of the storm. Only 1 case and 2 controls were not positive to grass pollen SPT; grass pollen; house dust; house dust mite; <i>C. herbarum</i> and <i>S roseus</i> (Bencard); <i>S roseus</i> (Dome); <i>S salmonicolor</i> (Hollister-Stier); D exitialis.
<b>Nottingham ED, UK.</b> <b>20 Jun 1984</b> (Alderman et al. 1986)	Letter to the editor	Before the TS 3 patients attended ED for acute asthma.  Following the TS until midnight 19 patients presented with asthma and 3 more came after midnight.	No increase in smoke or SO <sub>2</sub> observed during the storm event.  No change in spore counts during the storm event.  9/19 patients with wheezing had past history of hayfever. 10/19 previous asthma diagnosis.
<b>Leicester, UK.</b> <b>22 Jul 1989</b> (Allitt et al. 1997)	Book chapter	Late afternoon TS in Leicester 22 Jul, 32 hospital admission for asthma following the storm, compared to expected number of 4.3 for the same time period.	TS event, Rain was observed from 5pm until 7pm. Pollen and spores not present in large quantities immediately before the storm. Ascospores present following storm ( <i>Didymella</i> ), <i>Cladosporium</i> present before and after storm in modest levels.
<b>Peterborough ED, UK.</b> <b>24-25 Jun 1994</b> (Campbell-Hewson et al. 1994)	Letter to the editor	Following electrical storm, Thirty nine asthmatic patients presented to ED. The expected number is one case. Median age of cases was 28 years.	O <sub>3</sub> levels were high, 39 lightning strikes recorded, pollen count was high 48h prior to rain. Fungal spores; <i>Didymella</i> levels slightly raised and <i>Sporobolomyces rose</i> after the event. Ascospores; <i>Phaeosphaeria nigrans</i> and Diatrypaceae high rise in concentration. 13/39 no previous diagnoses of asthma, 22/29 suffer from hayfever.
<b>Luton GP clinic, UK.</b> <b>24 Jun 1994</b> (Higham 1994)	Letter to the editor	Following a TS, twenty three out of 56 calls to GP were for asthma. 24 out of 89 patients attending nearby ED presented with acute asthma or shortness of breath.	NA
<b>London ED, UK.</b> <b>24-25 Jun 1994</b>	Letter to the editor	Whipps Cross ED reports 55 people attended with asthma, (expected 5-6 people). Other acute asthma presentations; Newham 96; King George's, Ilford, 91; Royal London 62; Oldchurch 58; St Thomas's 44; Guy's 36; and Queen Mary's,	NA

(Murray et al. 1994)		Roehampton,20. Overall 462 patients in London EDs.	
<b>Nottingham, UK.</b> <b>Jun 24-26, 1994</b>  (Sutherland et al. 1994)	Letter to the editor	During the TS episode there was a high peak of patients reporting to the university hospital of Nottingham for exacerbations of asthma.	Pollen count was high at the time and air quality was poor.
<b>North-East London ED,</b> <b>24-25 Jun 1994</b>  (Venables et al. 1996)	Case control;  Supplementary material	Cases (n=102); patients presenting with asthma to ED between 6pm 24 Jun and 12am on 25 Jun. Controls (n=88) patients with asthma at other times that summer. 68 cases and 30 controls interviewed; 34 cases and 13 controls gave blood.	Hayfever; cases 90%, controls 63%. Asthma; cases 32%, controls 63%.  All cases had detectable specific IgE against mixed grass pollen, (91% very high).  Controls 31% detectable (38% very high).no difference in mixed moulds and dust mites. 2/3 cases aged 20-39. Reported presentations of "about 1500 to general practice".
<b>South-Eastern England, UK. 24 Jun 2005</b>  (Levy et al. 2007)	Report	During TA epidemic; 400% increase in 'difficulty breathing' calls to telephone advice line at NHS Direct and 50% increase in general practice out-of- hours emergency patient attendances.	The majority of patients presenting in casualty departments with acute asthma during TS are young atopic adults (20-40 years old) with no previous history of asthma.
<b>Ireland Army Community Hospital.</b>  (Turbyville 2012)	Abstract only	Retrospective data of patients on allergen immunotherapy over 3yr compared to weather data over the same period. Patient data included total number of immunotherapy injections received and number of local and systemic reactions recorded.	Weather data analysed in terms of rainfall alone ("wet" vs. "dry") and TS vs. non-TS based on whether at least 1 inch of rainfall recorded in 24 hours or if lightning recorded in the presence of rain. Total number injections recorded over the study period was 24,684 administered to 271 patients. Local reactions were significantly more likely to occur on TS days than on non-TS days (p=0.008). A subset of 27 patients identified who either only had adverse reactions or had majority adverse reactions with TS.
<b>Naples ED, Italy.</b> <b>4 Jun 2004</b>  (D'Amato et al. 2008)	Letter to the editor	Six adults (3 women and 3 men) aged between 38-60 and an 11 year old girl presented with severe bronchial asthma following a TS. All subjects were outdoor during the storm.	4/7 history of asthma, 2/7 history of rhinitis.  O <sub>3</sub> , NO <sub>2</sub> , respirable PM were not high. All seven patients were sensitized to <i>parietaria</i> species pollen, which was high a day prior to the event.
<b>Barletta, Italy.</b> <b>May 27 2010.</b>  (Losappio et al. 2011)	Descriptive; Supplementary	Violent TS occurred following a very hot morning (mean temp; 29oC).Between 3pm and 5am 27/28 <sup>th</sup> , 20 patients (age range; 9–81) presented to ED with severe asthmatic symptoms.	Mean pollen Count was 278 granules/ m <sup>3</sup> for olive pollen.  Twelve patients had known allergic rhinitis, of them six associated with asthma, but only two patients regularly on anti-asthmatic treatment. All patients sensitized to olive tree ( <i>Olea europaea</i> ) pollen, of whom seven were monosensitized, 10 patients also sensitized to grass, 7 to parietaria, 5 to compositae, 5 to cypress, 5 to house dust mites, 3 to dog and one to cat dander. No patient was sensitized to <i>Alternaria</i> .

<p><b>ER, Napoli Italy. 28<sup>th</sup> May 2012</b> (D'Amato et al. 2013)</p>	<p>Case Report</p>	<p>Description of the first case of relapse of near fatal TA occurring in a 36 years old, 20 weeks pregnant woman. She was involved in the 2005 epidemics in Naples and had a mild relapse in 2011 and a near fatal relapse in 2012 following a TS</p>	<p>The patient never experienced severe exacerbations when exposed to TS or <i>Parietaria</i> pollen separately. Sensitized to <i>Parietaria</i> (pellitory of the wall) pollen, as confirmed by both SPT and blood test.</p>
<p><b>Al-Khobar, Saudi Arabia. 2 Nov 2002</b> (Al-Rubaish 2007)</p>	<p>Review article event cited</p>	<p>Throughout Saturday, 2 Nov 2002, an epidemic of acute episodes of asthma after a heavy downpour of rain was observed by the A &amp;E Department, King Fahd Hospital of the University (KFHU), Al-Khobar, Eastern Province. Number of asthmatics requiring ED services increased during and following rains or TS.</p>	<p>Most patients (from nine hospitals) were not severely affected and were treated and released home. Only less than 1% needed the intensive care.</p>
<p><b>Ahvaz, Iran. Nov 2013</b> (Shoushtari et al. 2016)</p>	<p>Abstract only</p>	<p>Patients (n=585) presented to AJMU's 9 hospital ED in Nov 2013; cases; 284, controls; 267. More severe bronchial hyperresponsiveness during TS. Severity of symptoms and positive methacholine challenge higher for cases.</p>	<p>Higher rate of history of asthma and smoking were noted among Controls compared to cases (35.2% vs. 26.1%, p-value &lt;0.001) and (20% vs. 13.7%, p-value 0.02) respectively.</p>
<p><b>Atlanta, USA</b> (Fedeyko et al. 1998)</p>	<p>Supplementary material</p>	<p>During spring, high pollen count days were 3.9 times more likely to occur after a TS and 4 times more likely on days when the pollen count equalled or exceeded 40.</p>	<p>NA</p>

**Abbreviations;** Temp; Temperature, O<sub>3</sub>; Ozone, SO<sub>2</sub>; Sulphur Dioxide, NO<sub>2</sub>; Nitrogen Dioxide, PM; Particulate Matter, SPT; Skin Prick Test, NA; Not applicable, TS; Thunderstorm, TA; Thunderstorm Asthma, ED; Emergency Department, GP; General Practice, Jun; June, Nov; November, Jul; July.

\*Emergency room and the accident and emergency department, are both referred to as the emergency department.

## Quality of study design and weight of evidence

TA events are rare occurrences which are difficult to predict. Given their nature, every study of TA events has been undertaken in retrospective fashion. Case control studies offer the best level of evidence, compared to other retrospective methodologies used (Ryan 2013). From a total of 45 studies associated with TA found in Tables 2-5, only ten used a case control study design. From these ten studies, three analysed thunderstorm days as cases and non-thunderstorm days as controls. Four studies had a relatively small sample size; 18, 28, 38 and 56 participants, limiting the study findings to small confidence in result estimates, and large uncertainty. The remaining three studies were of large sample size; 198, 304 and 671 participants (Table 4).

Despite the large participant size, all case control studies are subject to selection bias; recruitment of cases and controls and observational bias; cases reporting their exposure. The Girgis et al. (2000) study, of the 1997 Wagga Wagga TA event, recruited total of 304 cases and controls. However, children aged less than seven years were excluded. In choosing to omit this age group, a selection bias becomes apparent; study results could differ from the results if this age group was included in the study. Similarly the Ilias et al. (1998) study of 198 participants only recruited people aged 15 to 44 years, meaning the results would only be representative of that age group. One of the most extensive TA epidemic episodes before the recent Melbourne event was reported by Higham et al. (1997), where they analysed a total of 671 cases and controls. However, a broad case definition of asthma was used which could have included other respiratory and cardiovascular conditions among the study participants.

The majority of other primary TA studies were undertaken using an ecological study design (Table 2 and 4). Ecological studies may be suitable for constructing a hypothesis, in relatively unknown epidemics such as TA. Ecological studies are valuable because this design allows for examination of a great number of independent variables in a large population size. However the possibility of ecological fallacy must be considered, as risk associations witnessed on the group level, may not be reflective of the effect on an individual level. Therefore it is of great importance, to recognise the potential flaws and limitations in studies of TA epidemics, when making evidence-based decisions.

Within the Australian context, there are a number of limitations in relation to TA that may be addressed through further research. Current knowledge on Australian TA epidemics, is based on ten papers. Two of these reports are published as Letters to the Editors, limiting the scope of the reported observations of the TA event (Egan 1985; Howden et al. 2011). Reports from the latest Melbourne TA epidemic of 2016 are yet to be published, leaving agency reports as the main source of information on this recent TA event (Inspector General of Emergency Management report 2017). From the remaining five papers, three were undertaken as case control studies. However, two studies had only 18 and 28 participants, whilst the last study had 304 participants (Wark et al. 2002; Bellomo et al. 1992; Girgis et al. 2000). The Canberra TA episode of 2014, is documented only through the press report. Airborne aeroallergen levels such as grass pollen were measured in three studies and allergic sensitisation to common allergens as assessed by skin prick testing (SPT) was reported in three papers. The evidence on causation of TA events in Australia is neither extensive nor conclusive.

Determination of an association between TA epidemics and putative causative factors can only be undertaken with large degree of uncertainty at present. Further research is needed, incorporating and modelling the effects of a broad range of causative factors. Commonly cited fungal spores (*Alternaria*, *Cladosporium* and *Didymella*), different pollens (including grass and in particular ryegrass), air pollutants (nitrogen dioxide, sulphur dioxide, ozone and particulate matter) and changes in climatic conditions should be investigated. Additionally, demographics should be focused on in much more detail with particular attention to ethnicity, sex and age. For future comparability the definition of TA "epidemics" should be standardized, such that there is a clear distinction between expected asthma admissions and an epidemic. The weight of evidence for such factors will be further considered in response to specific questions asked by the Department in relation to the causation and public health management of TA events.

## RESPONSE TO SPECIFIC QUESTIONS

### Question 1.

**Describe the epidemiology of TA, including TA epidemics including: Who is susceptible to TA?**

- a. **What is the spectrum of likely or documented health effects?**
- b. **What were the clinical outcomes for those affected i.e. number hospitalized, admitted to intensive care?**
- c. **How many deaths have been attributed to epidemic TA events?**

#### Response:

The capacity to clearly identify epidemiological features of TA is affected by use of different definitions for TA events and criteria for inclusion of patients on epidemic case days. There are currently also no good measures for gauging the severity of TA events except by the number of reports describing an event or number of people affected by TA during a particular epidemic. The recognition of the severity of an TA event will depend on the size and density of the population from which susceptible patients are affected and the geographical area included.

#### a. Who is susceptible to thunderstorm asthma?

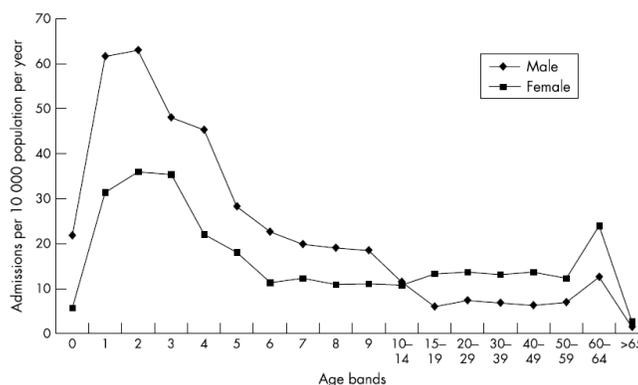
**The following characteristics are risk factors for TA.**

**Age:** There is a large distribution of age groups of people presenting to hospital for what has been described as a TA epidemic (Elliot et al. 2014; Losappio et al. 2011; Wardman et al. 2002). The majority of studies including for instance descriptive studies and case-control studies (Tables 2-5), report an average age of patients affected by TA to be young adults, predominantly between their twenties and thirties (Campbell-Hewson et al. 1994; Bellomo et al. 1992; Packe et al. 1986;1985; Davidson et al. 1996; Wardman et al. 2002; Wark et al. 2002). A number of studies on TA have been selective in age group inclusion, which means age group susceptibility estimates may not be accurate (Celenza et al. 1996; Girgis et al. 2000; Ilias et al. 1998; Lewis et al. 2000; Pulimood et al. 2007). However, there is an awareness of the effect of age on TA presentations exemplified by Newson et al., (1998) dividing of affected patients into two groups; 14 years and under and over 15 years. In that study the authors controlled for the annual trends in patterns of presentation of asthma in children, such as those associated with return to school peaks in asthma episodes. The effect of age on asthma is considered further in Question 5, under the sections on Childhood asthma and Triggers for asthma in childhood, and Question 7 under the section on Seasonal patterns in childhood asthma outside thunderstorms.

**Sex:** There is a lack of research on determining influence of gender on susceptibility to TA. Within limited number of research studies considering gender differences in patients presenting with asthma or breathing difficulties during TA events, it was found that; the number of female patients who needed admission was significantly higher than the number of male patients (34/242 vs. 6/195,  $p < 0.001$ ; Feli et al. 2015). In Australia, being a female was a predictor of presenting with asthma following a thunderstorm, RR 2.0 (95%CI: 1.2 to 3.4; Wark et al. 2002). Fifteen of sixteen patients affected by TA during the early Melbourne epidemic of 1983 were female (Egan, 1985).

The importance of age together with gender for asthma admissions in general is exemplified by asthma morbidity data from Scotland (Figure 7). Younger aged children and in particular boys, are most susceptible to asthma whilst asthma severity declines in adulthood and increases again after the age of 50 years and more so for women

(Scottish Morbidity Data Information and Statistics Division, Common Services Agency, NHS Scotland). Both age and gender are important modifiers of risk of asthma in general and should be carefully considered in the context of TA. The effect of age and gender on asthma and TA in particular is considered further in response to Question 5 under the sections on Childhood asthma and Triggers for asthma in childhood.



**FIGURE 8: ASTHMA ADMISSIONS (ICD J45) FOR ALL HOSPITALS IN SCOTLAND APRIL 2000 TO APRIL 2001 BY SELECTED AGE GROUPS AND SEX.** (source: Scottish Morbidity Data Information and Statistics Division, Common Services Agency, NHS Scotland)

**Allergic Sensitisation:** Sensitisation to certain allergens appears almost universal among TA affected patients. However it has been proposed that different populations from different continents may be susceptible to different allergens (D'Amato 2009; Pulimood et al. 2007; Girgis et al. 2000; Bellomo et al. 1992). Thunderstorm epidemics in Italy, have shown allergic respiratory symptoms with positive SPT response to *Parietaria* pollen among all patients coinciding with exposure to elevated ambient concentrations of this pollen. Those patients affected did not show sensitisation to other aeroallergens tested including grasses and other pollen grains or moulds (D'Amato 2009). However these results are based on a sample of seven people. In a subsequent analysis of TA affected patients (n=20) in Italy, a much smaller proportion of patients (35%) showed sensitisation to *Parietaria* (Losappio et al. 2011). Instead 100% showed sensitisation to olive tree pollen, 50% to grass pollen, 25% to *Compositae* pollen, 25% to cypress pollen and no patients were sensitized to *Alternaria* (Losappio et al. 2011). Neither of these studies reported the frequency of sensitisation to allergens in control subjects with asthma on non-thunderstorm days.

**Sensitisation to grass pollen:** In the UK, independent studies of two separate TA epidemics found 100% sensitisation to grass pollen in affected TA cases with asthma. Packe and Aryes (1986), Packe et al. (1986) found 17 of 18 cases affected by TA were sensitized to grass pollen but there was no difference to control subjects in sensitisation to any aeroallergen measures (house dust, house dust mite, *Cladosporium*, *Sporobolomyces* and *Didymella*). Venables et al. (1996) reported detectable levels of serum specific IgE to mixed grass pollen in all cases (n=34) compared with no detectable grass pollen-specific IgE in 31% of controls (n=4/13). However, in a separate UK study, sensitisation to *Cladosporium* or *Alternaria* species, have been recorded in 100% cases and only 45% of controls (p= <0.001; OR, 63.96; CI 3.52- 1143.9; Pulimood et al. 2007). Notably, whilst 50% of the 20 patients affected by TA in Italy were sensitive to grass pollen (Losappio et al. 2011), in this instance grass pollen was not considered the trigger for TA in these patients during this episode because half of the patients were not sensitive to grass pollen but they were all sensitive to olive tree pollen and olive tree pollen was the allergen present in the air at the time of the TA event (Table 5).

Sensitisation to ryegrass pollen appears universal in Australian epidemics of TA. Sensitisation rates have been reported to be significantly higher by Girgis et al. (2000) and Bellomo et al. (1992) ( $p=0.0001$  and  $p<0.05$ ) in cases (96% and 100%) compared to controls (64% and 56%), respectively. Furthermore, allergic skin reaction to ryegrass pollen has been demonstrated to be significantly ( $p=0.03$ ) larger in diameter for cases (median= 19mm) compared to controls (median= 0mm) (Wark et al. 2002). People may also be susceptible to TA if they are sensitised to *Cladosporium*; cases: (61%) vs controls: (35%), ( $p=0.02$ ) and starch granules extracts; cases (100%) vs controls (54%) ( $p<0.025$ ) (Girgis et al. 2000; Bellomo et al. 1992). Aeroallergens found not to be significantly elevated amongst patient affected by TA compared to patients with asthma on other days include *Alternaria* and tree pollen (Girgis et al. 2000; Bellomo et al. 1992).

**History of asthma/history of rhinitis:** History of both asthma and rhinitis has been documented in all TA epidemics. However it is still unclear what role each condition plays in the susceptibility to TA. Given the high prevalence of both conditions in TA, it is likely there is a direct association. However the exact role each disease entity plays in causation of the epidemic is still unclear (refer to Questions 9-11). Small descriptive studies outside Australia report the following in TA patients; previous history of asthma diagnosis in 23 to 94% of patients (Packe et al. 1986; Alderman et al. 1986; Campbell-Hewson et al. 1994; Wardman et al. 2002; Feli et al. 2015; Forouzan et al. 2014). Hayfever was reported in 35 to 100% of patients (Packe et al. 1986; Campbell-Hewson et al. 1994; Alderman et al. 1986; Wardman et al. 2002; Davidson et al. 1996). Additionally the first occurrence of asthma attack was reported in 44% of patients (Davidson et al. 1996). A case control study of the 1994 TA epidemic in London found more cases; 90% had a history of hayfever compared to controls; 63% (patients presenting with asthma on non-thunderstorm days), where as a history of previous asthma was less common (32% vs 63%) among cases compared to controls (Venables et al. 1996). In another case control by Pulimood et al. (2007), hayfever was also high in cases (92%), with the history of asthma being lower (69%). Additionally a history of asthma symptoms occurring only in summer was reported by 96% of cases. Some form of allergy has been reported in two separate studies from the UK and Iran, at 17% and 39% respectively (Wardman et al. 2002; Forouzan et al. 2014).

The presence of hayfever and asthma in Australian TA epidemics would appear to follow the same pattern as observed internationally. Recent hayfever has been observed in up to 90% of cases and 69% of controls presenting with asthma on non-thunderstorm days,  $p=0.001$  (OR 4.3 2.1-8.65; Girgis et al. 2000). A previous diagnosis of asthma was reported for 64% of patients with asthma on case days with thunderstorm in comparison with 82% of patients with asthma on control days without thunderstorm  $p=0.003$  (OR 0.38, 0.2- 0.73; Girgis et al. 2000). Allergic rhinitis has further been reported significantly higher in cases (100%) compared to two control groups in NSW episodes of TA (50% and 67%),  $p=0.03$  (Wark et al. 2002). The earlier studies of the Melbourne 1989 TA event, reported no significant difference between cases ( $n=100%$ ) and controls (81%) for hayfever (Bellomo et al. 1992). Thus multiple national and international reports of TA presentations, attendance or admissions provide evidence that during epidemics of TA, nearly all (90-100%) affected patients have a history of hayfever, many of whom (31-40%) had no prior known history of asthma.

**Smokers:** Smoking does not appear to be a risk factor in TA. As high as 87% of presenting TA patients have reported as not being smokers (Forouzan et al. 2014). Furthermore, comparing current smoking status in cases (16%) and controls (33%), current smokers had lower odds of suffering from TA that those with asthma at other times without thunderstorm, OR 0.39, (95% CI: 0.18±0.83,  $p=0.01$ ; Girgis et al. 2000).

**b. What is the spectrum of likely or documented health effects?**

Patients suffering from TA often present with symptoms consistent with acute exacerbation or flare up of asthma; shortness of breath, acute bronchospasms, cough, wheezing, chest pain and fever (Higham 1994; Levy et al. 2007; Celenza et al. 1996; Forouzan et al. 2014; Wark et al. 2002).

Shortness of breath (dyspnea) has been reported as the most common symptom, usually accompanied by wheezing with cough, being the other prevalent symptom, present in 45-75% of patients (Feli et al. 2015; Forouzan et al. 2014; Packe et al. 1986). The duration of symptoms has been reported to range from one to 24 hours, having a median duration of five hours, during the Calgary episode (Wardman et al. 2002). The 1994 England outbreak, witnessed a median duration of hospital stay to be three days. A further 15/531 patients originally not admitted returned with reoccurrence of symptoms within 48h of presentation (Davidson et al. 1996). Of the 640 patients attending ED clinics in the London area 12 patients with asthma symptoms during the 1994 TA episode had a history of chronic obstructive pulmonary disease (Davidson et al. 1996). It is unclear whether chronic obstructive pulmonary disease is a risk factor for TA or whether patients with respiratory diseases other than asthma were also affected by the TA event and experienced symptoms that were similar to those of asthma.

TA affected patients presenting to both the ED and GP clinics were considered as ones presenting with asthma, wheeze, or hayfever or allergy with wheeze or difficulty in breathing and all patients requesting an inhaler or asthma treatment (Davidson et al. 1996; Higham et al. 1997). Alternatively all patients diagnosed as having asthma were included, International Classification of Diseases (9) Code 493 (Girgis et al. 2000; Hajat S 1997).

**c. What were the clinical outcomes for those affected by TA i.e. number hospitalized, admitted to intensive care?**

Among patients who presented to hospital emergency departments with asthma symptoms during TA events, admission rates into the hospital has generally been low. In Australia during the 1987 Melbourne TA epidemic 26/154 (17%) presenting patient were admitted into the ED of which one patient required the ICU. Similarly during the 1989 TA epidemic in Melbourne, 47/277 (17%) patients were admitted into the ED, of which three required the ICU (Bellomo et al. 1992). In the recent Melbourne epidemic in 2016, 30 people were reportedly admitted to intensive care in hospitals across the city over these two days (Inspector-General for Emergency Management 2017).

Feli et al. (2015) in Iran also observed low hospital admission rates with 40/443 (9%) patients presenting with asthma during a thunderstorm receiving admittance into the ED, from which a further three needed care in the ICU. In the UK as low as 104/640 (16%) admission into the ED has been recorded, of which five admitted patients required the ICU (Davidson et al. 1996). An Italian study D'Amato et al. (2008), showed a much greater admission rate; all seven patients presenting with asthma were admitted for treatment, of whom one was admitted to the ICU.

**d. How many deaths have been attributed to epidemic thunderstorm asthma events?**

Overall the Australian Centre for Asthma Management reports a summary of deaths due to asthma:

- occur in all age groups but increase with age in both males and females
- are higher in females compared to males aged 35 and over, but similar in males and females aged 5-34
- peak in late winter for those aged 64 and over (Australian Institute of Health and Welfare, 2014).

“In Australia in 2011, asthma was certified as the underlying cause of 378 deaths (1.5 per 100,000 people) which represented 0.3% of all deaths in Australia. This included 17 deaths among people aged 5-34 (0.2 per 100,000 people in this age group). The median age at death due to asthma was 80 in 2007-2011” (Australian Institute of Health and Welfare, 2014).

**TATABLE 6: SUMMARY OF THE REPORTED DEATHS ATTRIBUTED TO TA.**

TA episode	Number of deaths attributed to TA
<b>Melbourne 1987:</b>	1 (Bellomo et al. 1992)
<b>London 1994:</b>	1 (Venables et al. 1997)
<b>Cambridge 2002:</b>	1 (Pulimood et al. 2007)
<b>Melbourne 2016:</b>	9 possibly attributed and referred to the state coroner (Inspector-General for Emergency Management, 2017)

**Summary**

TA impacts a wide distribution of age groups but predominantly young adults (in their 20s and 30s). Sensitisation to allergens and a history of rhinitis is universal. Prior asthma is present in only some affected people. Whilst there are a high number of calls for assistance to ambulance services and presentations at hospitals of patients with symptoms consistent with acute asthma, rates of admittance to hospital are lower. The number of ICU cases and deaths reported as a consequence of the Melbourne 2016 outbreak is well beyond any previous reports.

**Strength of evidence**

The sporadic nature of TA events requires that they are described and data analysed retrospectively which limits full understanding that might be gained by application of prospective longitudinal studies, cross-sectional studies or further use of case-control study designs. Many studies are descriptive reviews of series of observations or case control studies. There is no universally applied definition for TA episodes or use of universal criteria for inclusion of patients to TA research studies or definition of epidemic days of asthma. There is variability within reported studies on the inclusion of age groups of patients and asthma diagnosis of patients. Sometimes the International Classification of Disease 9 code 493 (asthma) is used. Other studies describe inclusion criteria based on symptoms (e.g. asthma, wheeze, or hayfever or allergy with wheeze or difficulty in breathing and all patients requesting an inhaler or asthma treatment; (Davidson et al. 1996).

**Gaps in knowledge**

- Incidence of asthma and severity of symptoms related to TA events for the local population of individuals affected
  - i) within the community who seek assistance from general practitioners and pharmacists,
  - ii) those who present to hospital ED departments,
  - iii) those who need to be admitted for ongoing care, and
  - iv) those patients who require ICU care.
- The demographics of cases (age, gender, and ethnicity), symptoms, disease history of allergic rhinitis and asthma, medication use, respiratory function and allergic sensitivity would assist in understanding risk factors for susceptibility to TA and differences in patient characteristics stratified by severity of symptoms.
- Data on the demographics, disease status, comorbidities of patients affected by TA who require admittance to respiratory wards or intensive care units compared with those patients who can be managed by within the ED, pharmacy or general practice.

## Question 2.

### What aetiological factors are thought to contribute to TA and particularly an epidemic TA event?

The aetiology of a disease refers to the study of the origins or causation of the disease. This review seeks to identify and evaluate the aetiological factors that contribute to the causation of TA epidemics. In the context of TA, there are a number of component conditions previously proposed as contributing factors for the causation of epidemics of asthma associated with thunderstorms. Discovery of the component causes of TA and how each of these interact will be dependent upon application of unified understanding of what a TA event is.

#### Response:

Currently there is no gold standard definition for TA, with studies reporting epidemics as increase in asthma attendances from two to tenfold (Bellomo et al. 1992; Venables et al. 1997). One study of asthma in six inland towns in New South Wales used thunderstorm days as cases and non-thunderstorm days as control days; epidemic days were when observed asthma attendances was four SDs above the expected number of cases and control days were defined as those within one SD of the mean of the asthma attendance rate, for the given time period during spring (Marks et al. 2001). Other studies use control days as days without thunderstorms within two weeks of the TA episode or same day of the year without TA episodes in previous years (Newson et al. 1998; Anderson et al. 2001).

Marks and Bush (2007) propose four common conditions observed in TA events (see Introduction).

Furthermore (D'Amato et al. 2016) (Introduction) identifies a strong temporal association between commencement of thunderstorms and outbreaks of asthma epidemics. It is further specified that TA epidemics only occur during pollen and outdoor mould seasons and in absence of high levels of air pollution. A major risk is identified for people not receiving anti-asthma treatment and people with allergic rhinitis. People staying indoor with windows closed and non-allergic people are not subject to TA epidemics.

Taylor et al. (2004) propose a mechanism for the occurrence of TA. Here they describe how dry updrafts, cold downdrafts, advancing outflows and electrical activity in thunderstorms, contribute to continuous uptake of pollen grains and their subsequent rupture and release at ground level. As the storm advances so does the risk to human exposure. Marks et al. (2001) demonstrated a significant association between thunderstorm outflows and occurrence of epidemics of asthma admissions. On case days, occurrence of outflows was 33%, compared to control days 3%, OR 15.0 (95% CI: 6.0 to 37.6).

Notably, an epidemic of acute asthma in absence of thunderstorms has been reported during Spring in the USA. A case control study examined 59 acute asthma cases (patients presenting within 2 weeks of peak pollen count) and 59 controls (presenting to hospital during same time period for anything other than asthma or rhinitis) during the peak pollen count period (May 19-26, 1986). Cases (92% >200 unites of IgE Ab) were found to be significantly more sensitized to ryegrass pollen compared to controls (14% >200 units of IgE Ab),  $X^2 = 69$ ;  $p < 0.0001$ ; OR = 69. There was no significant difference between cases and controls, in three other measured indoor allergens (mite, cockroach and cat) and prevalence of IgE Ab (Pollart et al. 1988). This indicates that thunderstorms are neither necessary nor sufficient in the causation of TA epidemics in California. However exposure to high concentrations of ryegrass pollen demonstrated a temporal association with sensitized patients presenting with acute asthma. The study makes no mention of rainfall or pollen rupture, challenging the requirement for pollen fragmentation as a necessary causative factor in TA epidemics. The study did not mention rainfall but online sources of historical

records indicate that there was no rain during the study period May 19-26 (WeatherSpark.) <https://weatherspark.com/history/31699/1986/Fairfield-California-United-States>.

Similarly an epidemic of acute asthma occurred in Brisbane in 1959. While no TA was recorded in Brisbane, on April 20<sup>th</sup> 1959 close to midnight, hundreds of people awoke with acute asthma, within a 40mile radius of Brisbane. The most common symptoms were chest tightness and choking. No unusual changes in temperature, barometric pressure or humidity were observed. However a temperature inversion was found to have occurred which was regarded as a potentially important factor in the aetiology of the acute asthma event (Morrison 1960).

One case reports on a pregnant woman who was involved in the 2005 Naples epidemic, relapsed in 2011 and experienced severe dyspnoea while outside during a thunderstorm in 2012. She was sensitized to *Parietaria* pollen, confirmed by both skin prick and specific serum IgE tests. All the patient's asthma episodes occurred during the *Parietaria* season, in presence of a thunderstorm. It would appear in this case, that both thunderstorms and *Parietaria* pollen are necessary causative triggers, but neither alone is sufficient to cause asthma in this patient (D'Amato et al. 2013). In the TA epidemic reported in Iran, it was reported that 16% of patients with TA had experienced similar symptoms on previous occasions in the presence of thunderstorms (Forouzan et al., 2014).

#### Key messages

Many primary studies and review articles propose theories for the aetiology of TA that require contribution of combinations of multiple contributing factors.

#### Strength of evidence

There is variability within reported studies on the inclusion of age groups of patients and asthma diagnosis of patients which sometimes is classified to International Classification of Disease 9 code 493 (asthma) whilst other studies describe inclusion criteria based on symptoms (e.g. asthma, wheeze, or hayfever or allergy with wheeze or difficulty in breathing and all patients requesting an inhaler or asthma treatment; (Davidson et al. 1996)). Additionally there is no universally applied definition for TA episodes.

Studies capture different types of epidemiological, environmental, climate and allergen exposure measures and employ a variety of analytical methods. Whilst many studies apply a case control study design, the rigor of statistical analysis and modelling of contributing factors has not been extensive. The rarity of events makes it difficult to conduct prospective controlled studies.

#### Gaps in knowledge

Application of a standardized definition of a TA epidemic and use of standard criteria for inclusion of cases of patients affected with asthma during thunderstorms and appropriate control Subjects.

Evidence on whether or not individuals in Australia who experienced symptoms of TA have had similar episodes on more than one occasion.

Understanding of the interaction between multiple conditions; age, gender, disease status, the aetiology of TA.

### Question 3.

**What spring or summer meteorological conditions (e.g. temperature, wind speed or direction, relative humidity, rainfall, thunderstorm electric or lightning activity etc.) are thought to contribute to conditions associated with an epidemic TA event?**

#### Response:

Many meteorological factors such as wind, rainfall, lightning, relative humidity and temperature and their changes have been hypothesized to induce asthma exacerbations independently or in conjunction with other factors (e.g. high bioaerosol concentrations; Table 10). These meteorological conditions as well as season and sun exposure index, can drive directly or indirectly the production, emissions and transport of bioaerosols (Weber 2003).

• **Thunderstorms are associated with sudden climatic changes including, but not limited to, decrease in pressure and temperature, increase in relative humidity and wind speed and sudden heavy rainfall.**

Packe et al. (1985) observed a correlation between onset of sudden climatic changes and the start of TA symptoms in patients affected by asthma during a TA outbreak. (Celenza et al. 1996) observed that different thunderstorm-related meteorological factors including number of lightning strikes, increase in rainfall, air pressure and relative humidity were independently associated with increased asthma presentations (6h lag; and 3h lag for temperature drop and rise in air pressure) during the large and wide spread and TA event recorded in England on June 24, 1994.

• **One of the observed trends is the sudden drop in temperature at the time of thunderstorm arrival.**

Celenza et al. (1996) observed that temperature change 6 hours before the asthma outbreak had a significant correlation with TA presentations during the severe London 1994 TA epidemic.

• **Outflows, wind speed and direction are often abruptly changed at the time of thunderstorm.**

Associations with asthma were strongest when wind gusts were intermediate and high (Grundstein et al. 2008). Moreover, Erbas et al. (2012) observed that peak in ED attendance (70 a day) was preceded by days of strong winds exceeding 90 km/h. Marks et al. (2001) observed that thunderstorms with outflows were observed on case days with epidemic levels of asthma presentations compared with only 3% of control days without epidemic levels of asthma presentations. A descriptive study of a TA event in southern/central England, United Kingdom in Jun 1994 observed strong thunderstorm outflows, sudden increases in wind speed and decrease in temperature preceded TA (Venables et al., 1997). However, in a descriptive time series study from 1987-1994 in the United Kingdom, Newson et al. (1998) failed to find significant association between thunderstorms with high speed wind gusts and days with epidemic asthma compared with control days.

• **Some TA epidemics are influenced by rainfall.**

Grundstein et al. (2008) observed that correlation of higher emergency department visits with thunderstorms accompanied by rainfall was not matched by emergency visits in thunderstorms with no recorded rainfall. High concentration of *Didymellia* spores was observed after the heavy rain (up to 12 mm/h) and at the time of asthma admissions (Allitt 2000). Lewis et al. (2000) observed increased ED attendance related to grass pollen counts on wet and stormy days with a marked effect of grass pollen on days of light rainfall with a two day lag (adjusted rate ratio 2.1, 95% CI 1.4, 3.3). Whilst rainfall is an important factor in thunderstorm associated asthma, few studies report on the scale of its effect (Grundstein et al. 2008). Most studies suggest rainfall as the proposed mechanism of rupture of bioaerosols. However, with respect to airborne levels of pollen, rainfall can have multiple effects by:

- Stimulation of grassland growth with increases in biomass and pollen production;
- Removal of bioaerosol by the wet deposition (Weber 2003; Laaidi 2001a);
- Fragmentation of pollen grains into the respirable starch aerosols (Schäppi et al. 1999).

**TABLE 7: EVIDENCE OF METEOROLOGICAL FACTORS ASSOCIATED WITH TA EPIDEMICS**

METEOROLOGICAL FACTORS	National event	Type of evidence	International event	Type of evidence
<b>Rainfall</b>			<b>TS epidemics 1993 to 2004, Atlanta, USA</b> (Grundstein et al. 2008)	Associations with asthma and TS with rainfall (P<0.05) but not for TS with no recorded rainfall (P=0.777)
<b>TS outflows</b>	<b>TS epidemics in 6 rural inland towns in NSW Jan 1995 - Dec 1998</b> (Marks et al. 2001)	TS outflows on 33% of case days but only 3% of control days (OR 15.0, 95% CI: 6.0-37.6). On case days with a TS within 80km, only 15% did not have outflows (OR 2.5, 95% CI 0.8 to 8.5).	<b>Southern/ Central England EDs and GP clinics, UK. 24/25 Jun 1994.</b>  (Venables et al. 1997)	In a descriptive study it was noted that strong TS outflow, sudden increase in the WS, decrease in temp (5°C), >30% of RH increase preceded TS associated with TA epidemic.
<b>Temp / Temp changes</b>			<b>TS epidemics 24/25 June 1994, south of UK</b> (Celenza et al. 1996)	Sudden decrease in Temp (6h lag) had the significant correlation with TS asthma presentations (P=0.04)
<b>Wind speed and gust</b>		Peak in ED attendance on days with TSs (70 per day) was preceded by days of strong winds exceeding 90 km/h. Erbas et al. (2012)	<b>TS epidemics 1993 to 2004, Atlanta, USA</b> (Grundstein et al. 2008)	Associations with asthma were strongest when wind gusts were intermediate (9.4 – 14.3 m/s) and high (>14.3 m/s)
<b>Lightning (sferics; atmospheric broadband electromagnetic signals)</b>			<b>TS epidemics 1987 to 1994 in 14 RHS, UK</b> (Newson et al. 1998)	Sferics were positively associated with asthma epidemics (P=0.0006 for high and P=0.06 for low sferics)
			<b>TS asthma events 1990 to 1994 in 14 RHS, UK</b> (Newson et al. 1997)	High sferics ([1 Sf/100 km <sup>2</sup> /day) are correlated with moderate increases in acute asthma admissions in two age groups, 0-14 years (RR:1.13, CI: 1.02 – 1.26) and 15+ years (RR: 1.28, CI: 1.15-1.43)
			<b>24/25 June 1994, south of England</b> (Higham et al. 1997)	The areas affected by TS that had the greatest number of lightning strikes (the peak number of lightning strikes per hour within 20 km) were those with the greatest increase in asthma cases (r=0.66 p<0.0001)
<b>Sudden climatic changes (multiple factors)</b>			<b>6 and 7 July 1983, Birmingham, UK</b> (Packe et al. 1985)	Described sudden climatic changes (fall in pressure and Temp, increase in RH, sudden heavy rain) at the time when TA symptoms began
<b>Seasonal variation</b>			<b>TS epidemics Jan 1990 to Dec 1996, Cardiff/Newport, UK</b> (Anderson et al. 2001)	Asthma admissions during TS increased; effect was more significant in warmer summer conditions (P<0.001)

**Abbreviations:** TS, Thunderstorm; TA, Thunderstorm asthma; T, Temperature; RH, Relative humidity; WS, Wind speed; WD, Wind direction; NO<sub>2</sub>-Nitrogen dioxide; SO<sub>2</sub>-Sulfur dioxide; O<sub>3</sub>- Ozone; PM<sub>2.5</sub>, fine particles with diameter of 2.5 µm or less; PM<sub>10</sub>, fine particles with diameter of 10 µm or less; RR, Relative risks; CI, confidence level; RHS, UK Regional Health Authority; GP, Grass pollen; SPT, skin prick test.

It has been demonstrated experimentally that after contact with water ryegrass pollen grains can rupture by osmotic shock and release about 700 starch granules with diameter range from 0.6 to 2.5  $\mu\text{m}$  (Suphioglu 1998; Suphioglu et al. 1992). These starch granules present in the ambient air as respirable-size allergen aerosols following the rainfall can be trigger an allergic airway response in susceptible individuals (Suphioglu et al. 1992). Moreover, immunoassays have been used to show that the starch granule fragments of ryegrass pollen contain one of the major ryegrass pollen allergens, Lol p 5 (Schäppi et al. 1999; Suphioglu 1998).

Moisture is thought to be an important factor in bioaerosol fragmentation by osmotic shock and formation of numerous small easily-respirable particulate allergens ( $<5\mu\text{m}$ ) that can penetrate into the lower airways (Knox 1993; Suphioglu 1998; Schäppi et al. 1999).

In the context of TA epidemics, ruptured pollen grains and fungal spores have been associated with asthma exacerbations. Bellomo et al. (1992) observed significant increase in frequency of SPT response to ryegrass starch granules in cases with asthma during TA episodes compared to control subjects with asthma on days without thunderstorms. A seven-fold increase of ruptured grass pollen particles coincided with the thunderstorm and subsequent TA epidemic in Wagga Wagga (Marks et al. 2001). Pulimood et al. (2007) also observed correlation between ruptured *Alternaria* spores and asthma admission rates during the thunderstorm epidemic in the UK of 2002.

Taylor et al. (2002) demonstrated in a simulated controlled environment how moisture causes pollen grains to rupture, forming small respirable allergen-loaded aerosols. The outcomes of these experiments confirmed that pollen can rupture in humidified conditions (light rainfall, dew, fog and lawn watering) and release the allergens in the form of respirable aerosols that could trigger an asthma response.

Taylor et al. (2004) suggested a mechanism to explain TA epidemics was the introduction of fragmentations of pollen grains in the cloud base. In this hypothesis pollen grains are carried by cold thunderstorm-related updrafts into the cloud base where high RH induces pollen rupture on small allergen particles. Allergen particles are then carried to the ground level by the thunderstorm downdrafts and dispersed by the outflow increasing the exposure to the susceptible individuals.

- The hypothesis that the outflows of the cold air can sweep up the pollen grains and/or fungal spores and concentrate them in the ground level increasing the bioaerosol exposure of susceptible people and asthma exacerbations, has been used in many publications but more as a proposed model than as evidence. To the best of our knowledge only Marks et al. (2001) showed this with respect to TA epidemic in Wagga Wagga. Thunderstorm outflows were detected on one-third of epidemic days compared to just 3 % of control days. They proposed that thunderstorm outflows rather than thunder or rain alone are an important cause of TA outbreak. Further examination of one TA-related epidemic revealed that its time correlates with arrival of thunderstorm outflow and with an increase (4-12 fold) in intact and as well as ruptured grass pollen grains (Marks et al. 2001). Notably, the mechanism of rupture of pollen grains during thunderstorms cannot readily be determined.
- Newson et al. (1997) and Newson et al. (1998) investigated lightning as a contributor to TA epidemics and observed that sferics (atmospheric broadband electromagnetic signals) were positively associated with asthma admissions. Newson et al. (1998) related days of high sferics with moderate increases in acute asthma admissions in two age groups, 0-14 years and 15+ years. Thunderstorm days with sferics and high average pollen counts ( $\geq 50$  grains/  $\text{m}^3/\text{day}$ ) present a risk factor for asthma admissions in both age groups (Newson et al. 1997). Although the probability of asthma epidemics on days with high sferic density is increased with grain pollen counts, the rate of false alarms would be still high (Newson et al. 1998). Higham et al. (1997) observed that areas of south England with the greatest number of lightning strikes were those with the highest increase in TA cases in one outbreak.
- O'Leary et al. (2005) conducted the modeled how particle charge affects its deposition within lungs in order to investigate the possibility that the charge of allergen particles contribute to TA. It was observed that

deposition of particles on lower airways (within the alveoli region where allergic response originate) was enhanced with particle charge and this effect was amplified by higher mobility of particles with smaller diameter. The results confirmed the hypothesis that TA may be related to charge accumulated on aeroallergen particles. The authors also suggested that this can be an explanation why TA is increased just at some time of the year (pollen season).

- Just one TA event has been reported to occur outside spring/summer period during November 2013 in Iran (Shoushtari et al. 2016; Forouzan et al. 2014).
- The effect of thunderstorm on asthma admissions was found to be more significant in warmer conditions (Anderson et al. 2001; Newson et al., 1998).

Burch et al. (2002) suggested that the most accurate predictor of development of spore plume (i.e. large and rapid increase in spore concentration) is a combined effect of increases in temperature, ambient pressure, wind speed, and dew point and that thunderstorm-related change in weather conditions can influence the formation of spore plume. Moreover, the same authors suggested that the day-specific weather conditions are more significant factors in spore plume formation than the ecological conditions.

#### Key messages

Many meteorological factors such as wind, rainfall, lightning, relative humidity and temperature and their changes have been hypothesized to contribute to TA episodes. Certain combinations of meteorological factors may be associated with TA. Weather parameters may directly or indirectly affect the incidence of TA exemplified by the multiple impact of rainfall on bioaerosol concentrations and form.

Whilst thunderstorm outflows or strong preceding wind gusts have been described on days with TA epidemics internationally, only one well designed Australian study shows that thunderstorms with outflows are significantly associated with episodes of increased spring time asthma on days with thunderstorms in the vicinity (Marks et al. 2001).

Several international studies indicate that lightning activity (sferics) is associated with TA episodes.

#### Strength of evidence

Many reports observe or describe that various climatic factors are associated with TA. However, often the statistical methodology employed to assess the degree of association is lacking or not clearly articulated. It is rare that the studies are hypothesis driven with application of statistical methods to test hypotheses or model the influence of multiple climate variables on asthma admissions during thunderstorm.

#### Gaps in knowledge

Understanding of the combined effects of climate factors on TA using appropriate methodologies such as multiple regression modelling.

Identification and quantification of the contribution of weather factors consistently associated with TA episodes.

#### Question 4.

**What evidence explains why epidemic TA events do not occur every spring or summer?**

- a. **What background environmental factors (e.g. air quality – fine particles, ozone etc.) may contribute to conditions associated with an epidemic TA event?**
- b. **What seasonal factors (e.g. wet winter or spring; vegetation index) may be associated with an epidemic TA event?**
- c. **What trends in agricultural harvesting (e.g. timing of hay bailing etc) may be associated with an epidemic TA event? (See Question 10)**

**Response:**

**Evidence of environmental factors that are associated with TA are summarized in Table 11.**

**a. What background environmental factors (e.g. air quality – fine particles, ozone etc.) may contribute to conditions associated with an epidemic thunderstorm asthma event?**

- Anderson et al. (2001) estimated the correlation between asthma admissions and different meteorological/environmental factors. Higher ozone concentrations were identified on days prior to the thunderstorm days compared to days that did not precede thunderstorms. After adjusting for thunderstorm and season, a positive correlation was observed between ozone enhancement in summer and increase in asthma admissions.
- The levels of air pollutants including O<sub>3</sub>, NO<sub>2</sub> and coefficient of haze were identified to be higher on thunderstorm days than on non-thunderstorm days in Canada 1997, but none of the pollutants had a statistically significant correlation with asthma admissions (Dales et al. 2003).
- The majority of the studies that investigated the influence of air pollution's indirect or direct contribution to TA epidemics, hypothesized increase of pollutants on preceding or thunderstorm days but did not employ statistical methods to test these hypotheses (Hajat S 1997; Pulimood et al. 2007; Venables et al. 1997; Wardman et al. 2002).
- During the severe TA epidemic in south UK in 1994, high ozone concentrations (daily average of 45 ppb) were identified at the time of TA in Cambridge and Peterborough compared to concentrations (daily average of 28.7 ppb) measured before and after the event (Campbell-Hewson et al. 1994).
- Hajat S (1997) observed high PM<sub>10</sub> levels on thunderstorm day, with both the daily maximum and daily average values being in the 90th percentile.
- Several pollutant levels increased on the day of the storm, including significant increase in PM<sub>10</sub> on day of TA epidemics however just suggestion of possible role in symptom development but not a statistical analysis done (Wardman et al. 2002).
- The levels of ozone were very high (exceeded 180 mg/m<sup>3</sup>, the high threshold as defined by the Department of Health Committee) before the thunderstorm (Pulimood et al. 2007).

Air pollution levels had a peak during a calm period before the thunderstorm in London area but levels were not unusually high (Venables et al. 1997).

**TABLE 8: EVIDENCE OF ENVIRONMENTAL FACTORS AND ALLERGEN SENSITIVITIES ASSOCIATED WITH TA EPIDEMICS**

Aerobiological factors	National event	Type of evidence	International event	Type of evidence
<b>Grass pollen</b>				
	<b>Two TA epidemics, 8 Nov 1987 and 29 Nov 1989, Melbourne</b> (Bellomo et al. 1992)	Significant increase in SPT response and its magnitude (P<0.05 and P<0.001) to ryegrass pollen among cases compared to controls;	<b>24/25 Jun 1994, south of England</b> (Venables et al. 1997)	High grass pollen counts (258 grains/m <sup>3</sup> ) two days before the TA outbreak; 12/16 patients had very high levels of IgE to grass pollen mix (classes 4-6) and just 2 of 16 had a negative IgE response to grass pollen mix.
	<b>30 and 31 Oct 1997, Wagga Wagga</b> (Girgis et al. 2000)	Significant increase in SPT response of cases (n=111; 96%) compared to controls (n=47; 64%) to ryegrass pollen (OR 23.6, 95% CI: 6.6 - 84.3, P=0.0001)	<b>24/25 Jun 1994, South of England</b> (Hajat S 1997)	High grass pollen counts (258 grains/m <sup>3</sup> ) two days before the TA outbreak; Increased asthma attendances (consulting general practitioner) associated with enhanced grass pollen counts on TS epidemic day (RR: 6.7, 95% CI: 4.55, 9.72; P<0.0001); Extremely high grass pollen levels of 258 grains/m <sup>3</sup> (3 days lag)
	<b>27 Oct 1998, Newcastle</b> (Wark et al. 2002)	All affected cases SPT positive to all grass pollens tested, especially ryegrass with median wheal diameter of 19.5 mm (range 7 to 25 mm)	<b>24/25 June 1994, London, UK</b> (Venables et al. 1996)	All cases had specific IgE against mixed grass pollen (Pharmacia "CAP") with 91% at very high values while grass pollen-specific IgE was undetectable in 31% of controls and only 38% of controls had very high values.
			<b>29 and 30 July 2002, Cambridge and Derby, UK</b> (Pulimood et al. 2007)	grass pollen sensitisation significant in the Poisson modelling of all admissions but focus of case/control study
	<b>19 and 20 Nov 2003, Melbourne</b> (Erbas et al. 2012)	During severe TS, daily ED attendance reached max of 70 visits/ day; consistent with TS-related asthma associated with the preceding days of extreme grass pollen counts	<b>24/25 June 1994, south of England</b> (Celenza et al. 1996)	Sudden increase in grass pollen conc. (9h lag) correlated with TS asthma presentations
	<b>TS epidemics in 6 rural inland towns in south eastern Australia Jan 1995 to Dec 1998</b> (Marks et al. 2001)	In one episode of severe TA, an arrival of TS coincided with increase (4 fold) of intact grass pollen grains and epidemic onset		
	<b>25 Nov 2010, Melbourne</b> (Howden et al. 2011)	Pollen counts were extreme (>100 grains/ m <sup>3</sup> ) during some days before the TS but moderate on TS day		
<b>Raptured grass pollen</b>	<b>TS epidemics in 6 rural inland towns in NSW for the period from Jan 1995 -Dec 1998</b> (Marks et al. 2001)	In one episode severe TA, arrival of TS coincided with increase (7 fold) of ruptured grass pollen particles and epidemic onset		
	<b>Two TA epidemics, 8 Nov 1987 and 29 Nov 1989, Melbourne</b> (Bellomo et al. 1992)	Significant increase in SPT response ryegrass starch granules (P<0.025) among cases compared to controls		

<b>Weed pollen</b>			<b>4 June 2004, Naples, Italy</b> (D'Amato et al. 2008)	Close temporal association between arrival of TS, increase in conc. <i>Parietaria</i> pollen (up to 144 grains/m <sup>3</sup> on 3 June) and asthma epidemic onset
<b>Tree pollen</b>			<b>27 and 28 May 2010, Puglia, Italy</b> (Losappio et al. 2012)	All 20 patients positive SPT to <i>Olea Europaea</i> (olive tree) and max conc. Olive pollen was 170 grains/m <sup>3</sup>
<b>Fungal spores</b>				
<b>Alternaria</b>	<b>30 and 31 Oct 1997, Wagga Wagga</b>  (Girgis et al. 2000)	Negative effect of Alternaria SPT and asthma on days with TA compared with patients with asthma on control days without TS	<b>29 and 30 July 2002, Cambridge and Derby, UK</b>  (Pulimood et al. 2007)	Conc. <i>Alternaria</i> higher than the threshold (>100 spores/m <sup>3</sup> ) on time of epidemics  Increase in SPT of cases (23/26) compared to controls (14/31) to <i>Alternaria</i> (OR 9.31, 95% CI: 2.3 – 37.6, P=0.0008)
<b>Didymellia</b>			<b>6 and 7 July 1983, Birmingham, UK</b>  (Packe et al. 1985)	Large and sudden increase in number of <i>Didymellia</i> spores at time of TA outbreak
			<b>29 and 30 July 2002, Cambridge and Derby, UK</b>  (Pulimood et al. 2007)	Exceptionally high conc. of <i>Didymellia</i> on 30 and 31 July; Correlation between spores of <i>Didymellia</i> species and asthma admission rates (OR 1.65, 95% CI: 1.4-1.9, P < 0.0001)
			<b>2 July 1989, Leicester, UK</b>  (Allitt et al. 1997)	High conc. <i>Didymellia</i> spores (approx. 60,000 m <sup>-3</sup> ) after the storm at the time of asthma admissions; Strong gusty winds lifted the pollen in the air (WD change) and then rain cause the grain rapture; sudden change in meteorological factors
<b>Cladosporium</b>	<b>30 and 31 Oct 1997, Wagga Wagga</b>  (Girgis et al. 2000)	Significant increase in SPT response of asthma patients on case days with TS (n=71; 61%) compared to asthma patients on control days without TS (n=26; 35%) to <i>Cladosporium</i> (OR 2.8, 95% CI: 1.2 – 6.3, P=0.02)	<b>29 and 30 July 2002, Cambridge and Derby, UK</b>  (Pulimood et al. 2007)	Conc. <i>Cladosporium</i> spores higher than threshold (>3.000 spores/m <sup>3</sup> ) at time of epidemics; correlation of <i>Cladosporium</i> spores and asthma admissions (OR 1.47, 95% CI: 1.2-1.8, P = 0.0002)
			<b>TS epidemics identified from 1993 to 1997, Ottawa, Canada</b>  (Dales et al. 2003)	<i>Cladosporium</i> was the main spore type contributing to effect of fungal spores on asthma emergency visit during the TS days P<0.0001; Conc. total fungal spores doubled (from 1512 to 2749 /m <sup>3</sup> ) on TS days compared to non-TS days.

<b>Ruptured fungal spores</b>		<b>29 and 30 July 2002, Cambridge and Derby, UK</b>  (Pulimood et al. 2007)	Correlation of broken <i>Alternaria</i> spores and asthma admission rates (OR 2.21, 95% CI: 1.5-3.3, P < 0.0001)
<b>Other fungal spores</b>		<b>6 and 7 July 1983, Birmingham, UK</b>  (Packe et al. 1985)	Large and sudden increase in number of <i>Sporobolomyces</i> spores at the time of TA outbreak
<b>Combination of spores</b>		<b>29 and 30 July 2002, Cambridge and Derby, UK</b> (Pulimood et al. 2007)	Increased SPT of cases (26 /26) verses controls (14/26) to <i>Alternaria</i> or <i>Cladosporium</i> (OR 64.0, 95% CI: 3.6 – 1143.9, P<0.001)

**Abbreviations:** TS, Thunderstorm; TA, Thunderstorm asthma; T, Temperature; RH, Relative humidity; WS, Wind speed; WD, Wind direction; NO<sub>2</sub>-Nitrogen dioxide; SO<sub>2</sub>-Sulfur dioxide; O<sub>3</sub>- Ozone; PM<sub>2.5</sub>, fine particles with diameter of 2.5 µm or less; PM<sub>10</sub>, fine particles with diameter of 10 µm or less; RR, Relative risks; CI, confidence level; RHS, UK Regional Health Authority; GP, Grass pollen; SPT, skin prick test.

AIR QUALITY FACTORS	National event	Type of evidence	International event	Type of evidence
<b>Ozone (O<sub>3</sub>)</b>			<b>Jan 1990 - Dec 1996, Cardiff/Newport, UK</b>  (Anderson et al. 2001)	Higher ozone conc. on days prior to the TS days than on days prior non-TS days (p = 0.03). After including TS and season in the model positive correlation between increasing ozone in summer and increasing asthma admissions (p=0.02).
<b>Combination of factors</b>			<b>TS epidemics identified from 1993 to 1997, Ottawa, Canada</b>  (Dales et al. 2003)	Air pollutants (O <sub>3</sub> , NO <sub>2</sub> and coefficient of haze) were each independently higher (P < 0.0001) on TS days than on non-TS days, but none of the pollutants had a statistically significant effect on asthma

COMBINATION OF METEOROLOGICAL/ENVIRONMENTAL FACTORS	National event	Type of evidence	International event	Type of evidence
			<b>Asthma ED attendance (including TS asthma) from 1993 – 1996, Derby, UK</b>  (Lewis et al. 2000)	Increase in ED attendance related to grass pollen counts on stormy and wet days; most significant on days of light rainfall (adjusted RR for $\geq 50$ vs $< 10$ grains/m <sup>3</sup> at lag 2 days = 2.1, 95% CI: 1.4, 3.3).
			<b>TS epidemics from 1987 to 1994 in 14 RHS, UK</b>  (Newson et al. 1998)	High spheric density and grass pollen counts increased the probability of asthma epidemics, but only 15% (95% CI: 2-45%)
			<b>TS asthma events from 1990 to 1994 in 14 RHS, UK</b>  (Newson et al. 1997)	TS days with sferics and high average pollen counts ( $\geq 50$ grains/m <sup>3</sup> /day) present a risk factor for asthma admissions in two age groups, 0-14 years (RR:1.16 , 95% CI: 1.04 - 1.31) and 15+ (RR: 1.47, 95% CI:1.32 - 1.64)
			<b>24/25 June 1994, south of England</b>  (Celenza et al. 1996)	TS-related number of lightning strikes, increase in rainfall, air pressure and RH were each independently associated with increases of asthma presentations (6h lag; and also 3h lag for Temp drop and rise in air pressure)
			<b>31 July and 1 Aug 2000, Calgary ED, Canada</b>  (Wardman et al. 2002)	Reported increased conc. of algae at the time of the TS but no statistical analysis); high winds and drop in the pressure and increased PM <sub>10</sub> at the day of TS but no evidence that these factors associated with asthma admissions

**Abbreviations:** TS, Thunderstorm; TA, Thunderstorm asthma; T, Temperature; RH, Relative humidity; WS, Wind speed; WD, Wind direction; NO<sub>2</sub>-Nitrogen dioxide; SO<sub>2</sub>-Sulfur dioxide; O<sub>3</sub>- Ozone; PM<sub>2.5</sub>, fine particles with diameter of 2.5 µm or less; PM<sub>10</sub>, fine particles with diameter of 10 µm or less; RR, Relative risks; CI, confidence level; RHS, UK Regional Health Authority; GP, Grass pollen; SPT, skin prick test.

Other environmental pollutants have been considered but not found to be associated with TA; NO<sub>2</sub>, SO<sub>2</sub>, PM<sub>2.5</sub> and/or PM<sub>10</sub>

Notably, several studies observed negative association between increased pollutant levels (including O<sub>3</sub>, NO<sub>2</sub> and SO<sub>2</sub>) and TA incidence suggesting that air pollution was not a necessary factor in TA;

- Alderman et al. (1986) - No increase of SO<sub>2</sub> or smoke in the air during the storm event.
- D'Amato et al. (2008) - Ozone, nitric dioxide, respirable particulate matter were not high.
- Bellomo et al. (1992) - thunderstorm events were not related to atmospheric pollution (O<sub>3</sub>, SO<sub>2</sub> and NO<sub>2</sub>).
- Celenza et al. (1996) - There is no evidence that pollutant concentrations (O<sub>3</sub>, SO<sub>2</sub> and NO<sub>2</sub>) were independently related to the increase in asthma presentations.
- Lewis et al. (2000) - “no hint of interactions between any of ozone, nitrogen dioxide or black smoke in determining morbidity. If outdoor levels of ozone or nitrogen dioxide amplify the response of an allergic asthmatic to outdoor aeroallergens, these effects are relatively minor determinants of levels of acute asthma morbidity in this community”.
- Packe et al. (1985) - (SO<sub>2</sub> and black smoke) air pollution was not the factor.

However, other reports investigating a potential influence of air pollution on TA found the outcomes were not statistically significant or just descriptive;

- Hajat S (1997) - PM<sub>10</sub> was found to have been high on the 24 June (thunderstorm day), with both the daily maximum and daily average values being in the 90th percentile.
- Pulimood et al. (2007) - Ozone concentrations increased daily and on July 29 exceeded 180 mg/m<sup>3</sup>, the high threshold as defined by the UK Department of Health Committee; and levels of ozone were very high before the thunderstorm on July 29.
- Venables et al. (1997) - Air pollution levels in the London area were not unusually high on 24 June and did not exceed air quality I-h guidelines (World Health Organisation 1987) but did peak during the calm, still period before the thunderstorm.
- Wardman et al. (2002) - Several pollutants levels increased on the day of the storm; significant increase in PM<sub>10</sub> on day of TA epidemics however just suggestion of possible role in symptom development but not a statistical analysis done

**b. What seasonal factors (e.g. wet winter or spring; vegetation index) may be associated with an epidemic thunderstorm asthma event?**

There is no strong evidence base to explain why TA events only occur in some and not other years. However, certain ecological indicators and drivers of pollen production are implicated. The vegetative index incorporates within the one greenness index the sum of factors influencing plant biomass and as such serves as an indicator of seasonality and variability between seasons (Seddon et al. 2016).

- La Nina patterns may influence the periodicity of TA episodes (Hilary Bambrick). Whilst there may be too few documented events, there is some circumstantial evidence based on coincidence of TA in 2010 and 2011 with La Nina weather patterns. Mostly but not always (Erbas et al. 2012), wet winter precedes springtime TA epidemics in Melbourne (de Morton et al. 2011).
- Indices of rural and urban grassland greenness correlate with airborne grass pollen levels over seasons and may be a useful tool for monitoring and early prediction of grassland productivity (Devadas et al. 2016; see Question 13).
  - La Nina weather patterns that drive wet winters in Australia have markedly increased in the last 100 years (Cai et al. 2015).
- Notably, epidemics of asthma in the UK are infrequent, even though thunderstorms and rainfall occur several times each year during the grass pollen season between May and June (Pulimood et al. 2007).
- The concentration of bioaerosols during the thunderstorm event can depend on weather conditions over prior months. For instance, Allitt (2000) observed that *Didymella* ascospores were low at all sites after the rain at the

time of a severe thunderstorm over England but same authors speculate that it is due to the dry weather over the previous period (3 or 4 week before the 24 June).

**c. What trends in agricultural harvesting (e.g. timing of hay baling etc) may be associated with an epidemic thunderstorm asthma event?**

Perennial ryegrass pollen (*Lolium perenne*), is Victoria’s most commonly sown pasture grass occupying over 4 million hectares. Notably, in Australia TA temporally coincides not with curing but with pollen release. However, grassland browning or curing is monitored by the Country Fire Association (CFA) project on grassland curing Victoria. Other stakeholders who monitor grassland patterns of greenness (see Question 12) and browning at the end of the season include;

- Bushfire CRC
  - TERN AusCover.
  - <http://agriculture.vic.gov.au/agriculture/grains-and-other-crops/crop-production/victorian-winter-crop-summary>
  - Bureau of Meteorology (NDVI changes)
- Friesen et al. (2001) observed high levels of different fungal spores during the combine harvesting period and suggested that many of the spores can be dispersed by wind long distances from the harvesting place.
  - In Derby, UK the main months for *Alternaria* release and its high levels coincide with the main month for combine harvesting (Corden et al. 2001). Therefore Corden et al. (2003) indicated that *Alternaria* sensitive individuals in arable areas of UK must be aware of possible increased levels of *Alternaria* at harvest time that may cause exacerbation of asthma.
  - Harries et al. (1985) identified positive skin prick tests to *Didymella* in 4 patients tested in London 1983 and all had the respiratory symptoms over summer period, usually either after rain or following the cereal harvesting.
  - Allitt et al. (1997) suggested possible combination of factors that contributed to high concentration of *Didymella* spores after the storm in Leicester, England, 1989, and one being a large amount of cereal leaf available during the thunderstorm period due to cereal harvest activities.
  - Pulimood et al. (2007) observed the strong correlation between levels of ruptured *Alternaria*, *Didymella* and *Cladosporium* species with asthma admissions during the severe thunderstorm incident in UK, summer 2002. The thunderstorm occurred at harvest time when high levels of fragmented fungal spores were observed therefore the authors attributed this phenomenon to harvesting or grass mowing activities preceding the event. The authors also suggested that farming practices in the UK were influenced by rainfall because harvests would be brought forward to spare crops from rain damage, increasing the number of spores. Combination of severe thunderstorm and simultaneous harvesting activities provide the conditions that can trigger the asthma epidemic outbreak (Pulimood et al. 2007).
  - Grains and canola grown in Wagga Wagga are harvested in summer, temporarily after the spring TA episodes (Mitakakis et al. 2001), indicating crop harvesting unlikely to be causative factor in TA in this region. The concentration of *Alternaria* spore in nearby wheat and cotton crops in two rural towns of NSW, Wagga Wagga and Moree, during the harvesting and control periods Mitakakis et al. (2001). *Alternaria* concentrations were among the highest observed worldwide and high concentrations persisted for six months in Wagga Wagga and ten months in Moree. It was observed that crop maturation affected the level of spores in the air more than harvesting. High *Alternaria* concentrations were observed after the rainfall and warm temperatures in both towns. Wind direction was one more meteorological factor that correlated with spore concentration in Wagga Wagga.

**Key messages**

Exposure to bioaerosols including grass pollen particularly in Australia and the UK, as well as certain mould spores, are consistently associated with TA epidemics.

Evidence from multiple studies indicates that ozone is a factor associated with thunderstorm activity during TA events, this appears to be less important for asthma admissions to hospital.

Combinations of factors for example ozone and grass pollen appear to be important for TA epidemics.

**Strength of evidence**

Many studies considered the role of air pollution in TA events but did not find significant positive associations. It is possible that these studies may not have appropriately adjusted for these effects or that air pollution was not the primary exposure of interest.

**Gaps in knowledge**

Thorough analysis of combined effects of pollutants with other meteorological and environmental factors using appropriate methodologies such as multiple regression modelling.

Additional studies of the contribution to the causation of TA epidemics of particulate air pollutants, in particular diesel exhaust, as well as volatile pollutants in Australia and overseas.

### Question 5.

**Describe the environmental and meteorological factors that can result in exacerbations or first onset of asthma in general.**

#### Response:

Here we consider first onset of asthma in the age groups the disease is first diagnosed in childhood and adulthood in general as well as first onset asthma in the context of TA. The influence of environmental and meteorological factors will be considered in relation to known asthma triggers for both age groups. Within the overall context of this review, the role of respiratory viral in the inception of asthma and exacerbation of asthma as key environmental factors in asthma must be considered. Further information on environmental bioaerosol and meteorological factors that can exacerbate asthma are considered in question 4 (TA) and 6 (other than thunderstorm).

We define first onset asthma in the context of thunderstorms as those patients presenting to primary (general practice) or tertiary health services with symptoms consistent with asthma during TA episodes who have respiratory allergies (allergic rhinitis/ hayfever) with allergic sensitivity to inhalant aeroallergens (mostly grass pollen in Australia) but without a previous known history or diagnosis of asthma. Susceptibility and disease status of patients who may be susceptible to first onset asthma during a thunderstorm will be addressed in questions 8 to 11.

#### Childhood asthma

In the literature, asthma is frequently referred to as childhood-onset asthma and adult-onset asthma. However, it is difficult to define the onset of childhood asthma or early-onset asthma as there is no specific known cut-off age and no valid test to diagnose asthma at a very early age (less than 2 years). Early childhood during the ages of three to six years is when asthma is usually diagnosed. There is evidence showing first asthma episode occurring for most asthma patients (95%) before the age of 6 years (Masoli et al. 2004). During primary school years, girls experience less severe wheeze episodes than boys (Almqvist et al. 2008). At a later age (11 years), young males and females are shown to have similar prevalence of asthma, 7.7% and 7.4% respectively. However, after the age of 16, prevalence of asthma is more observed in females (6.2%) than males (4.3%; Vink et al. 2010; See Figure 7). It is important to consider that such age-dependent gender differences in susceptibility may mask the influence of gender on asthma associated with thunderstorms. Childhood-onset asthma is associated with several risk factors including family history of atopic diseases, genetic predisposition, allergic rhinitis (allergic sensitisations), exposure to tobacco, and bacterial colonisation (Bisgaard et al. 2010; Jackson 2016). Early life inflammation associated with febrile, wheezy lower respiratory viral infections are important risks for development of childhood asthma and asthma exacerbations (Busse et al. 2010; Sly et al. 2010; Fu et al. 2014). In particular, allergic sensitisation and early life wheezy appear to be a synergistic risk factors for childhood asthma (Jackson et al. 2008; Jackson et al. 2016; Sly et al. 2010).

#### Adult onset asthma

Late-onset or adult-onset asthma are terms used to describe when asthma symptoms first appear in adulthood. The age of diagnosis in the case of late-onset asthma ranges between 12 to  $\geq 65$  years of age (Miranda et al. 2004; Gibson et al. 2010). The knowledge around the prevalence and risk factors triggering adult-onset asthma is incomplete. A difficulty arises when attributing a specific condition as the cause or a trigger factor of an asthma episode, or whether breathing difficulties are a symptom of a comorbid condition. One example is obesity which has been considered as both a trigger factor and a comorbid condition for first adult-onset asthma (Holguin 2012). Notably syndromic surveillance of asthma in US indicated that whilst in children asthma was usually the first or second diagnosis listed, with wheezy bronchiolitis being a common secondary diagnosis, for adults asthma was often the second diagnosis behind cardiovascular disease (Possible triggers of adult-onset asthma include: exposure to irritants in the workplace (Dykewicz 2009), environmental pollutants such as cigarette smoking (Strachan et al. 1996; Polosa et al. 2008), female sex hormones (Melgert et al. 2007), upper airway disease (Guerra et al. 2002), respiratory infections (Rantala et al. 2011), aspirin and paracetamol intake (Thomsen et al. 2008), obesity (Beuther et al. 2007; Brumpton et al. 2013), and stress (Lietzén et al. 2011). Notably, being female is a risk factor for late onset non-allergic asthma (van den Berge et al. 2009).

In both children and adults, respiratory viruses are important triggers of asthma exacerbations (Zambrano et al. 2003; Busse et al. 2010). Patients with asthma show an impaired capacity to mount an effective type 1 innate interferon response to respiratory viral infections. Thus whilst patients with asthma may not suffer a higher number of colds, they suffer more severe and prolonged respiratory symptoms (Corne et al. 2002).

A recent large international multicenter genome wide association study of over 20,000 patients with hayfever and asthma identified 11 loci with increased odds ratios for association with this combined phenotype. Notably, several of these loci encode gene for proteins that are related to innate and adaptive immune functions and are expressed in relevant inflammatory cell types (Ferreira et al. 2014).

### Triggers of asthma in children

Complex genetic factors and severe wheezy lower respiratory tract viral (respiratory syncytial virus, human metapneumovirus, and rhinovirus) infections *during first years of life* are risk factors for developing asthma (systematic review (Régner et al. 2013)). (Jackson et al., 2008; Wu et al. 2008). Other studies also show that the risk of lower respiratory infection is increased in children with asthma and atopy predisposition (Goetghebuer et al. 2004; Trefny et al. 2000). Respiratory viral triggers underlie as much as 67-80% of asthma admissions in early childhood. The most severe asthma exacerbations leading to hospitalisation are associated with respiratory viral infection, most often rhinovirus (Busse et al. 2010).

Susceptibility of allergic asthma increases when early infections with respiratory syncytial virus (RSV) occur due to modulations in regulatory T cell function and thus increases IL-4 production (Krishnamoorthy et al. 2012). The contribution of variability in the IL-4R pathway and its effect on T helper 2 immunity might explain the above mentioned subphenotypes because early onset asthma in childhood subgroup differs in the polymorphism profile (SNPs) of the IL-4R gene (Hesselmar et al. 2012).

Seasonal fluctuations in asthma admissions have been observed globally and coincide with back to school periods and winter. Secondary seasonal increases in asthma presentation in children can occur in spring as reported in a number of studies (Erbas et al., 2015). Notably, pollen exposure independent of human rhinovirus infection and allergic sensitisation was associated with asthma admission in Melbourne children and adolescents (Erbas et al., 2015).

### Triggers of asthma in adults

Acute lower respiratory infections increase the risk of developing new adult-onset asthma (Rantala et al. 2011). One explanation is the way antigens are presented, in people of a certain age group, leading to decreased specific antibody responses. Respiratory infections in this case cause injuries in the airways, inflammation, due to subtle immune deficiencies, which repetitively leads to asthma (Dahlberg et al. 2009). Another explanation is that environmental exposures, including occupational exposures, and respiratory pathogens can act as triggers for asthma onset.

Incident asthma has been shown to be related with smoking in patients with allergic rhinitis (Polosa et al. 2008). A synergistic or an additive effect on asthma onset can be due to cigarette smoking and abundant airborne allergen exposure.

**Key messages**

Family history of allergic disease including allergic rhinitis and early life wheezing febrile lower respiratory tract infections risk factors for childhood-onset asthma. Adult onset asthma is less dependent on family history of allergic disease and additional types of triggers including exposure to workplace irritants, environmental pollutants are associated with asthma. Other co-morbidities including obesity are risk factors for adult-onset asthma. Boys are more affected by asthma and like to be admitted to hospital for asthma exacerbations before puberty whereas females are more affected by asthma and more likely represented in hospital admission in adulthood.

Many studies of TA events indicate that many (up to 40%) of patients severely affected by asthma symptoms under these circumstances have not previously had a diagnosis of asthma.

Outside the pollen season, exposure to respiratory viruses, particularly rhinovirus and more specifically the rhinovirus strain C, is an important trigger of asthma in adults and children (see Question 7).

**Strength of evidence**

Multiple studies in Australia and elsewhere (UK) report grass pollen as a trigger for first onset asthma in the context of TA events in patients with a history of allergic rhinitis. This is based on allergic sensitivity to grass pollen, and exposure to high airborne levels of grass pollen. Several studies also provide evidence that fungal spore exposure and fungal sensitivity is associated with cases of asthma on days with thunderstorms and may also be a contributing factor.

**Gaps in knowledge**

Adequately investigation of differences between age and gender in patients affected by TA compared to matched control subjects without asthma or with asthma at other times. This is likely to be important given possible differences in underlying co-morbidities and the influence of age and gender in the nature history of asthma (see Question 1, Figure 6).

## Question 6.

**Summarise the evidence that metrological conditions (other than thunderstorms such as temp change, humidity change, high winds, other) or specific environmental conditions (high mould, pollution, pollen, other) have been shown to cause (or are associated with) a smaller rise in asthma exacerbations across the community rather than an epidemic TA events.**

### Response:

The role of meteorological conditions in inducing asthma exacerbations in general is still unclear. Although the strength of evidence to prove causation is high, the role of weather is difficult to test and prove. Different meteorological conditions should be considered as mostly factors interact with each other and it is a challenge to determine correlation between a single meteorological factor and asthma (Laaidi 2001a). The evidence linking asthma exacerbations generally with air pollution is sufficient and reported in many studies. Other environmental factors including dust storms and soy bean dust are summarized here. It is important to emphasize the limitations of the scope of this response due to the broad and extensive nature of the literature and the need to focus this review on TA.

### Pollen exposure

Outside the context of epidemics of TA, exposure to pollens has been associated with seasonal increases in asthma presentations including ragweed (Robertson et al., 1974; Laaidi et al. 2003; Bass et al. 2000) and tree pollen (Gleason et al. 2014; Ito et al. 2015; Zhong et al. 2006; Babin et al. 2007). Allergic sensitivity to grass pollen can precede the development of allergic asthma in children from Germany (Hatzler et al. 2012) and airborne levels of grass pollen are associated with hospital admissions for asthma in Melbourne Children (Erbas et al. 2012; Erbas et al. 2007; Erbas et al. 2015) and adults in California (Pollart et al., 1988). A causal relationship between grass pollen challenge and induction of allergic airway inflammation has been demonstrated (Suphioglu et al. 1992). In a study of asthma presentations to general practice in the Paris area, amongst pollens assessed (*Betula*, *Cupressa*, *Fraxinus* and *Poaceae*), exposure to elevated levels of airborne grass (*Poaceae*) pollen showed the strongest association with asthma attacks (adjusted RR 1.54; 95% CI 1.33-1.79) (Huynh et al. 2010). A study of 2617 young adults with asthma from Europe showed that for those who showed seasonal variations in asthma attacks, those in Southern Europe who were sensitized to grass pollen were more likely to experience exacerbations in spring or summer than winter (Canova et al. 2013).

### Asthma and meteorological/environmental factors summarized by (Shea et al. 2008):

- Over the past 50 years the earth's temperature has markedly increased, increasing the frequency and intensity of extreme incidences including heat waves, floods, tropical storms and hurricanes;
- Air pollution and aeroallergens are playing the critical role in estimation of global climate change effect on allergic respiratory diseases;
- Temperature increase influences the increase in concentration of secondary pollutant, ozone;
- Ambient air pollution increases the frequency and severity of asthma attacks and the number of symptomatic days;
- Pollen, air pollution, and weather interact and affect the clinical expression of allergic disease;
- Climate change is measurably affecting the timing, distribution, quantity, and quality of aeroallergens and changing the distribution and severity of allergic disease;
- Climate change alters local weather patterns including minimum and maximum temperature, precipitation, and storms, all of which affect the burden of allergic disease;
- Warmer temperatures promote production of ground level ozone which worsens asthma.

## Weather

- Combination of meteorological factors, including mean temperature, water vapour pressure, relative humidity and maximum wind, was associated with asthma exacerbations in children (5-14 years old) over the period of 4 years in Spain (Hervás et al. 2015). In another study done in Bermuda the relative humidity, temperature, and northeasterly winds, were thought to be direct contributors to asthma exacerbations due to lack of air pollution and aeroallergens (Carey et al. 1986).
- Ambient temperature and change in ambient temperature are recognized as a risk for respiratory morbidity (Ye et al. 2012). Comprehensive research in six Australian cities observed an association between ambient temperature and reduced lung function in asthmatic children (7-12 years old; Li et al. 2014). A study performed in Brisbane observed that both hot and cold temperatures have an effect on ED for childhood asthma (Xu, et al. 2013).

The significant association between cold temperatures, especially cold spells and increased risk of pediatric visit for asthma was observed (Näyhä et al. 2011).

A statistically significant association was found between the large diurnal temperature range and increased ED admissions for childhood asthma in Brisbane over the period from 2003 to December to 2010 (Xu et al. 2013).

- On the night April 20, 1959, violent asthma outbreaks had been reported by hundreds of people in Brisbane (Morrison 1960). The time of the asthma outbreak was coincident with a temperature inversion, when air beneath the inversion layer could not rise and was trapped with concentrated particulate matter and gaseous species.
- The increase in temperature attributed to global warming indirectly affects the pollination period of some plant species, bringing forward flowering time and prolonging the pollen season into autumn (Beggs 2016; Watts et al. 2015; Pachauri et al. 2014). Moreover, there is some indication that climate variation may extend the life of fungal spores in the air (Wang 2016).
- Changes in ambient temperature and humidity seemed to have an influence on ED visit for pediatric asthma (1 and 2-day lag; Mireku et al. 2009). A recent study reported the increased risk of asthma ED visit with increase in wind speed and low ambient relative humidity in Korea (Kwon et al. 2016).

Number of emergency visit for asthma exacerbations was increased during the specific weather condition called Santa Ana winds, in California in the period 1990 – 1993. However, the increase is found to be small (3.12 vs 2.16 visit per day; Corbett 1996).

- Weather is closely related to pollen and pollinosis (production, release and dispersion of the pollen) but also it is important to consider direct influence of weather on the allergic symptoms (Laaidi 2001a). (Laaidi 2001a) observed that strong winds and anticyclonic conditions with fog and temperature inversions were directly associated with development of asthma symptoms.

## Environmental factors in asthma epidemics

### Air pollution

- Often the respiratory diseases are directly associated with the level of atmospheric pollutant (Pope III et al. 1991). For instance, the systematic review done by Khreis et al. (2017) observed the association between the risk of asthma development in children and the exposure to traffic-related air pollution, especially significant for black carbon, NO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>10</sub> exposures. The overall evidence suggesting that air pollutants such as ozone and particulate matter decrease lung function, trigger asthma exacerbations and increase the hospitalisation for asthma is also sufficient (Eder et al. 2006; Tatum et al. 2005). Gleason et al. (2014) observed the association between ambient air pollutant ozone and PM<sub>2.5</sub> with increases in pediatric emergency department asthma visit (leg 0) during the warm weather season in New Jersey. Moreover, the significant associations were found between ozone concentrations and asthma-related ED visit, especially for 5–12 year olds (up to 4 days leg) in Columbia (Babin et al. 2007). Air pollutants interact with aeroallergens and can modify the properties of the antigens (Wang 2016).
- Number of recent review papers including the work of Shea et al. (2008), (Kim et al. 2011) and (D'Amato et al. 2016) have summarized the evidence suggesting the significant role of ambient air pollution in increased frequency and severity of asthma attacks. Some of the important pollutants and their association with the asthma are listed below.
  - Nitrogen dioxide is a precursor of photochemical smog and therefore an important air pollutant of urbanized and industrial regions with its main sources being vehicle exhausts and power plants. It is an important precursor of tropospheric ozone. Nitrogen dioxide has been associated with changes in lung function and increases in allergen sensitivity, as well as with increased ED presentations among children.
  - Ozone is an important air tropospheric pollutant. The exposure to the increased levels of ozone can induce inflammation of upper and lower airways, reduce the lung function, symptoms of asthma, increase the risk of asthma exacerbations, hospital and ED admissions, and excess mortality. It is hypothesized that exposure to increased concentration of ozone can increase the allergic response to the allergens. These effects are more marked during the warm season.
  - Particulate matter can trigger the asthmatic response. PM<sub>10</sub> (particles with diameter of 10 µm or less) was also observed to have a strong association with asthma. PM<sub>2.5</sub> (particles with diameter of 2.5 µm or less) can be inhaled deeply into the lungs at the alveoli level and induce the asthma outbreak.

### Dust storms

- Dust storms are associated with respiratory diseases including asthma (Goudie 2014; Chien et al. 2012; Kanatani et al. 2010).
- Exacerbation in asthma symptoms in adults noted on days when Asian Dust carried pollen in comparison with dusty days without pollen (Watanabe et al. 2011).

### Soybean dust

- Soybean dust has been reported as an important contributor to asthma outbreaks and some of the studies are described below.
  - In Barcelona, 26 outbreaks of asthma and 11 deaths were reported over an 8-year period and the study established the link with inhalation of soybean dust during the soybean unloading at the city harbor. It is observed that 74% of cases had the specific IgE antibodies on soybean antigen compared to 4.6% of controls (Antó et al. 1989; Antó et al. 1993).

- An epidemic outbreak influenced by the soybean dust was also identified in Cartargena, Spain, and authors emphasized that the soybean exposure was not just in the harbor but also through the town (Navarro et al. 1993).
- In Naples, more than 100 patients were admitted to hospital in one day in December 1993. The asthma outbreak was associated with soybean dust that was inhaled during the unloading a cargo of soybean (D'amato et al. 2001).

In New Orleans, days of asthma outbreaks between 1957 and 1968 were associated with days when vessels carrying soy bean were in harbor (White et al. 1997).

#### Key messages

Outside of the context of TA events, weather factors including temperature, humidity and wind changes have been shown to increase asthma incidences in Spain, Australia, Korea and USA. There is evidence that ambient air pollution is a factor in increased frequency and severity of asthma exacerbations. Bioaerosol particles including dust and soybean dust have been associated with respiratory diseases in Columbia and increases in asthma in Spain.

#### Strength of evidence

There is an extensive body of literature relating to the influence of air quality factors and asthma but complete review is beyond the scope of this report.

#### Gaps in knowledge

the short-term effects of multiple weather conditions on exacerbation of asthma..

The direct impact of long-term trends in climate variables and air quality parameters associated with global warming on asthma in general are needed.

## Question 7.

**What is the evidence that thunderstorms cause a small increase asthma exacerbations and what is the proposed mechanism (ie is the mechanism different to osmotic shock of pollen leading to allergic fragments being inhaled during thunder-storm outflows)?**

### Response:

Small increases in frequency of asthma exacerbation are detected in longitudinal studies of records of healthcare services such as hospital ED, primary healthcare networks encompassing GP clinics and pharmacies. At GP clinics and ED centres we would expect presentation of severe exacerbation, as observed in TA studies. Another aspect to consider within the scope of this question is evidence of whether thunderstorms alone cause or are associated with increase in severity as well as frequency of asthma exacerbations.

### Seasonal patterns in childhood asthma outside thunderstorms:

The influence of thunderstorms on increases in asthma exacerbations must be considered in the context of observed patterns of presentations associated with seasons of the year and certain patterns of human behaviour exemplified by the return to school peak (February in Australia and September in UK and US).

Back to school peaks in asthma hospital admissions are associated with lower respiratory virus infections particularly human rhinovirus (Jackson et al. 2008), as a consequence of increased spread of infection due to the resumption of close proximity of children upon at this time of year (Hanigan et al. 2007). The less common strain human rhinovirus C is detected in cases with more severe symptoms (Mackay et al. 1992).

### Patterns of hospital admissions in children may not be consistent with community exposure to viral triggers

A recent study of school children in Sydney indicates that whilst human rhinovirus is a trigger for hospital admissions for asthma, exposure to human rhinovirus in school children with asthma in the community has a continuous pattern throughout the year, particularly HRV A and C strains. Whereas HRV B coincided with the winter peaks in asthma hospital admissions, detection of HRV (combined, A, B or C) in children with asthma within the community did not associate with back to school asthma peaks (Stelzer-Braid et al. 2016).

### Factors underlying back to school asthma

- Preceding periods of low use of asthma medication may be a contributing factor in the “back to school” peaks in asthma admissions in Canada (Hanigan et al. 2007).
- Co-exposure to ragweed pollen in autumn may also be important in back to school asthma (Im et al. 2005).
- Children who are more severely affected from asthma exacerbations over autumn and winter due to lower respiratory tract infections, frequently human rhinovirus, have an allergic phenotype with sensitisation to allergens, particularly indoor aeroallergens including house dust mite (Olenec et al. 2010). Early life atopy and wheezy lower respiratory tract infections have been shown to have synergistic effects on development of asthma in childhood (Jackson et al. 2012).
- Cross talk between innate immunity to rhinovirus and immunity to allergens (e.g. up regulation of the high affinity receptor for IgE; FcεR1) may contribute to mechanism underlying the influence of respiratory viral infection and atopy (Subrata et al. 2009).

### **Increases in severity of asthma exacerbations with thunderstorms:**

Within the context of thunderstorms, EDs have generally assigned patients a diagnosis of asthma, e.g. ICD9 code 493, without specifying severity of the exacerbation. A possible method of identifying small increases in severity of asthma exacerbation could be done by identifying differences in numbers of patients who presented to the ED but were not admitted. It is possible that the patients presenting without admittance could be managed whilst waiting or being attended in ED. However studies rarely report data on presentations, admissions and ICU.

### **Pharmacy assistance:**

Another important aspect to investigate is the role of pharmacies in dealing with acute demand from patients affected by respiratory symptoms during thunderstorms. It was reported that patients were turned away from hospital ED services and directed to go to community pharmacies to access Ventolin during the recent TA epidemic (Haggan 2016).

### **Longitudinal studies of hospital ED services:**

- While no TA epidemics have been reported in Greece, a longitudinal study (1985-1992) examined the difference between asthma ED attendance on thunderstorm and non-thunderstorm days (Ilias et al. 1998). No difference in asthma attendance was observed in relation to thunderstorms. Furthermore, there were no counts of aeroallergens performed or examinations of patient sensitisation characteristics that could attribute changes in frequency of exacerbations to airborne aeroallergen exposure. As the study does not adjust for aeroallergen exposure as no counts were performed, the study results would suggest that thunderstorm alone are not sufficient to significantly increase asthma ED presentations.
- A Canadian longitudinal study (1992-2000), examined the associations between meteorological conditions and ED presentations for asthma in children. Study findings show that the mean, median and daily maximum number of hospital visit was lower on days with thunderstorms ( $P < 0.04$ ). This indicates that thunderstorm alone had no association with asthma visit in children. However, when adjusting for seasons, summertime thunderstorm activity was associated with an OR of 1.35 (95% CI: 1.02–1.77) for asthma visit relative to summer period with no thunderstorm activity (Villeneuve et al. 2005). This study suggests that summertime may act as a confounder between thunderstorm and children's ED asthma visit. This could be explained by exposure to high levels of airborne pollen summer, indicating that pollen levels and thunderstorm together cause increases in asthma presentations compared to thunderstorm alone or pollen alone.
- In another longitudinal study (1993-2004) investigating the association between thunderstorm activity and asthma ED visit, results showed a 3% increase in asthma visit on thunderstorm days (Grundstein et al. 2008). The study was conducted in Atlanta, USA and had no aeroallergen count data or patient sensitisation characteristics (Grundstein et al. 2008). The findings would suggest thunderstorm alone are not sufficient to cause epidemics, while they do cause a slight increase in ED presentations for asthma.

### **Mechanisms of how thunderstorm affect asthma exacerbations:**

In a study incorporating aeroallergen counts with thunderstorm activity, high sferics densities were found to be over represented in asthma epidemics. Adjusting for grass pollen further increased the probability of an epidemic to 15% (95% confidence interval 2–45%). From 56 identified epidemics in the study, two thirds were not preceded by thunderstorm. Notably, most epidemics of asthma were not associated with thunderstorm or unusual weather conditions, and most thunderstorms, even following high grass pollen levels, do not precede asthma epidemics (Newson et al. 1998). The study findings suggest thunderstorm alone are not sufficient to cause TA epidemics. However the presence of thunderstorm and the presence of thunderstorm and high pollen levels are risk factors for TA

epidemics, which means it can be expected that thunderstorm alone may cause a small increase in asthma ED presentations in some circumstance (Grundstein et al. 2008).

Another Canadian longitudinal study (1993-1997) examined the relationship between ED asthma visit in children with regard to thunderstorm and aeroallergens. Over the study period ED asthma visit in children produced a rate of 8.6 on non-thunderstorm days and 10 on thunderstorm days, representing a 15% increase ( $p < 0.05$ ), (Dales et al. 2003). These findings are in contradiction to the findings of Villeneuve et al., 2005 (Villeneuve et al. 2005). However Dales et al., 2003 further found an increase in total fungal spores to the seasonal mean was associated with a 2.2% (0.9% SE) increase in asthma visit. Furthermore during thunderstorm, concentration of fungal spores was found to almost double. These findings would suggest thunderstorm alone could only be responsible for a small increase in asthma ED presentations, while the presence of both thunderstorm and aeroallergens could vastly increase the number of asthma presentations.

A case report of a pregnant woman experiencing severe dyspnea, while she was outside during a thunderstorm in 2012. She was involved in the 2005 Naples TA epidemic, with a relapse in 2011. Skin prick and blood tests indicated sensitisation to *Parietaria* pollen. The patient acute asthma episodes only occurred during the *Parietaria* season, in presence of a thunderstorm. It would appear in this case, that both thunderstorms and *Parietaria* pollen are necessary causative triggers, but neither alone is sufficient to cause TA (D'Amato et al. 2013).

#### There are reports on the role of thunderstorms in asthma with mixed outcomes:

Published evidence for a role of thunderstorm alone to be associated with small increases in asthma is discrepant. Once aeroallergens were adjusted for, thunderstorms appeared to cause a significantly increased number of asthma visits compared to non-thunderstorm days. More specifically thunderstorm alone have been shown to cause none to a small increase in asthma ED presentations.

There is no specific data or suggestion that the mechanisms would differ between small increases in asthma admissions compared with epidemic asthma associated with thunderstorms. The proposed factors include the contribution of meteorological factors; outflows, change in relative humidity and or combined with lightning and ozone exposure, and aerobiological factors; high to extreme exposure to grass pollen or fungal spores. One might presume, though evidence has only been described in Australia, that rupture of pollen grains by osmotic, mechanical (in the case of fungal spores) or electrical (by activity of spherics) plays a role in delivery of allergen containing particles in breathable sizes.

#### Key messages

Longitudinal studies indicate that thunderstorms alone can be a contributing factor in significant increases in asthma exacerbations.

Not all thunderstorms are not a sufficient cause of TA events. Particular characteristics including outflows and electrical activity are associated with TA events.

#### Strength of evidence

There is a body of evidence indicating that the influence of weather and in particular thunderstorm conditions on asthma exacerbations is complex.

#### Gaps in knowledge

Within Australia, we are aware of no studies examining specifically the role of primary healthcare networks and pharmacists in managing thunderstorm-associated increases in asthma admissions.

Investigation of the role of pharmacy and general practice in managing asthma patients during thunderstorms *per se* or TA epidemics is needed.

**Question 8.**

**What are the proposed factors (environmental, meteorological, and social) that may turn a small increase in exacerbations of asthma into an epidemic increase?**

**Is there a threshold or combination of factors that have been proposed?**

**Response:**

**Proposed factors**

Combinations of factors including meteorological, environmental and individual susceptibility appear to be associated with TA episodes. Whilst each factor can have some effect on incidence of asthma exacerbations, together a number of these factors appear to increase the likelihood and magnitude of TA. Evidence of the contribution of each condition has largely been drawn from retrospective studies using case- control methodologies, linear regression or statistical assessment of correlations. Without more complex multi-parameter modelling of the interactions of combinations of these factors it is difficult to know the relative importance of each factor and whether these factors have an additive effect or synergistically amplify the severity or incidence of TA. Examples of the absence of one or other of these factors in the circumstances of TA, indicates that alone none of these factors is an essential cause of epidemics of asthma.

**TABLE 9: FACTORS ASSOCIATED WITH THUNDERSTORM ASTHMA EPISODES**

Type of factor	Condition
<b>Meteorological</b>	<ul style="list-style-type: none"> <li>• Presence of thunderstorm</li> <li>• Thunderstorms with outflows</li> <li>• Thunderstorms with lightning</li> <li>• Presence of rainfall prior to onset of TA event</li> </ul>
<b>Environmental</b>	<ul style="list-style-type: none"> <li>• High to extreme levels of allergenic bioaerosols particles; frequently grass pollen particularly in Australia, in the days preceding on and day of TA event</li> <li>• Breathable allergen-containing granules from ruptured pollen grains (or mould spores)</li> <li>• High production of grass pollen likely due to preceding wet winter (OR high release of certain mould spores likely due to harvesting practices)</li> </ul>
<b>Individual</b>	<ul style="list-style-type: none"> <li>• Sensitisation to triggering aeroallergen</li> <li>• History of allergic rhinitis, often without a history of asthma</li> <li>• Being outside</li> <li>• Lack of use of inhaled corticosteroids</li> <li>• Being in 20s to 30s</li> </ul>

**Thresholds**

High concentrations of aeroallergen exposure are associated with TA; each of the Melbourne events occurred on days with high or extreme concentrations of grass pollen. These events often follow several days or a series of days with high to extreme grass pollen levels (see Table 3; (Erbas et al. 2015)). This suggests a high concentration of grass pollen is required to evoke symptoms of bronchial hyperactivity and breathing difficulties. Consistent with this hypothesis, Kiotseridis et al. (2013) found using symptom surveys in children in Sweden from 7 to 18 years, that symptoms in the eye and nose commenced at lower thresholds (30 grains/ m<sup>3</sup>) of grass pollen exposure than symptoms in the lungs (50 grains/m<sup>3</sup>).

Too few events have occurred to identify a threshold of exposure that is associated with symptoms of hayfever and asthma) in susceptible individuals or thresholds of exposure for epidemic TA in Australia.

Thresholds for eliciting symptoms in response to pollen exposure depend on location (Moverare et al. 2011) and are relevant to disease status of the individual and symptom experienced in hayfever and asthma.

Davies et al. (1973) - UK, >50 grains per cubic meter.

Johnston et al. (2009)– Darwin, >10 grains per cubic meter associated with pharmaceutical sales for antihistamines.

There is a non-linear effect of grass pollen and asthma ED presentations in children in Melbourne up to a threshold, after which the effect flattened off. However, the threshold level is somewhere between 20 and 50 grains/ m<sup>3</sup> (Erbas et al. 2015; Erbas et al. 2012).

### Priming of sensitivity

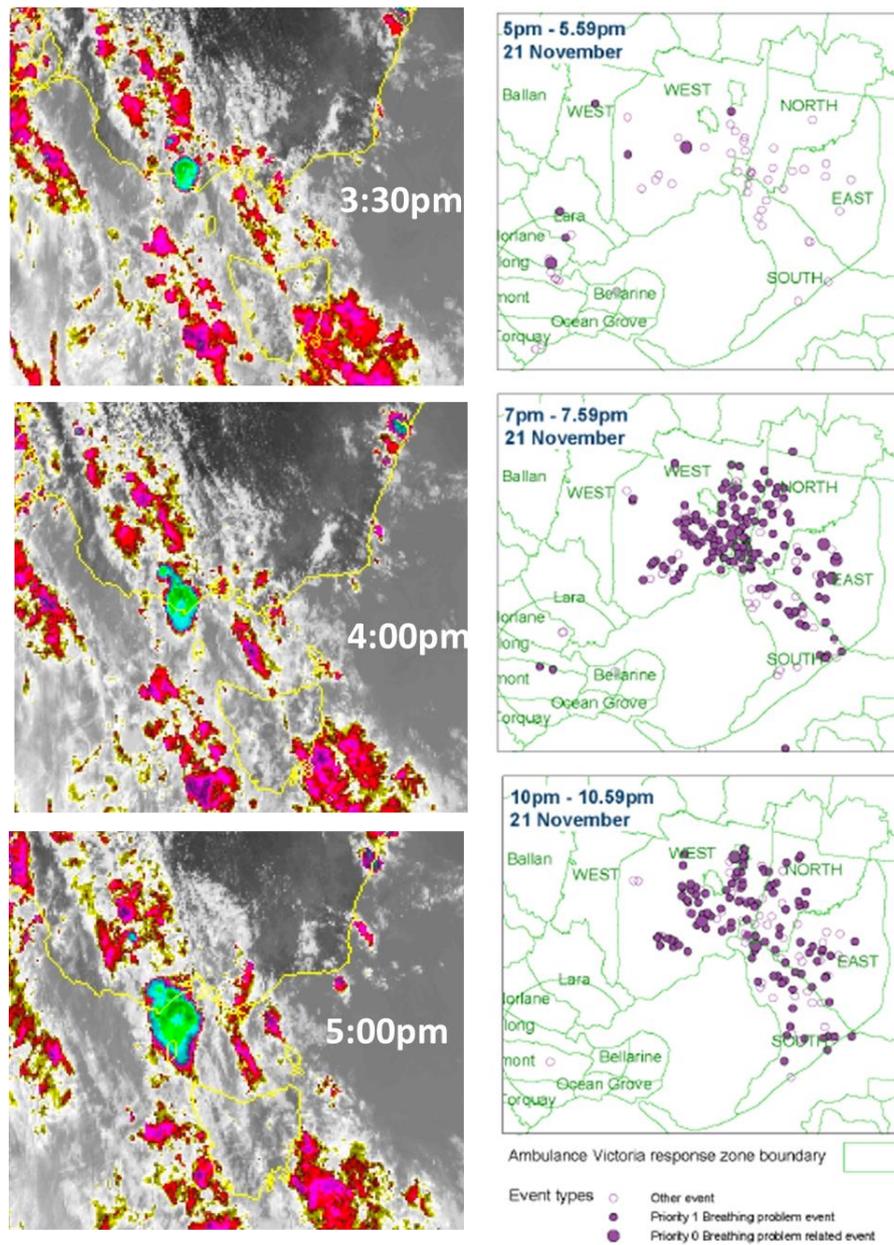
Increased sensitivity to allergens by priming allergic inflammation by pre-exposure to trees and or perennial indoor aeroallergens (house dust mites; Katelaris et al. 2004).

Later in the season sensitivity to allergic rhinitis may occur at low thresholds of exposure due to priming from a boost of synthesis of specific IgE levels (Naclerio et al. 1997; Niederberger et al. 2007). Additionally allergen-specific IgE levels can increase expression of the high affinity receptor for IgE on inflammatory cells such as basophils and dendritic cells but not mast cells, conferring greater sensitivity to cross linking by allergen with subsequent exposure to the specific allergen (Naclerio et al. 1997).

A further contributing factor to priming and later season severity may be changes in allergenicity of the pollen later in the season. During the multicenter HIALINE study across Europe, the potency of pollen that is the concentration of the group 5 allergen (Phl p 5) within the pollen grain increased later in the season. In Australia, we have the capability to measure allergen content within airborne pollen samples but this is not currently used. (Schappi et al. 1998) presented one of the first studies of measurement of allergen content within pollen; Lol p 5 allergen was measured in fractions of air samples collected in Melbourne. However, as yet there is no longitudinal or regional data on variability of the potency of grass pollen in Australia.

### Social Factors

- Many reported thunderstorm events showed peaks in ambulance calls (Inspector-General for Emergency Management 2017) and hospital presentations initiating in the evening and overnight (Summary Timeline Tables).
- Reports from Australia and elsewhere indicate that many affected people recall being outside at the time of the thunderstorm or at the time of onset of the epidemic. However, there may be a recall bias to this information because the retrospective nature of the studies and use of a questionnaire administered up to 4 weeks after the episode.
- The November 21 episode of Melbourne 2016 exemplifies the role of this factor; at the time preceding the TA epidemic, many people would have commenced their commute home from daily activities. Anecdotally, on hot steamy days Melbournians like to head to the beach or pools to seek relief from the heat, where they may be likely to be caught outside in the event of an evening thunderstorm.



**FIGURE 9: SATELLITE IMAGES OF THE THUNDERSTORM OVER MELBOURNE AND TIME SEQUENCE OF AMBULANCE VICTORIA ACTIVITY ON NOVEMBER 21 2016 AND HOW IT DEVELOPED OVER THE DAY.** Left panel; Satellite images of the thunderstorm over Melbourne on November 21 2016 and how it developed over the day. The green area represents very cold cloud-top temperatures of the thunderstorm complex. Regional and Mesoscale Meteorology Branch (RAMMB) of NOAA/NESDIS/Supplied (Newbiggin, Huete, Ebert, Davies, Silver, Beggs (conversation 2017). Right panel; Time sequence of Ambulance Victoria activity on November 21, 2016 (INSPECTOR-GENERAL FOR EMERGENCY MANAGEMENT 2017).

**Mental health factors**

The risk of exacerbations, emergency visit and hospitalisations increases in patients with severe asthma who also have a psychological dysfunction in comparison to those who don't (ten BRINKE et al. 2001). The percentage of psychiatric morbidity in patients with severe asthma ranges between 25% (Vamos et al. 1999) and 49% (Heaney et al. 2005); the most common psychiatric disorders are depression and anxiety. However, it is not clear if psychological dysfunction is caused by the exacerbations or is the result of the continuous psychological stress of going through severe asthma

symptoms and/ or recurrent life-threatening events. The influence of mental health on TA has not been investigated or referred to in the literature described herein. Paulley (2002 noted in a Letter to the editor that some asthma patients recall how a relative conveyed anxiety during thunderstorm and that noise, or emotion evoked by noise, can trigger an asthma attack.

#### **Key messages**

Factors that combine to increase asthma exacerbation include meteorological (thunderstorms, thunderstorms with lightning and/or outflows); environmental (high grass pollen levels), and; individual susceptibility factors (sensitisation to the triggering aeroallergen e.g. grass pollen, history of hayfever with or without asthma, being outside, not using asthma preventer medication and being young.

Alone no condition is necessarily sufficient to always induce asthma but combined effects of meteorological, environmental and individual factors appear necessary for TA outbreaks. Combinations of conditions appear to amplify the severity and scale of asthma episodes at one time. The contributing co-factors may be specific to the local circumstances (e.g. olive pollen in Italy).

Thresholds of grass pollen exposure depend on the context of the symptom; higher pollen exposures are needed to trigger asthma than eye and nose symptoms.

The level of sensitivity to grass pollen allergens, priming of the immune system by exposure to other allergens, social factors and other disease entities (mental health, obesity and or cardiovascular disease) may increase an individual's susceptibility to asthma during thunderstorms.

#### **Strength of evidence**

The quality of evidence for the role of outflows in TA is good. Several studies indicate lightning is involved but the evidence is not exhaustive nor providing a complete and consistent knowledge base of all features of thunderstorms that are associated with asthma.

There is a strong body of evidence from Australian studies to indicate that high levels of exposure to grass pollen and sensitisation to ryegrass pollen are key susceptibility risk factors for TA.

There is insufficient evidence on the individual susceptibility factors for TA amongst the population with allergic rhinitis and sensitivity to grass pollen allergens.

#### **Gaps in knowledge**

Modelling of how multiple factors interact (synergistically) to cause epidemic increases in asthma exacerbations.

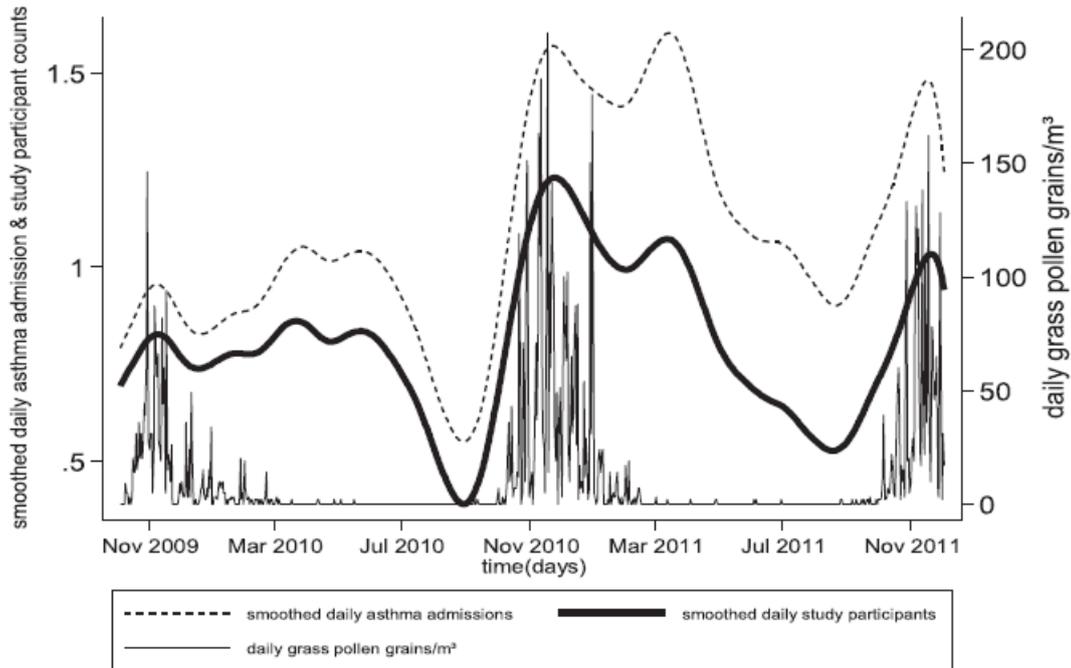
Individual susceptibility factors and characteristics of people at risk of TA.

Levels and patterns of allergic sensitivity with grass pollen allergens of patients affected by TA compared with healthy individuals and other patients with pollen allergies who were not affected by TATA.

**Question 9.**

**What are the major aeroallergens in ryegrass pollen?**

**What other pollen types are associated with spring/summer hayfever or asthma?**



**FIGURE 10: THE TOTAL NUMBERS OF ASTHMA ADMISSIONS TO THE ROYAL CHILDREN'S HOSPITAL AND PARTICIPANTS ENROLLED IN THE MELBOURNE AIR POLLEN CHILDREN AND ADOLESCENT HEALTH STUDY (SMOOTHED) AND THE SEASONAL DISTRIBUTION (IN DAYS) OF AMBIENT GRASS POLLEN DURING THE STUDY PERIOD (ERBAS ET AL. 2015)**

**What are the major aeroallergens in ryegrass pollen?**

Ryegrass is the most abundantly planted fodder crop in Victoria. It has been identified by SPT as an allergen associated with TA in Melbourne and Wagga Wagga (Bellomo et al. 1992; Marks et al. 2001).

Note, that pollen from different grass species cannot distinguish between by light microscopy (Salih et al. 2009; Davies et al. 2015b). Thus aerobiological data of on grass pollen counts can only indicate levels of grass pollen and not the species (not ryegrass pollen).

However, ryegrass pollen is strongly and specifically recognized by Victorian patients with grass pollen allergy as evidenced by SPT, immunoblot, ELLISA and BAT and cross inhibition assays (Davies et al. 2011) Bass, 1984 #4302).

The geographical distribution of ryegrass is consistent with its association with spring TA in Victoria (Derrick 1929;1962;1966; Sharwood 1935).

Ryegrass represents one of a number of allergenic temperate grass species of the Poideae subfamily. Other known species common in Victoria include *Phalaris*, *Dactylis glomerata* (Davies et al. 2015b).

Its allergens have homology with allergen components of Timothy grass but also there are some differences recognized immunologically by patients (Anderson et al. 2001; Chabre et al. 2010; Nony et al. 2015) and Timothy grass is rare in Australia ([www.australianvirtualherbarium.com.au](http://avh.ala.org.au/#tab_simpleSearch); [http://avh.ala.org.au/#tab\\_simpleSearch](http://avh.ala.org.au/#tab_simpleSearch)).

**TABLE 10: MAJOR ALLERGENS OF RYEGRASS POLLEN AND REACTIVITY OF PATIENTS WITH GRASS POLLEN ALLERGY**

Allergen family	About this allergen	Ryegrass pollen allergen	Frequency of IgE reactivity	Timothy pollen allergen	Frequency of IgE reactivity
<b>Group 1</b>	Contained in cytosol beta-expansin, glycosylated	Lol p 1*	87%	Phl p 1*	83-95%
<b>Group 2 and 3</b>	expansin C-terminal domain	Lol p 2* and Lol p 3*	63%	Phl p 2* Phl p 3	55-65% 60%
<b>Group 4</b>	Berbine bridge; glycosylated	Lol p 4*		Phl p 4*	70-75%
<b>Group 5 and 6</b>	Homology with ribonuclease; localised to starch granules	Lol p 5*	Up to 85%	Phl p 5* Phl p 6*	50-95% 44-75%
<b>Group 7</b>	calcium binding protein			Phl p 7*	7-10%
<b>Group 10</b>	Homology with cytochrome C proteins	Lol p 10			
<b>Group 11</b>	Homology with trypsin inhibitor	Lol p 11*	65%	Phl p 11*	32-43%
<b>Group 12</b>	Proflin; actin binding	Lol p 12		Phl p 12*	15%
<b>Group 13</b>	Polygalacturonase, glycosylated	Lol p 13		Phl p 13*	50%

(Davies et al. 2016; Suphioglu 2000)

Whilst the frequency of serum IgE reactivity with the ryegrass pollen allergens is provided as cited by (Suphioglu 2000) most of the studies from which the primary data were described report the molecular characterisation of allergen components that were newly discovered at the time. These studies used small sample sizes (often 20 to 30 subjects) without describing the demographics (age or gender), diagnosis of allergic disease (hayfever, eczema, and or asthma), other measures of allergic sensitivity (SPT) or disease severity. Additionally, the size of the control groups was small (sometimes as few as one to three serum donors) and rarely included other disease control subjects to demonstrate specificity of IgE reactivity with particular allergen components to relevant patient groups.

- Large cross-sectional studies of well-defined patients and control groups have not been undertaken with standardized allergen components of ryegrass pollen, the major allergenic grass species that is abundant in Victoria.

The molecular allergen components of Timothy grass pollen are well studied and available commercially for testing individually (ImmunoCAP, Thermofisher) and as part of a multi-allergen array (ISAC chip) developed in Europe for quantifying levels and patterns of sp IgE to grass pollen allergens (Davies et al. 2016; Scala et al. 2010). A number of these tests may be appropriate for Victoria (which has a temperate climate where patients are predominantly exposed to temperate grass pollen allergens), for rapidly evaluating serological responses of patients who experienced TA during the recent episode. Patients from Melbourne with allergic rhinitis show high levels of sensitivity to ryegrass pollen extract and the major allergen component Lol p 1 (Davies et al. 2011; Tamborini et al. 1997; Griffith et al. 1991). However, there may be important allergen components of ryegrass (for instance Lol p 5) and of subtropical grass pollens (Pas n 1, Cyn d 1, Sor h 1, Sor h 23 (Davies et al. 2008; Campbell et al. 2015; Smith et al. 1996), that would be informative to evaluate in well-defined patient groups in Australia (Victoria included), particularly in the context of TA.

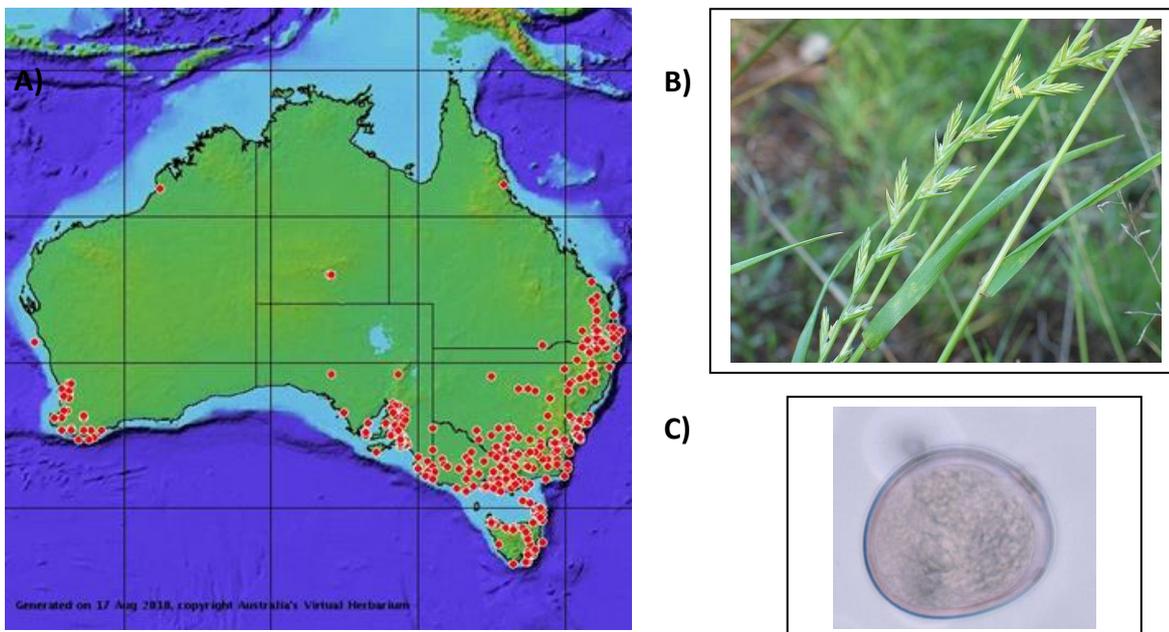
The allergen Lol p 5 of ryegrass has a high degree of species specificity exemplified by only 56% amino acid identity in the primary sequence with its analogous allergen in Timothy grass pollen (Phl p 5). In contrast the other major ryegrass pollen allergen, Lol p 1, has a high percentage amino acid identity (91%) with its homologue of Timothy grass (Phl p 1; Appendix IX) which has been standardized and available commercially. Thus whilst recombinant Phl p 1 may suffice in

Australia to measure concentrations of specific IgE reactivity with temperate grass pollen group 1 allergens, Phl p 5 may not be suitable as a substitute for Lol p 5.

- Lol p 5 allergen component of ryegrass pollen that is contained within the ruptured pollen starch granules which may be an important airborne allergen for inducing allergic airway inflammation during episodes of TA (Schäppi et al. 1999).
- Outside of the context of TA a study of 140 patients from Italy with allergic rhinitis were tested for serum IgE reactivity with Phl p 1, Phl p 5, Phl p 7 and Phl p 12; low specific IgE to Phl p 5 was significantly associated with no asthma ( $p < 0.001$ ; Savi et al. 2013).

Levels of serum IgE to the group 5 grass pollen allergen Lol p 5 may be an important biomarker for progression from allergic rhinitis to asthma (Davies, personal communication).

Accurate measurement of the concentrations of specific IgE to Lol p 5 (Suphioglu et al. 1998) including its isoforms (Suphioglu et al. 1999) may be of use in identifying patients with hayfever who are at risk of developing symptoms of asthma during TA events. Notably, the isoforms of Lol p 5 may display some heterogeneity in patient serum IgE reactivity given they are quite diverse in primary amino acid sequence (Refer to Question 11). Use of currently available Phl p 5 allergen for testing may not provide a true indication of Australian patient serum IgE reactivity with Lol p 5 and its isoforms, of which there are three.



**FIGURE 11: RYEGRASS. A) RYEGRASS DISTRIBUTION IN AUSTRALIA (AUSTRALIAN VIRTUAL HERBARIUM) B) IMAGE OF RYEGRASS FLOWERS C) LIGHT MICROSCOPY IMAGE OF GRASS POLLEN GRAIN.**

### What other pollen types are associated with spring/summer hayfever or asthma?

#### Subtropical grass pollens

Other grass pollens; subtropical Panicoideae (Bahia, Dallas, Johnson) and Chloridoideae (Bermuda, Rhodes) are important grass pollens in Australia, including parts of Victoria. However, Dallas grass, *Paspalum dilatatum*, Bermuda grass, *Cynodon dactylon*, are subtropical grasses that are also common in Victoria. Subtropical grass pollens may also pose a threat for allergic respiratory disease now and in the future with changes in species distribution anticipated with climate change (Davies 2014). However, these subtropical species of grass are unlikely to be contributing significantly to airborne grass pollen levels in November at the time when TA events have occurred. Subtropical species predominantly flower latter in the grass pollen season in summer and autumn (Derrick 1962).

Regional differences in allergic sensitivity to different pollen allergens depend on local exposure to species that are prevalent in the local environment (Davies, 2014).

### Weed pollen

*Parietaria* pollen has been linked with episodes of TA in Italy (D'Amato et al. 2008).

However, other weed pollens including Ragweed have been associated with asthma exacerbations outside of thunderstorm events (Laaidi et al. 2003; Bass et al. 2000).

Notably ragweed currently has a low distribution on the east coast of Australia (Australian Virtual Herbarium) but there is some evidence of sensitisation in Australia (Rimmer et al. 2015; Bass et al. 2000; Thompson et al. 2013). Ragweed has potential to become an important trigger for allergic respiratory diseases in Australia with climate change.

**TABLE 11: WEED ALLERGENS**

Species name	Biochemical name	Allergenic molecule	Prevalence among patients
<b><i>Ambrosia artemisiifolia</i></b> (ragweed)	<u>Amb a 1</u>	<u>Pectate lyase</u>	<u>&gt;95%</u>
	<u>Amb a 4</u>	<u>Defensin-like protein</u>	<u>20-40%</u>
	<u>Amb a 6</u>	<u>Non-specific lipid transfer protein</u>	<u>20%</u>
	<u>Amb a 8</u>	<u>Profilin</u>	<u>35-50%</u>
	<u>Amb a 9</u>	<u>Polcalcin (2 EF-hand calcium binding protein)</u>	<u>10-15%</u>
	<u>Amb a 10</u>	<u>Polcalcin (3 EF-hand calcium binding protein)</u>	<u>10-15%</u>
	<u>Amb a 11</u>	<u>Cysteine protease</u>	<u>66%</u>
<b><i>Parietaria Judaica</i></b> (pellitory)	<u>Par j 1</u>	<u>Non-specific lipid transfer protein</u>	<u>95%</u>
	<u>Par j 2</u>	<u>Non-specific lipid transfer protein</u>	<u>80%</u>
	<u>Par j 3</u>	<u>Profilin</u>	<u>nd</u>
	<u>Par j 4</u>	<u>Polcalcin (2 EF-hand calcium binding protein)</u>	<u>6%</u>
<b><i>Plantago lanceolata</i></b> (English plantain)	<u>Pla l 1</u>	<u>Ole e 1-like protein</u>	<u>86%</u>

Data on sensitisation frequency from patients with allergic rhinitis in Germany (Gadermaier et al. 2014), except for Amb a 11 (Bouley et al. 2015); the sensitisation prevalence to each allergenic molecule among patients sensitized to the natural extract may vary in different geographic regions (Gadermaier et al. 2016).

### Tree pollen

Only one paper links TA with tree pollen exposure; 278 grains/m<sup>3</sup> olive tree pollen was present in the air and all of 20 patients affected with TA were sensitive to olive pollen in Italy (see Table 5) (Losappio et al. 2012).

However, outside the context of TA, exposure to aggregated tree pollens (sometimes specified as oak and pine) have been associated with asthma exacerbations in children and adults (Gleason et al. 2014; Ito et al. 2015; Zhong et al. 2006; Babin et al. 2007).

**Key messages**

Many patients suffer from both allergic rhinitis and asthma and patients may show allergic sensitivity to the same allergen sources.

Ryegrass pollen is the main temperate grass pollen allergen source implicated in triggering TA in Australia.

Other temperate grasses as well as subtropical species may also contribute now and in future to the burden of disease associated with grass pollen allergy including TA.

There are two clinically important major allergens of ryegrass; the group 1 (Lol p 1) and the group 5 (Lol p 5). The group 1 is a founder allergen for grass pollen allergy and a marker for disease onset whilst the group 5 allergen may be associated with a prognosis of asthma.

**Strength of evidence**

The weight of evidence that high levels of grass pollen exposure and allergic sensitivity to ryegrass pollen allergens are important factors for TA in Australia is strong.

**Gaps in knowledge**

Use of allergen components specific to locally relevant grass pollen to identify prognostic biomarkers of TA.

Testing of levels and patterns of serum IgE reactivity allergen components from within grass pollens may provide indications of which grass pollen-allergic patients with hayfever are at risk of asthma, particularly during thunderstorms.

**Question 10.**

**What are the major aeroallergens in fungal spores? Which fungal spores have been associated with epidemic TA?**

**Response:**

The American Asthma and Allergy Foundation notes that “although there are many types of molds, only a few dozen are known to cause allergic reactions”. Moulds most likely to trigger an allergic response include the following:

<i>Alternaria</i>	<i>Epicoccum</i>	<i>Mucor</i>
<i>Aspergillus</i>	<i>Fusarium</i>	<i>Pencillium</i>
<i>Aureobasidium (Pullularia)</i>	<i>Helmin-thosporium</i>	<i>Rhizopus</i>
<i>Cladosporium (hormodendrum)</i>		

*Cladosporium* and *Alternaria* produce non-thermotolerant allergens and their spores elicit allergic reactions when present in the air at certain concentrations; 100 spores/m<sup>3</sup> of *Alternaria* is sufficient to evoke allergic symptoms whilst symptoms are associated with high levels of *Cladosporium* (3000 spores/m<sup>3</sup> air; Nasser et al. 2009; Gravesen 1979). According to the WHO/ IUIS Allergen Nomenclature Committee, a number of allergens have been characterized from fungal species relevant to TA.

**TABLE 12: MAJOR AEROALLERGENS IN FUNGAL SPORES RELATED TO THUNDERSTORM ASTHMA.**

Fungal species :  Biochemical name:	<i>Alternaria alternata</i>	<i>Cladosporium herbarum</i>	<i>C. cladosporioides</i>
Unknown	Alt a 1*	Cla h 2	
Acid ribosomal protein P1	Alt a 12	Cla h 12	
Acid ribosomal protein P2		Cla h 5	
Aldehyde dehydrogenase	Alt a 10	Cla h 10	
Disulfide isomerase	Alt a 4		
Enolase	Alt a 6	Cla h 6	
Glutathione-S-transferase	Alt a 13		
Heat shock protein 70	Alt a 3		
Manganese superoxide dismutase	Alt a 14		
Mannitol dehydrogenase	Alt a 8	Cla h 8	
Ribosomal protein P2	Alt a 5		
Serine protease	Alt a 15		
Transaldolase			Cla c 14
Vacuolar serine protease		Cla h 9	Cla c 9
YCP4 protein	Alt a 7	Cla h 7	

### Fungal allergens relevant to respiratory disease and TA

The major aeroallergen component from *Alternaria* spores is Alt a 1 (KLEINE-TEBBE et al. 1993; Aden et al. 1999). Patients with asthma or rhinitis sensitised to *Alternaria* show high percentage (93-98%) of Alt a 1- specific IgE and IgG specific antibodies (Vailes et al. 2001; Asturias et al. 2005; Postigo et al. 2011). For *Cladosporium*, the known allergens are cross-reactive with other fungal allergens with one aeroallergen being specific for *Cladosporium*; Cla h 8 (Simon-Nobbe et al. 2008). Approximately 57% of *C. herbarum*-sensitised allergic patients, with IgE to *C. herbarum* total protein extract by immunoblotting, were IgE reactive to purified recombinant Cla h 8 (Simon-Nobbe et al. 2006). There is the presumption that mono-sensitisation to *Cladosporium* is not common due to the cross-reactivity of the aeroallergens (Aplin et al. 2003). The major allergens of *Penicillium* are classified as group 13 and group 18 which are also known as alkaline and vacuolar serine proteases (Chou et al. 1999). IgE reactivity to Pen ch 13 in asthmatic patients increases from 17% to 42% with age indicating it is more relevant for adults than children (<10 years; Chou et al. 2003). Detection of mono-sensitisation may be an issue with *Penicillium* as with *Cladosporium* due to the cross-reactive nature of the allergens (Aplin et al. 2003). Many allergens have been identified in *Aspergillus*; however, the two major allergens are Asp f 2 and Asp f 4 with sensitisation frequency of 96% and 92% (Kurup et al. 2000) respectively. The most common allergens for sensitisation among allergic bronchopulmonary aspergillosis (ABPA) patient are Asp f 9 (Cramer 1998) and Asp f 34 (Glaser et al. 2009). Although these allergens are important, limited number of studies to date state how relevant they are clinically. Other allergens have been associated with occupational respiratory allergies in older workers, from different *Aspergillus* species (Doekes et al. 1999). From the genus *Candida*, the allergen Cand a 1 showed high IgE-binding frequency relative to non-reactive bands by immunoblotting, 77% of the tested sera from 30 asthmatic patients being positive to Cand a 1 (SHEN et al. 1989). Sera of asthmatic patients with serum IgE to *C. albicans* showed 56% frequency of IgE specific for Cand a 3 (Chou et al. 2003).

### Fungal spores and thunderstorm asthma

TA episodes have been associated with individuals being sensitised to *Alternaria* and/ or *Cladosporium*. One study, describing the UK 2002 event and clinical characteristics, showed associations between high levels of *Didymella*, *Alternaria*, and *Cladosporium* species during a thunderstorm (see Tables 4 and 8; (Pulimood 2007). This event thunderstorm resulted in 26 asthma admissions, one asthma-related death, with 23 of the patients testing positive for *Alternaria*-specific IgE (Pulimood et al. 2007). Other studies in the UK associated epidemic asthma events due to increased levels of *D. exitialis* which grow in grass leaves (Punithalingam 1979), after thunderstorms. The event in Birmingham reported by Packe et al. 1985, noted the sudden increase of *Didymella* and *Sporobolomyces* in the air during and after the thunderstorm. In the 1984 UK event in Nottingham (Alderman et al., 1986), there was no factor accounting for the observed change in weather and asthma attacks. However, changes in *D. exitialis* fungal spore concentration were present and this spore type was reportedly associated with asthma causation (Harries et al. 1985). The thunderstorm that hit England in 1989 released high numbers of *Didymella* (Alitt 1997) but these spores were not directly correlated with hospital asthma admissions. However, summer asthma had previously been associated with allergy to fungal spores and respiratory allergy has been known to be caused by *D. exitialis* and *Sporobolomyces* (Harries et al. 1985). These two fungi are released into the air during and after rainfall and are thus known as damp-air spores (Hirst 1953). In a case-control study of asthma on thunderstorm days in NSW, Girgis et al. (2000) observed that patients presenting with asthma symptoms on case days when thunderstorm occurred showed 61% frequency of sensitivity by skin prick test to *Cladosporium* spores compared to patients presenting on control days without thunderstorms (adj OR 2.8 CI 1.21 to 6.29; p = 0.02). Interestingly, there was a lower frequency of 32% of patients on case days versus 42% of patients on control days who were SPT positive for *Alternaria* (OR 0.3; CI 0.11 to 0.58; p = 0.001), suggesting a protective effect of sensitisation to *Alternaria* spores in this cohort but collinearity could be a confounder.

### Harvesting practices and fungal spores (see Question 4c)

Agricultural harvesting leads to release of *Alternaria* spores. Pulimood et al (2007) observed a strong connection between TA admissions and broken *Alternaria* spores. The thunderstorm occurred at the time of harvesting when high levels of fragmented fungal spores were observed. Therefore authors proposed that thunderstorm at the time of harvesting when levels of fragmented spores are high can be a trigger of asthma epidemic. It was proposed that the harvesting process can induce spore fragmentation. Moreover, the same authors suggested that farming trends can contribute to the increased spore levels before the thunderstorm because farmers concerned with threats to their crops by the impending storm would bring harvesting forward to save the crop. This practice would thus increase number of spores just before the thunderstorm.

In support of this proposed theory, others have observed that large amounts of fungal spores were released during combine harvest of wheat (Friesen et al. 2001). Wheat harvesting liberates immense numbers of fungal spores, many of which then can be dispersed long distances in wind currents.

Children living in Wagga Wagga and Moree in NSW have high allergy and asthma prevalence with sensitisation to *Alternaria*. Matakakis et al., 2001 studied cotton and wheat crops near the two towns to determine the source of *Alternaria*. The spores sampled across the two years showed that spore concentrations peaked after warm temperatures and recent rainfall more than after harvest. Outdoors during warm, moist seasons, the mean fungal spore concentration has been documented to reach 50,000 or more spores/m<sup>3</sup> of air (Pashley et al. 2012; Barnes et al. 2000).

### Mechanisms of action

*Alternaria* extracts exert proteolytic activity (Snelgrove et al. 2014) leading to asthma exacerbation by inducing the production of the proinflammatory cytokines IL-6 and IL-8. Susceptibility to fungi in asthmatic patients can potentially be due to the overexpression of the protease (PAR) type 2 receptor (Arbes et al. 2005). Another observation for the association between severe asthma and fungal sensitisation is increased steroid-resistant IL-33 levels in fungal-sensitised children in comparison to non-fungus-sensitized patients (Castanhinha et al. 2015). The extent and immune mechanisms by which mould sensitivity affects atopic patients is not clearly defined. In large broad population based study conducted by the National Center for Health Statistics to determine the health and nutritional status of the US population (NHANES II and III) the frequency of mould sensitisation was 13% (Arbes et al. 2005). In a study of 824 patients between 5 and 65 years old with allergic rhinitis and/or asthma the frequency of sensitisation to mould spores was as high as 78% (Bartra et al. 2008). Moulds could be a major contributor to severe asthma episodes (Agarwal et al. 2009), and when airborne fungal spores peak, the frequency of asthma-related deaths is reported to increase (D'Amato et al. 2016; Khot et al. 1984).

### Fungal spores and asthma

The most relevant fungal species causing allergic sensitisation are the those belonging to the Ascomycetes family: *Alternaria*, *Aspergillus*, *Botrytis*, *Epicoccum*, *Fusarium* and *Penicillium* species (Agarwal et al. 2009). Fungi of *Alternaria*, *Cladosporium*, *Aspergillus* and *Penicillium* that are present outdoor, release spores in spring and summer, without the presence of thunderstorms, triggering asthma exacerbations (Atkinson et al. 2006). In adults, sensitivity to mould is a contributor to asthma severity which may result in hospital admission (O'Driscoll et al. 2005; Salvaggio et al. 1971; Jenkins et al. 1981; Delfino et al. 1997; Newson et al. 2000) also evidenced in the review by Baxi et al., 2016). In asthmatic children, exposure to outdoor fungal spores increases susceptibility to asthma exacerbations (Downs et al. 2001; reviewed in Tham et al., 2014; Baxi et al 2016). Persistent and severe asthma has been specifically associated with *Alternaria* and *Cladosporium* sensitisation (Zureik et al. 2002). Asthma episodes resulting in death or near-fatal incidents were recorded in southeastern Minnesota, between 1980 and 1989. Patients in the study were shown to be sensitised to *Alternaria* species which is commonly present in the atmosphere in the US especially in grain-growing areas, the Midwest, where it is more abundant (O'Hollaren et al. 1991). The increase in *Alternaria* levels was also associated in asthma deaths in Chicago during the period 1985 and 1989 (Targonski et al. 1995). Additional seasonal reported asthma deaths were in the eastern region of the UK in August of the year period 2001-2003 (Harrison et al.

2005), in Scotland (Durham et al. 1992), and in Ontario, Canada during the months of September and October of the period between 1979 and 1986 (Mao et al. 1989).

### Quality issues of fungal extracts for diagnosis

An issue with diagnosis of allergic sensitivity to fungal allergen is the extract quality. Extracts for detection of allergy to fungal species may be derived from mycelia or spores but the expression of fungal proteins including the allergen components of these tissues varies. A number of fungal allergens are proteases suggesting a mechanism for their pathogenic effects upon encounter with airway epithelium. Protease activity of allergen extracts may affect the quality and stability of extracts used for diagnosis. Additionally, as many of the allergen components of *Cladosporium* are cross-reactive with equivalent allergen components of *Alternaria* confounding the detection of taxon specific sensitisation. The consequences of this are two-fold. Firstly, due to the potential proteolytic capacity of fungal extracts there may be differences in potency of reagents used in diagnosis due to variability in the presence and maintenance of allergen components within fungal extracts between species, batches and suppliers. Reports on fungal allergy in the context of TA rarely included control subjects with no history of allergic disease or asthma. Secondly, if there is only one species-specific allergen of *Cladosporium*, then the specificity of diagnosis of fungal allergy may be confounded by sensitivity to other fungi such as *Alternaria*.

### Key messages

Fungal spore allergens are noted to be an important factor in hospital asthma admissions outside the context of TA.

Rainfall and harvesting practices may increase the release of some mould species prior to the arrival of thunderstorms rendering some individuals at risk of TA.

In Australia, *Cladosporium* fungal spores may be a contributing factor for some patients suffering TA exacerbations but the frequency of sensitisation and importance is lower than grass pollen.

### Strength of evidence

The timing and volume of rain falling during the days or hours prior to the TA event are not always clearly recorded. However, this may be an important factor influencing fungal spore release.

There are concerns with specificity and quality of reagents used in allergy testing for fungal spore sensitivity.

### Gaps in knowledge

The level of contribution of allergic sensitisation to fungal allergens to allergic respiratory disease including TA, in Australia.

The frequency of allergic sensitisation measured by SPT and specific IgE to fungal spore allergens in patients with asthma during epidemic TA outbreaks compared with patients on other days and healthy control subjects in the Australian community without asthma or other respiratory symptoms.

### Question 11.

**Do the same allergenic materials trigger the allergic response in diagnosed asthmatics experiencing TA compared to spring/summer hayfever sufferers experiencing TA symptoms?**

**Is the severity of response different and why?**

#### Response:

Hayfever or seasonal allergic rhinitis is typically triggered by exposure to outdoor aeroallergens. For patients in Australia, grass pollen is the major outdoor aeroallergen.

Patients with allergic asthma have high frequency of response to perennial indoor aeroallergens; house dust mite, animal dander, mould as well as outdoor aeroallergens including pollens.

Patients with hayfever have a higher frequency of asthma than other individuals without hayfever. Conversely, as many as 80% of patients with asthma have allergies and comorbidities including allergic rhinitis (Corren 1997; Bousquet et al. 2008). Almost 100% of atopic patients with asthma exacerbations have allergic rhinitis (Linneberg et al. 2002; Thomas 2006).

Whilst asthma and hayfever are separate disease entities, there is a continuum of allergic inflammation between the upper and lower airways (ARIA; Allergic Rhinitis Impact on Asthma International Consensus; Bousquet et al., 2008 & 2015). Here the key clinical characteristics of relevant asthma types and immunopathological factors underlying allergic asthma and hayfever are summarized.

#### Immunopathology of allergic asthma

A number of endotypes of asthma exist that are characterized by the involvement of different types of inflammatory cells; eosinophilic, neutrophilic, mixed (ie, both neutrophils and eosinophils found), and paucigranulocytic (few or no granulocytes in the sputum; Simpson et al. 2006; Green et al. 2007), which may involve co-contributions of a number of causative factors. Triggers for asthma exacerbation and response to therapy may differ between the subtypes of asthma. This discussion will focus on allergic asthma because this is the most common endotype of asthma and the phenotype associated with TA triggered by aeroallergen exposure.

Chronic lower airway inflammation characterized by eosinophilia and goblet cell hyperplasia accompanied by structural changes in airway including collagen deposition and smooth muscle involvement (Murdoch et al. 2010). Clinically, patient symptoms include shortness of breath, reduced airflow (measurable by spirometry), airway hyper-reactivity, tight chest, cough, mucous production, and bronchospasm. Episodes of allergic asthma symptoms can be reversible by short or long acting beta agonists and preventable by use of prescribed inhaled corticosteroids (Szefer et al. 2002; Bjermer 2008).

Many studies demonstrate the correlation between the severity of asthma and increase in eosinophilic inflammation (Louis et al. 2000; Bousquet et al. 1990). Sensitivity to aspirin in adult-onset disease has been associated with persistence of eosinophilic inflammation in severe asthma (Miranda et al. 2004). The symptoms in patients with eosinophilic inflammation are heightened. These patients are more prone to exacerbations than if features of other pathological phenotypes of asthma are present (Green et al. 2002; Payne et al. 2001).

In the context of TA, Wark et al., conducted an investigation of the immunological characteristics of a small number (six) patients who experienced acute TA in Hunter Valley, New South Wales. This study showed that subjects assessed were all allergic to grass pollen, particularly ryegrass pollen, and compared to age and gender matched control subjects showed characteristics consistent with and typical of allergic asthma; for example elevated levels of eosinophils in sputum samples, marked eosinophil cationic protein elevation and more lymphocytes staining positive for the interleukin 5 (which promotes allergic responses) (Wark et al., 2002).

### **Immunopathology of hayfever**

Hayfever (allergic rhinitis) is characterized by sensitisation to aeroallergens, specific IgE production to aeroallergens systemically (Bousquet et al. 2008; measurable by SPT or serum immunoassay; ImmunoCAP), nasal epithelial inflammation, mast cell activation, histamine and inflammatory mediator release leading to watery rhinorrhea (Broide 2010). It is associated with symptoms of chronic nasal inflammation and blockage, sleep apnea, otitis media, conjunctivitis as well as asthma (Leynaert et al. 2000; Guerra et al. 2002; Walls et al. 2005).

When exposed to outdoor allergens such as grass and tree pollen patients with allergic rhinitis typically show symptoms related to allergic sensitisation.

Allergic rhinitis development or worsening is promoted by fungal allergen sensitisation or exposure. It has been shown that susceptibility to bronchial asthma is greater in patients with mould allergies and patients show high exhaled nitric oxide (FeNO) levels (Kołodziejczyk et al. 2016).

Bronchial airway responsiveness is induced and eosinophil counts are increased in the sputum samples of patients with seasonal allergic rhinitis after nasal allergen challenge (Bonay et al. 2006). Notably ryegrass pollen and ryegrass pollen starch granules can induce symptoms of bronchial hyperreactivity (Suphioglu et al. 1992).

Allergic rhinitis can effectively be controlled by pharmacotherapy based on intranasal corticosteroids and antihistamines (Walls et al. 2005). Good control of hayfever can ameliorate symptoms of asthma (Scadding et al. 2008).

Allergen-specific immunotherapy has been shown with meta-analysis to be an efficacious and cost effective treatment for patients with severe allergic disease whose symptoms cannot be managed adequately by pharmacotherapy (Calderon et al. 2007; Calderon et al. 2011; Berto et al. 2008). In a small study allergen specific immunotherapy for grass pollen allergy in children was found to reduce allergic rhinitis and prevent progression of asthma with provide sustained benefits up to 10 years post cessation of treatment (Moller et al. 2002; Niggemann et al. 2006; Jacobsen et al. 2007). The benefits of allergen-specific immunotherapy include the amelioration of symptoms, reducing acquisition of new allergen sensitisations and slowing progression of disease from rhinitis to asthma (Calderon et al. 2011).

A Cochrane Systematic Review of subcutaneous (injection) allergen-specific immunotherapy for the treatment of asthma included 87 clinical trial, 27 of which were for pollen allergy (Abramson et al. 2010). Most of the trials reviewed for grass pollen immunotherapy included patients over 10 through to under 50 years. The results showed that there were significant reductions symptom scores, medication use and improvement in allergen induced airway hyperreactivity but no change in lung function.

Treatment of patients with allergic rhinitis with allergen immunotherapy has been shown to be more economical than long term pharmacotherapy for allergic rhinitis in children and adults (Hankin et al. 2010 & 2013). A systematic review of the pharmaco-economic benefit of allergen immunotherapy for rhinoconjunctivitis or asthma alone was less clear (Simeons 2012), in the context of patients with hayfever and asthma, review of five studies of sublingual immunotherapy and three of subcutaneous immunotherapy found consistently three years of immunotherapy to be effective and “less expensive than pharmacotherapy” over all. The results applied to studies with children, adolescents and adults. A number of considerations affected the cost-effectiveness including the societal benefit and costs of lost productivity but its value depends on the target population and cost of immunotherapy.

In an Australian context, allergen immunotherapy is not covered by the pharmaceutical benefits scheme and may not be reimbursed from private health funds.

### **United airway disease**

Whilst there are immunological and physiological differences between the disease entities of allergic rhinitis and allergic asthma, the concept of a united airway disease is widely appreciated amongst clinical immunologists (Bousquet et al. 2015; Setticone 1986; Parikh et al. 1997). However, asthmatics with allergic rhinitis may include only a subset of asthma patients with allergic asthma.

Points of evidence that provide causative links between hayfever and asthma include;

- Epidemiological association of hayfever and allergic asthma (Bousquet, et al. 2008)
- Co-sensitivity to aeroallergens in both asthma and hayfever (Bousquet et al. 2008)
- Longitudinal studies of children demonstrate progression from asymptomatic sensitisation to grass to rhinitis and asthma (Hatzler et al. 2012)
- Treatment of grass pollen allergy in children slows progression to asthma
- Shared genetic associations with asthma and hayfever (Ferreira et al. 2014)

**The influence of disease severity upon risk of thunderstorm asthma has not been well addressed.**

Most studies only report frequency of sensitisation to particular allergens and not the level of sensitisation preventing discernment of any correlations between size of SPT and IgE concentrations.

Bellomo et al., 1992 report higher SPT wheal size in response to ryegrass pollen in thunderstorm cases (Bellomo et al. 1992).

However, diagnosis currently conducted as a dichotomous outcome; sensitisation Yes or No. SPT is used as part of a clinical diagnosis in conjunction with clinical history and physician knowledge (ASCIA guidelines 2016; [https://www.allergy.org.au/images/stories/pospapers/ASCIA\\_SPT\\_Manual\\_March\\_2016.pdf](https://www.allergy.org.au/images/stories/pospapers/ASCIA_SPT_Manual_March_2016.pdf)). Notably, 20% of normal healthy people may show sensitivity to aeroallergens by SPT. However, asymptomatic college students in the US who showed positive SPT responses to allergen were more likely to have symptom of rhinitis three years later (Settipane 1986). Thus diagnosis of allergy must be undertaken in the context of a relevant clinical history. For routine diagnosis, many clinicians rely on SPT undertaken within their rooms rather than serum IgE measurement provided externally by immunopathology services (Hamilton et al. 2010). Whilst the size of allergen SPT reactions were positively associated with airway hyperactivity, levels of serum specific IgE showed a closer positive relationship to airway hyperactivity in children in school children in coastal Newcastle NSW (Peat et al. 1986) indicating a relationship between severity of symptoms and size of SPT wheal and level of total and allergen-specific IgE.

Serum IgE testing provides a cut off above which specific IgE is reported as positive and the class or concentration of specific IgE is indicated, thus allowing for interpretation of level of sensitivity or its relationship with disease status (Pastorello et al. 1995). Specific concentrations of IgE to particular allergen components of peanut (Ara h 2) may prove to be a useful clinical prognostic marker for risk of anaphylaxis in response to peanut ingestion in sensitized children (Santos et al. 2014; Dang et al. 2012). However, for grass pollen specific IgE there are no clinical guidelines on use of level of sensitivity for determining diagnosis, disease severity or prognosis.

In relation to level of sensitisation to grass pollen and disease severity the following studies are relevant;

- Lack of specific IgE to Phl p 5 in Europeans associated with asthma (Savi et al. 2013)
- specific IgE to Phl p 4 associated with asthma (DaAmici 2010).
- specific IgE to Phl p 1 precedes onset of symptoms of allergic rhinitis and asthma (founder allergen) (Hatzler et al. 2012)
- Ratio of specific IgE to total IgE provides an indication of likely success of allergen-specific immunotherapy (Di Lorenzo et al. 2009).

TA appears to have a very rapid onset coinciding with the arrival of the storm. Calls to emergency services commence well within the first hour of arrival of the thunderstorm (Inspector-General for Emergency Management, 2017; Downs et al. 2001). However, many more patients continue to call for help or present to ED through the night and into the next day. When describing asthma epidemics in Spain (Barcelona and Tarragona) due to soybean allergen exposure, (Picado 1992) reported that late phase allergic reactions were not evident. He suggested that these reactions either did not happen or followed so closely after the initial immediate reaction that late phase allergic reactions could not be detected. Knox and Suphioglu did not observe a late phase response to airway challenge with ryegrass pollen starch granules but salmeterol bronchodilator was given after the induction of early phase response (Suphioglu et al. 1992),

preventing development of a late phase asthmatic reaction. Challenge of subjects from Canada with ragweed pollen allergen resulted in both early and late phase asthmatic responses (Robertson et al., 1974). Whilst data is not available from recent TA event in Melbourne, is reasonable to speculate that late phase allergic reactions play a role in TA in Melbourne because patients continue to experience and present with symptoms throughout the night and into the next day, well after the pollen counts had dropped to low levels and the storm had passed. Late phase reactions would be consistent with escalation of symptoms four or more hours after the peak thunderstorm exposure. That most patients who experienced TA in previous events were not using inhaled corticosteroids (Wardman et al., 2002; Losappio et al., 2011) is consistent with and suggestive of the possibility that allergen-induced, IgE dependent late phase allergic reactions contribute to the severity of allergic airway responses in TA.

### Key messages

Whilst hayfever and asthma are distinct disease entities, the underlying immunopathogenesis of allergic airway disease of the upper and lower airway show overlapping features.

A number of endotypes of asthma exist and these are characterized by involvement of separate inflammatory cell types. Allergic asthma associated with heightened allergic type (T helper two) immunity to aeroallergens, and excessive eosinophil production and a preponderance for engagement of early innate airway inflammation that favour development of immune pathways that lead to allergic responses.

Patients with allergic asthma are likely to be at greater risk of TA.

There are reports of association of between levels of allergic sensitivity to grass pollen and risk of asthma in general and asthma during thunderstorms.

### Strength of evidence

There is strong evidence of shared immunopathology of allergic rhinitis and allergic subtypes of asthma and that exposure to aeroallergens including grass pollen can trigger airway symptoms. There is a growing understanding that different levels of exposure to allergen and timing of exposure may be associated with development of symptoms in different parts of the mucosal system (eyes, nose) and airway (lungs). Whether thresholds of sensitivity to particular aeroallergens is associated with disease severity or progression from allergic rhinitis to asthma in the context of TA is speculative.

### Gaps in knowledge

There are few studies, including in Australia, that carefully investigate the clinical, genetic or immunological features of patients who experience TA.

There are no published cross-sectional studies investigating levels or patterns of sensitisation to grass pollen allergen components comparing allergic rhinitis and asthma and health subjects in Australia.

No longitudinal studies tracking natural history of hayfever and asthma with levels and patterns of sensitisation to relevant allergens (ie ryegrass allergen components and or subtropical grass pollen allergens) in Australia.

No studies in Australia investigate thresholds or patterns of grass pollen allergen sensitisation that are associated with disease severity or progression from rhinitis to asthma among at risk population groups.

## Question 12.

**What long-term model or algorithms are documented for predicting potential epidemic TA events?**

**What data inputs (i.e. key risk factors) have been used?**

### Response:

Models for the prediction of TA epidemics rely on real-time access and integration of high quality multiple data sources. These include data relating to standard weather parameters collected at multiple monitoring sites; including temperature, solar radiation exposure, precipitation, wind speed and direction, humidity, barometric pressure, as well as parameters relevant to storms with broader synoptic coverage; air mass trajectories, storms, sferics, lightning, thunder heard. Thunder heard records are subjective measures and may provide an incomplete dataset. Airport storm data may be a more reliable data source (personal communication, Prof Ed Newbiggin and Dr Jeremy Silver, University of Melbourne).

Additionally models need to incorporate sources of locally important allergenic bioaerosols including in Australia grass pollen and certain mould spores (including but not limited to *Cladosporium*), their daily concentrations and landscape phenology (Davies et al. 2015a).

### Landcover, pollen monitoring and prediction of pollen aerobiology

The ability to monitor the production of the grass pollen from the rural source is an important part of data required to inform predictive models for grass pollen concentrations in city. This may be achieved by placement of additional pollen monitoring sites in strategically located peri-urban and rural regions that are most likely to contribute to the airborne grass pollen loads during the time when TA pose the greatest threat. Knowledge of grassland phenology cycles and pollen release is an important factor in prediction of pollen aerobiology. Dual use of remote sensing capabilities can identify landcover populated by grasses and grassland greenness indices as a measure of grassland biomass based on the specific wavelength at which plants absorb light (Ma et al. 2015; Luvall et al. 2011). This capability has potential to provide valuable early information with broad synoptic coverage on grassland greenness, pollen productivity and season timing but the models have not yet been integrated with weather parameters for develop a short-term operational forecast system.

However, conventional methods for sampling and monitoring airborne pollen utilise volumetric spore collection traps with monitoring methods that are labour-intensive, site specific, and hampered by a sparsity of sampling sites.

Short-term, predictive pollen forecast models may assist in management of symptoms and disease (Laaidi 2001b; Guillam et al. 2010; Hill et al. 1979). Seasonal forecast models seek to predict the start of a local pollen season and peak days with high pollen airborne pollen concentrations. These models utilise predictive meteorological variables (e.g., temperature, relative humidity and precipitation), to estimate diurnal variations, daily average values or seasonal characteristics of the pollen season and may include empirical regressions (such as correlation, factor and hierarchical multiple regression analysis) with airborne pollen concentrations (Smith et al. 2006; Laaidi 2001b; Stach et al. 2008; Ong et al. 1995; Oteros et al. 2013). Meteorological factors directly influence levels of airborne pollen. Pollen production depends on primary factors including moisture, sunlight (photoperiod) and temperature that affect the growth and development of plant species. Release of the pollen depends on secondary factors including sunlight, rainfall and relative humidity that affect blossoming, while pollen transport is influenced by the tertiary factors mainly wind speed and direction. Other short term pollen forecasts rely on local expert knowledge and patient symptom reports (Thibaudon, personal communication Royal National Aerobiological Service, France 2015). These localised pollen forecast models are not applicable to other sites or comparisons between different biogeographical locations because locally abundant grass taxa may have different ecological drivers for biomass production and pollination (Green et al. 2004). Phenological models can predict the start, peak and end of the pollen season based on the timing of phenological phases (Galan et al. 2014; Oteros et al. 2013; Scheifinger et al. 2013). Pollen forecasting systems require real-time phenological observation systems. Furthermore, pollen forecasting would benefit from high resolution spatial phenology (Scheifinger et al. 2013; Skjoth et al. 2013). Other observation-based approaches for pollen monitoring utilise time series-series modelling of inter-annual variations in pollen concentrations (Aznarte M et

al. 2007; Scheifinger et al. 2013) or meteorological data-driven machine learning and computational intelligence methods (Voukantsis et al. 2010). Several process-based models using input data on thermal forcing or chilling requirements (Linkosalo et al. 2008) and photoperiod (García-Mozo et al. 2009) have tested the prediction of pollen seasonality.

Satellite remote sensing data of climate and ecologically relevant variables can complement local pollen aerobiology data. The rapid development in satellite-based monitoring of phenology is promising for incorporation of satellite-data into the phenological models (Luvall et al. 2011; Skjoth et al. 2013). Pollen emission is strongly related to the observations and modelling of flowering phenology, as beginning of flowering coincides with the beginning of pollen emission (Frenguelli et al. 2010). It was observed for an instance that birch bud burst (that can be accurately monitored by remote sensing method) can be an indicator of birch pollen release in Finland (Scheifinger et al. 2013). Satellite data provide synoptic and repetitive updates of land cover conditions and land use activities that can be used to monitor vegetation phenology status and characterise ecosystem changes and sensitivity to climate variability at high spatial resolution (Seddon et al. 2016; Chapman et al. 2014; Justice et al. 1998; Cleland et al. 2007; Fitter et al. 2002). Phenological modelling, remote sensing systems (such as satellites and real time digital cameras) of the vegetation cycle and sensitivity to climate variability have been significantly improved over the last decade (Scheifinger et al. 2013). Satellite based time series Vegetation Index (VI) data and geo-spatial analysis provide spatially accurate estimates of the onset of pollen season (Karlsen et al. 2009) and location of pollen sources (Skjøth et al. 2013). Karlsen et al. (2009) developed a model for near real-time monitoring of birch flowering with the aim to monitor the start of the birch pollen season; the model applied during the spring time in Norway 2009 showed mostly good correlation with pollen trap data. This model is however not appropriate for the areas where long-distant transport has an important role as the pollen transport was not incorporated. Estrella et al. (2006) integrated pollen count concentration data and phenometrics of three pollen types (*Betula*, *Poaceae*, *Artemisia*) and the study revealed the significant temporal divergence between pollen counts and local flowering dates with irregular spatial patterns.

Pollen forecast models need to be mindful of their purpose and how they will be used (Emberlin et al. 1999; Emberlin et al. 1993; Smith et al. 2005;2006; Stach et al. 2008). Modelling of the pollen season index can be useful for forecasting the following features of the pollen season:

- Season start and end
- Season peak
- Season severity and yearly fluctuations in total pollen load.

Whilst models can be useful for predicting overall trends in the pollen season characteristics, the capacity to predict in real time, daily or weekly forecasts is challenging to achieve accurately due to variability and complex interaction of multiple factors influencing pollen aerobiology over broad regions with pollen counts at one particular site.

### Pollen transport models

It was thought that airborne pollen always originates from the local sources, with micro- and local-scale pollen transport. Micro- and local scale transport is defined as an initial dispersion of pollen grains from anthers of the plant and transport over the first kilometer(s) from the source (Sofiev et al. 2013). This approach only considered the meteorology, aerobiology and phenology of the plants in their local environment. However, this traditional approach of considering the local environment as the only origin of the pollen was changed due to the growing convincing evidence of the pollen transport within continental and across intercontinental levels (Sofiev et al. 2013). The phenological observations alone examined particular location therefore might not suffice to determine the timing of the pollen season and allergenic impact on patients due to the transport of pollen grains from greater distances (Ranta et al. 2006; Skjøth et al. 2007; Makra et al. 2016; Siljamo et al. 2008). It is therefore important to take into account the pollen release from plants (emissions) from near- but also possible far-sources of the pollen and pollen characterisation and transport patterns.

Wind is the main meteorological factor associated with the dispersion and transport of pollen grains in the atmosphere. Laaidi (2001a) determined that pollen scattering is enhanced by high winds. Additionally, higher wind speeds promote release of pollen from inflorescences and facilitate their long-distance travel (Beggs 2016). In general, pollen is subject to regional and long-distance atmospheric transport (Sofiev 2017). Bioaerosols can be

transported over hundreds or even thousands of kilometers as they are mostly light coarse particles (density of  $800 \text{ kg m}^{-3}$ ) (Beggs 2016; Siljamo et al. 2007). An intensity of the vertical mixing also has an important role in regulating the release of pollen to the middle and upper parts of the boundary layer from the plant and remixing and keeping the bioaerosols in the air preventing their deposition on the ground. Due to their low density, pollen grains can be easily uplifted to the air from the ground by low wind speeds and low turbulence intensity. Mould spores utilize the same mechanisms of transport but their smaller sizes likely increase their lifetime in the air (Beggs 2016). It is estimated that expected climate change-related reduction of the wind speed will result in less mechanically induced turbulence and thus release of pollen and will additionally result in shorter transport distances of wind borne pollen. Consequently, near-source regions (regions close to the wind-pollinated species) will have higher concentrations of pollen, while far-source regions will have lower pollen concentrations (Beggs 2016).

Pollen transport modelling studies are often based on two approaches; the most widely used are observational studies applying inverse model analysis, in order to determine the origin of sources that affect a specific site (source apportionment). Inverse studies are dominated by the simple back-trajectory analysis computed based on the Lagrangian trajectory model in order to identify the most frequent and significant pollen source areas. Different pollen species have been the focus of inverse Lagrangian back-trajectory analyses such as ragweed (Stach et al. 2007; Cecchi et al. 2007; de Weger et al. 2016), birch (Veriankaite et al. 2010; Skjøth et al. 2007), and olive pollen (Hernández-Ceballos et al. 2011). This approach enables identifying the source of pollen by directing trajectories back in time from the initial pollen measuring site. A Hybrid Single-Particle Lagrangian Integrated Trajectory (HYSLIT) (Draxler et al. 1998; Stein et al. 2015) and ACDEP (Atmospheric Chemistry and Deposition) (Hertel et al. 1995) models are examples of models based on Lagrangian trajectory approach that have been applied in pollen transport analysis. For instance, the HYSPLIT model allows using different meteorological data archives, changing the number of starting locations, choosing the random time duration option, type of trajectories and different air masses heights. A more complex approach than Lagrangian trajectory encompasses a large number of Lagrangian particles, which allows inclusion of the effects of atmospheric diffusion, atmospheric transformation and pollen removal processes (Lagrangian disperse approach). For an instance, the System for Integrated Modelling of Atmospheric Composition (SILAM; <http://silam.fmi.fi>) is based on Lagrangian particle models. Furthermore, it was observed that Lagrangian methods suffer from the limited spatial representativeness of a single Lagrangian particle. Therefore, more comprehensive (Eulerian adjoin dispersion) modelling has been introduced and applied (Veriankaite et al. 2010) which allows to compute the sensitivity of observed values to emission fluxes, chemical transformations and meteorological conditions that can affect the specific observation (Sofiev, Belmonte, et al. 2013).

The second modelling approach is forward forecasting based on simulation of pollen production, emission, transport, deposition, re-suspension and sometimes even, the health impact using the set of input data (Sofiev, Belmonte, et al. 2013). The models that have been used as a pollen forecasting system in Europe is the SILAM dispersion model. Many studies in Europe have been using SILAM (Sofiev 2017; Prank et al. 2013; Sofiev et al. 2006 & 2013; Ranta et al. 2006) which is a widely used chemical transport model. SILAM has incorporated source terms (input data) for alder, birch, grass, olive, ragweed, and mugwort pollen (Sofiev 2017). Important pollen-related atmospheric transport processes included in the model are transport with wind (advection) (Sofiev et al. 2015), turbulent mixing (diffusion) (Sofiev 2002) and grain removal by wet deposition (based on scavenging coefficients) and dry deposition (based on resistance analogy) (Kouznetsov et al. 2012). The essential input for SILAM dispersion model is meteorological data (precipitation, winds etc.) taken from weather prediction models. The transport of the airborne pollen in the atmosphere is driven by relative humidity (loss or gain of water and pollen rupture), temperature and UV radiation (loss of viability), but also by interaction with oxidants in polluted environments (Sofiev, Belmonte, et al. 2013). However it is supposed by the model that pollen is inert non-reactive species without physicochemical interaction in the atmosphere (Prank et al. 2013). High humidity conditions can induce rupture of pollen grains and release of aeroallergens that are assumed to have longer residence in the air than pollen grains (Sofiev et al. 2013). Importantly, these models depend upon existence of a broad network of monitoring stations, of which there are at least 600 in Europe. Pollen emission data in SILAM relies on input from the extensive pollen production maps that cover the Europe continent (Sofiev 2017).

Further review of pollen transport modelling is available elsewhere. Efstathiou et al. (2011) has listed the pollen dispersion modelling studies that were investigated large-scale pollen emissions and long-range transport of pollen.

Makra et al. (2016) has summarised studies that observed the contribution of the highly allergenic ragweed pollen from the long-distant sources at a target monitoring site. Most of the studies were performed in Europe using the HYSPLIT and ACDEP pollen transport models and applying the single back-trajectory analysis. The same author, Makra et al. (2016), emphasized the need to use 3-D back-trajectory clustering, by grouping the single back-trajectories in order to facilitate pollen data interpretation, identification of potential sources areas and pollen transport patterns and increase data reliability.

In summary, knowing the pollen sources, bioaerosol concentration obtained from pollen monitoring sites, phenological data of the areas surrounding the pollen collection locations, contribution of non-local wind-pollinated species and patterns of distant pollen air masses (atmospheric transport, transformations and pollen removal from the air), meteorological data (temperature, relative humidity, rainfall, wind direction and wind speed) that drive pollen cycle stages (development, production, release, transport and removal processes), as well as the ecological sensitivity to climate variability are all essential parameters of a reliable pollen forecasting system.

The limitation of the pollen transport from rural production regions and forecasting airborne levels in urban environments in Australia is due to the lack of the above mentioned key variables that are essential to the models and sparse pollen monitoring locations. The spatial distribution of models relies on the number of the monitoring stations which is the major limitation in Australia. The representativeness of the existing monitored sites should be questioned. Currently collection points (the receptor site) for monitoring of grass pollen levels are limited to one or few urban sites of capital cities in eastern Australia. One of the approaches to overcome this deficiency is extrapolation of the findings for the pollen-related data at one site to the larger areas. This extrapolation of pollen aerobiology to overcome the restrictions of restricted *in situ* pollen monitoring may be achieved with remote sensing (Appendix IV; Devadas et al. (2016)). Satellite remote sensing in conjunction with phenocams provide opportunity to monitor land cover and vegetation phenology (including grass flowering and pollen release) (ARC Discovery, Appendix II) characterize the changes and sensitivity of the ecosystems to climate variability (Seddon et al. 2016). The challenge is to characterise the broad range of landscapes in Australia (observed by satellite-derived land cover) which effects concentrations, type and seasonality of airborne pollen (Devadas et al. 2016). Moreover, it is recognized that grasses are sensitive biome to changes in climate, landscape and species invasions (Ma et al. 2015; Susan Moran et al. 2014). Whilst a large proportion of the grass pollen loads in the case of Melbourne are generated by fodder crops in rural regions including the north west agricultural zones (de Morton et al. 2011), a further necessary piece of the predictive model is the transport of the airborne grass pollen from the rural source to collection points in the city. Pollen dispersion modelling can be based on combining the pollen emission from the source (e.g. grasses in rural Victoria) and pollen transport models. The key parts for the pollen forecasting should be considered including productivity of grass landcover, grassland phenology and pollen release, the meteorological data, atmospheric transformations that pollen grains can undergo and removal processes. The phenomenon of the long-scale pollen transport should not be neglected.

### Outcomes of the Australian Aerobiology Working Group

Pollen monitoring in Australia and New Zealand has occurred sporadically with inconsistent collection and counting methodologies and has been under-resourced (Beggs et al. 2015). Australia has a wide variety of landscapes which affect the abundance, species and seasonality of airborne pollens as well as patient sensitivities (Haberle et al. 2014; Nony et al. 2015; Davies et al. 2011). Starting in 2013, the Australian Aerobiology Working Group, which precedes the AusPollen partnership was sponsored by the Terrestrial Ecological Research Network (Australian Centre for Ecological Analysis and Synthesis. 2016) ([http://www.aceas.org.au/index.php?option=com\\_content&view=article&id=113](http://www.aceas.org.au/index.php?option=com_content&view=article&id=113)). Existing pollen count data records sourced from 17 sites in different regions of Australasia and three French comparator sites were synthesised and analysed (Davies et al. 2015b). Currently available pollen count data sets showed distinct regional and seasonal variability in airborne pollen levels.

The main Australian Aerobiology working group outcomes were;

1. Diverse species contribute to airborne pollen, consistent with the wide range of local ecologies and environmental conditions in Australia and New Zealand (Haberle et al. 2014).
2. A striking variation in the timing and level of airborne grass pollen is evident across years at each site and between cities (Beggs et al. (2015) (see Figure11).
3. Spatiotemporal variability in grass pollen season is related to latitude. Secondary grass pollen peaks observed in summer extend the duration of the grass pollen season and are likely to be due to subtropical grass species (Medek et al. 2016).
4. Innovative satellite remote sensing of land cover and greening of grass biomass shows a strong correspondence to grass pollen aerobiology and may be useful in modelling airborne grass pollen in Australian and overseas (French) sites (Devadas et al. (2016)(Appendix IV).
5. Collaborative trans-disciplinary research teams focused on aerobiology can influence policy and impact on human respiratory health and ecosystems research (Lynch et al. 2014; Davies et al. 2015a).

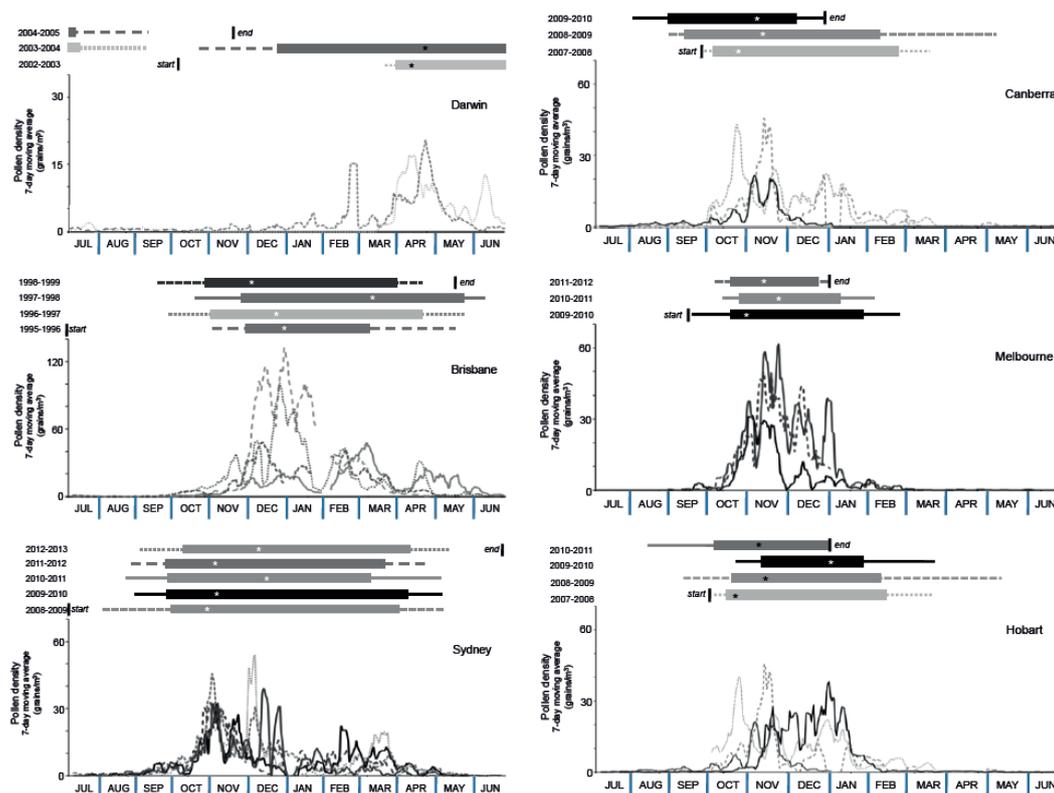


FIGURE 12: CALENDARS OF EXPOSURES FOR GRASS AND BY STATE

(Beggs et al. 2015)

### Other pollen monitoring research and services include:

AirRater program in Tasmania led by Australian Aerobiology participants (Associate Professor Fay Johnson) of which local pollen levels are to be included,

Wagga Wagga Asthma Collaborative lead by Charles Sturt University in partnership with the New South Wales Asthma Foundation (Dr Bruce Graham).

Deakin Airwatch (Assoc Prof Cenk Suphioglu) <https://www.deakin.edu.au/students/faculties/sebe/les-students/airwatch>

Adelaide Aerobiology Laboratory (Dr Allen Gale) supported by Asthma Foundation of South Australia

Notably, whilst grass pollen forecasts are seemingly available on a number of existing commercial websites, they are not based on actual pollen data and are inaccurate (unpublished analysis).

### Predicting thunderstorms associated with asthma

- Newson et al. (1998) observed that not all thunderstorms are associated with episodes of increased asthma and that meteorology and pollen data used in the study were not sufficient in providing reliable predictions.
- (D'Amato et al. 2016) suggested that wider range of meteorological parameters have to be included in models to accurately forecast TA episodes.
- Only one paper provides clear evidence for association of thunderstorm outflows with days with TA epidemics; Marks et al. (2001) reported a tenfold increase in thunderstorm outflows between days with TA and other days without thunderstorms from 3% of thunderstorms on controls days to 33% on case days. Whilst outflows are a factor increasing the likelihood of asthma epidemics on days with thunderstorm, the penetration of the effect was only 33% of thunderstorm on case days. Thus it would be necessary to consider outflows in a predictive model of TA but it may not be sufficient for prediction of whether particular days with thunderstorms would lead to asthma epidemics.
- Lightning activity also appears to be repeatedly linked with TA (see Question 3; Table 7). This factor should be incorporated into predictive models for TA.

It may be possible to predict bioaerosol concentrations 2h preceding the thunderstorm based on meteorological conditions and warn sensitive individuals about increasing abundance of airborne bioaerosols on days with storms (Grinn-Gofron et al. 2013).

Despite deficiencies in knowledge of which thunderstorms are likely to cause asthma epidemics on high pollen count days in Victoria, the risk to the population of individuals with hayfever and uncontrolled asthma who are allergic to grass pollen is sufficiently high that there may be some worth in integration pollen forecasting models with prediction of storms.

**Key messages**

Not all thunderstorms are associated with TA episodes.

Evidence that grass pollen is the major trigger for TA in Australia is strong (Table 8).

The key parts for pollen forecasting should include productivity of grass landcover, grassland phenology and pollen release, meteorological data, atmospheric transformations that pollen grains can undergo and delivery of pollen allergens to populated areas.

**Strength of evidence**

There is a growing body of evidence of the key parameters for forecasting of TA epidemics. However; more in-depth analysis is needed to identify all contributing factors and how they interact with each other in causation of TA events.

Evidence is building that phenology modelling and remote sensing of grassland coverage and productivity can address to an extent some of the limitations of current (receptor) sites for monitoring of grass pollen levels in Australia.

**Gaps in knowledge**

Identification of key meteorological factors associated with thunderstorms that significantly increase the risk of an occurrence of TA epidemics.

Methods for prediction of parameters of thunderstorm (e.g. outflows and lightning) in advance that are needed to establish operationally functional forecast systems.

Long term trends in pollen aerobiology over broad geographical areas and the capacity to robustly predict short-term, local airborne pollen levels.

**How to address these knowledge gaps**

The AusPollen Partnership pollen monitoring network is identifying and evaluating key factors for models and forecasting, however this is at a research stage and meteorological parameters have not been incorporated. Development of a functional prediction model for TA epidemics in Australia is out of the scope of the current project.

The AusPollen Partnership has demonstrated capacity to synthesise a strong evidence base for pollen aerobiology in Australia and has fostered inter-sector collaborations and knowledge transfer frameworks. Pollen monitoring in Australia is currently limited to a few sites in capital cities. Phenology monitoring and remote sensing offer an important capacity for inferring grass production and pollen aerobiology, models of pollen levels need to be informed by a broader representation of pollen collection site to validate the input data for pollen forecasts. Partnership with service providers including the Bureau of Meteorology may provide an opportunity to build capacity and develop an operational forecast system for grass pollen exposure and TA epidemics.

### Question 13.

**What early warning (or alert) systems have been developed (and by whom) that are specific to potential epidemic TA events?**

**Response:**

Previous research has attempted to predict outbreaks of TA, examining both pollen count and thunderstorm activity. Newson et al. (1998) identified asthma epidemic days as periods of exceptionally high asthma admissions, which were compared to asthma admission on other days with a log-linear autoregressive model. Their findings produced unfavourable results with respect to predicting asthma outbreaks using meteorological data and pollen count data. Most thunderstorms, even in periods of high grass pollen levels, were not followed by an epidemic. Furthermore, most epidemics were not associated with thunderstorms (Newson et al. 1998). Other unexamined or unexplained meteorological variables associated with thunderstorms must influence the causation of asthma, and will need to be identified prior to accurate modelling and implementation of early warning systems (D'Amato et al. 2016). The hypothesised multiple contributing co-cause nature of TA epidemics, should investigate the utility of including a wider range of bioaerosol and climatic variables as well as patient characteristics and social factors in developing an early warning systems (Dabrera et al. 2013).

Lewis et al. (2000) reported that ED asthma attendance had an association with increasing grass pollen counts during rainy periods of the grass pollen season. This was most apparent on days of light rainfall (adjusted rate ratio for  $\geq 50$  vs  $< 10$  grains/m<sup>3</sup> at lag 2 days = 2.1, 95% CI 1.4 to 3.3). However earlier work has reported no relationship between asthma admissions and rainfall ( $r=0.09$ ), with further no evidence of an interaction between rainfall and grass count, total pollen count or fungal spore counts in relation to asthma admissions (Anderson et al. 2001). The multiple ways in which rain exerts effects on airborne pollen levels is considered in question 3.

Most TA studies have not included extensive demographic or social measures, which could be essential in increasing accuracy in predicting TA outbreaks in an early warning model and identifying subgroups of the population at risk. Age has been considered only in a limited way, with stratification into broad age brackets. Furthermore, a number of studies have excluded younger and/or older patients, which appears to have been done so in an arbitrary fashion. Whilst there are reports of females being more affected by TA, there is insufficient evidence to determine a causal link between gender and TA (Wark et al. 2002; Feli et al. 2015). Other factors such as ethnicity and occupation have not been studied at all in the context of vulnerability to TA. While social variables such as the location of patients during the thunderstorm, and compliance with use of asthma medicine have been considered.

Whilst a number of TA sufferers report no previous history of asthma or no previous diagnosis of asthma, there appears to be consistent reporting that nearly all affected patients had a history of hayfever. An early warning system would require a robust method of including all individuals at risk, so that no susceptible individuals at risk miss out from the benefit of an early warning system (Dabrera et al. 2013). As such, practical application of an early warning system for TA would not readily be achieved with current practice and knowledge.

However, a number of networks and inter-sector partnerships, some well-established, provide specific information on aerobiological factors that are involved in triggering hayfever symptoms that may have utility in providing alerts targeting TA. The considerations for standardisation of counting and monitoring as well as the capacity to accurately forecast short-term pollen aerobiology will be provided here. The purpose of the pollen monitoring networks and their capacity to engage with the affected public will be described.

## Europe

European aeroallergen network (EAN), provides pollen and fungal spore data from over 600 sites across 38 European countries. Up to 226 different aerobiological particles are evaluated. This data is used models such as SILAM and COSMO-ART to create forecasts with visual maps of wind transport of pollen “clouds” across Europe. The EAN offers a mobile app, for which a three day forecast is available for Austria, Germany and Sweden. Additionally, the EAN offers a pollen diary; here people are able to report their symptoms and burden of disease. A comparison can then be made with the concentration of aeroallergens present to establish preventative measures. The RNSA integrates such information with physician reports and pollen counts to provide a pollen forecast. Such tools also provide insights into the exposure levels of pollen bioaerosols that are associated with inducing symptoms in affected individuals using a citizen science approach.

(European aeroallergen network.) <https://www.polleninfo.org/country-choose.html>

**United Kingdom** The National Pollen and Aerobiology Research Unit (University of Worcester), in partnership with the Met office produce and supply pollen forecasts for the UK. Daily forecasts are provided from mid-March until the end of September of each year. These forecasts are made accessible by the public through newspapers, radio, television and online websites. Key data for the generation of these forecasts include; pollen monitoring, weather forecasts, local vegetation, typography and previous history of biological and weather factors influence on pollen production (Buters et al. 2015).

The seasons for three key allergenic pollen types are covered at specific times of the year:

Tree pollen - late March to mid-May.

Grass pollen - mid-May to July.

Weed pollen - end of June to September

An additional monitoring of fungal spores associated with inducing allergic disease (*Alternaria*, *Aspergillus*, *Cladosporium*, *Didymella* and *Epicoccum*) is undertaken.

The UK office of Meteorology (Met office) provides an interactive online map to provide the public with pollen aerobiology across the UK. This is done through three key factors; Met office data, social activity and symptom data reported from pollen-allergic people. Notably, the pollen map indicates that the midlands region of the UK through to the southeast of the country has a very high average grass pollen count historically. We note that all of the epidemic TA events in the UK have occurred in this part of the country ("TA).

## Australia

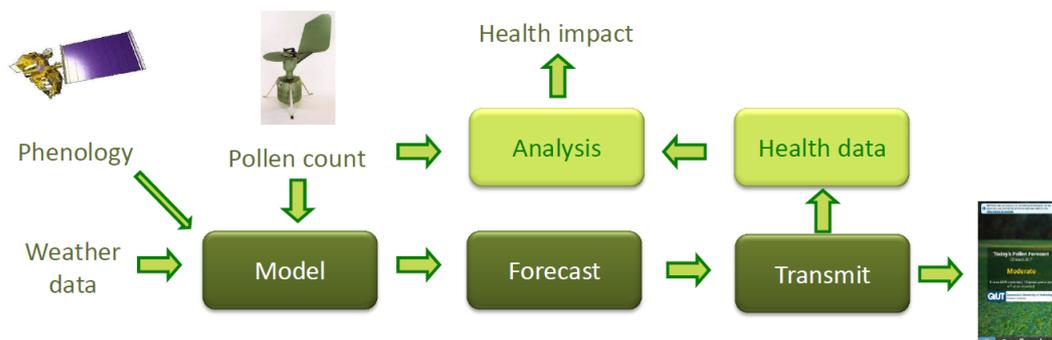
The AusPollen Partnership is establishing a standardized national pollen count network in Australia. The contributing partners include the peak professional body for clinical immunology and allergy; Australasian Society for Clinical Immunology and Allergy; the non-government organisation providing patient information; Asthma Australia, The Bureau of Meteorology, MeteoSwiss (Switzerland), Commonwealth Scientific and Industrial Research Organisation and Stallergenes Australia, who are all key stakeholders in care and education of allergy and asthma patients, and in the establishment of operational forecast systems for airborne pollen.

The aim of the AusPollen Partnership is to provide information on local grass pollen levels to both patients and health care professional initially across Australia’s major cities (Sydney, Melbourne, Brisbane and Canberra). The AusPollen Partnership uses a series of site-specific applications for mobile devices can be downloaded freely to directly provide pollen index to patients in the community (Appendix I). As a warning system the main outcomes will seek to help manage hayfever and asthma in the affected population and enable affected people to avoid exposure to pollen allergens. Education of asthma and hayfever trigger and therefore encourage effective use of prescription medication.

**AusPollen Partnership Project aims:**

1. Inform patients in the community of local grass pollen levels using a standardized pollen count network and smart phone app.
2. Evaluate the components needed to build an innovative validated grass pollen forecast system
3. Provide public stakeholders with education tools for managing respiratory health in people with pollen allergies and data for future health service planning and policy development.
4. Evaluate the short-term impact of the local pollen alerts on quality of life and how this empowers patients to better manage their own pollen allergy symptoms.

## AusPollen workflow



Whilst currently outside of the AusPollen partnership, pollen monitoring occurs at two additional sites in Melbourne (Deakin AirWatch), monitoring reporting total pollen levels occurs in Adelaide (Adelaide Aerobiology Laboratories sponsored by Asthma Foundation of South Australia), and a multifaceted and geographically broad short-term air quality project including pollen monitoring has been undertaken in Tasmania (AirRater).

### United States of America

The National Allergy Bureau (NAB) is a section of the peak professional body of clinical immunologists the American Academy of Allergy Asthma and immunology (AAAAI). The NAB reports on current airborne pollen and mould levels at 87 sites across the whole of USA and some parts of Canada and Argentina. For both pollens (tree, weed and grass) and moulds up to the top three species present at particular sites are included in reports. An interactive map is featured where people can find levels of pollen or/and mould; not present, low, moderate, high or very high. A mobile phone application is available with the same available information.

(American Academy of Allergy Asthma and Immunology.) <https://www.aaaai.org/global/nab-pollen-counts>

TABLE 13: COMPARISON OF POLLEN MONITORING AGENCIES ACROSS THE WORLD

	EAN	UK Met office	AusPollen	NAB
<b>Aeroallergens measured</b>	P, F	P, F	P	P, F
<b>Forecasting</b>	✓	✓	✓	✗
<b>Interactive map</b>	✓	✓	✗	✓
<b>Mobile app</b>	✓	✗	✓	✓
<b>Pollen diary</b>	✓	✓	✓	✓

P: Pollens, F: Fungal spores

### Considerations for standardized pollen monitoring in Australia

#### Instrumentation and collection sites

Difference in application of methods of pollen collection (Burkard (Hirst 1952) or Rotarod (Hirst 1952)), collection site location and trap height means that the pollen concentrations determined by a particular pollen count service are representative of pollen exposures for that site and may not be directly comparable to other pollen count services or sites (Haberle et al. 2014; Davies et al. 2015a). How a given pollen monitoring service represents exposure of the population over a broad geographical area and individual exposure levels are not well understood (Katelaris et al. 2004; Rieux et al. 2008). The applicability and comparability of pollen monitoring can be enhanced by standardisation of instrumentation, collection site characteristics and counting methodology. The current standard for Asia Pacific was developed by an expert working party under the auspice of the WAO (Hasnain et al. 2007). However there is room for considerable flexibility in the collection and count methods within this standard procedure. One of the reasons for provision for flexibility of site locations include necessary local site considerations; convenient access, safe access, vicinity to laboratory and power availability to the trap are often the key factors in choice of collection site.

#### Training in aerobiology and count techniques

Training on pollen counting procedures is available from European Academy of Allergy and Clinical Immunology and the European Aerobiology Network who run basic and advanced pollen monitoring schools. Similarly, training and certification of counters is provided by the US National Allergy Bureau. Members of The AusPollen team have participated in European Aerobiology Network and US National Allergy Bureau pollen aerobiology training and certification.

#### Validation, quality control and certification

In Australia, pollen monitoring (AusPollen) sites adhere to the WAO Standard for Asia Pacific (Hasnain et al. 2007). Specific national standards for pollen monitoring and counting techniques have not been applied but the process of establishing and implementing standards for pollen collection and counting including site and counter validation studies (Galan et al. 2014; Oteros, Galan, et al. 2013) are integral objectives of the current NHMRC AusPollen Partnership and will commence this year. The count validation studies are scheduled for the agenda for June 1-3, 2017. Minimum requirements for counting and reporting cover parameters including collection, staining, magnification and area of the slide (Galan et al. 2014; Oteros, Galan, et al. 2013). Variability across the network and between sites will be evaluated and monitored.

### Future automation and real-time monitoring capabilities

Automated real-time pollen monitor prototypes based on a variety of technologies are under development (Oteros et al. 2015; O'Connor et al. 2013). There are no systems currently in production and the available prototypes are expensive, have low accuracy at low pollen concentrations and may not function well in Australian environmental conditions. However, if such devices were evaluated, appropriately adapted to Australian conditions, then these capabilities could complement and validate remote sensing data and a central manual pollen count site to provide a wider ground-truthing of grass pollen levels across Australia and contribute to a broad pollen aerobiology data network. AusPollen will be trialing the Plair automated pollen (Crouzy et al. 2016) count instrument (Meteorology Switzerland) as part of its research program. Automated pollen-monitoring devices need to be robust for our environment, produced by a company with a sustainable business model capable of providing long-term technical support and software upgrades and sensitive and specific for grass pollen at concentrations that occur in Australia.

#### Key messages

No specific alert systems exist for TA but networks exist internationally to alert populations of variations in pollen levels which are a precursor to TA.

The AusPollen Partnership is building a framework for a national standardized pollen monitoring network with tools for disseminating the pollen information directly to patients and interested people in the community, engagement with key stakeholders to facilitate knowledge transfer and generation of education materials. Through partnerships there is additional capacity to generate components of pollen forecast system. However, development of an operational TA prediction model is beyond the current scope.

#### Strength of evidence

Few studies have evaluated the public health benefits of providing pollen information to participants.

#### Gaps in knowledge and capability

Collaboration between agencies who contribute to air quality monitoring, including monitoring of airborne allergenic bioaerosols, the Bureau of Meteorology and academic institutes with expert knowledge of pollen allergy and pollen aerobiology.

Geographically broad capacity and distribution of standardized and validated pollen monitoring services.

Operational, evidenced-based forecasting systems to inform public health warnings and TA alerts a TA alert system to directly notify hospital emergency departments, ambulance services, pharmacies and primary healthcare networks of an impending risk TA event.

### Question 14.

**What public health messaging specific to TA has been used in the past? Was the messaging evaluated?**

**Response:**

This literature search revealed little published information on public health messaging and alerts for TA in the management of TA. A number of studies considered the capacity to predict TA events based on current knowledge, but considered the level of false positive alerts would be unacceptably high (Marks et al., 2001; Newson et al., 1998). Marks et al. (2001) concluded that “the low specificity of predicting thunderstorms with outflows” was the main limitation to prediction of TA. Newson et al., (1998) concluded that whilst pressure, humidity and wind gusts were not useful in predicting TA events, the strongest risk factor high grass pollen and thunderstorms still only predicted “a small minority of TA epidemics”.

In a systematic review by Dabrera et al. (2013), which considered 35 publications on TA, a number of public health recommendations for the UK were made:

- Asthma patients sensitive to known thunderstorm related aeroallergens may be advised to shelter indoors and close windows;
- Asthma patients should have easy access to their prescribed asthma medications such as inhalers; Health professionals’ advice to these patients about how to deal with acute asthma following thunderstorms, should follow national guidelines for Asthma;
- A proportion of TA patients will never have suffered acute asthma before; health services must therefore be prepared for increased asthma-related presentations; and
- Acute health services should be made aware of the possibility of TA and consider including excess acute asthma episodes within their business continuity plans.

Whilst the academic literature does not contain sufficient information on public health messaging and its evaluation, a number of peak professional respiratory and allergy organisations and non-government organisations that provide support to asthma patients provide advice on minimizing risk of TA and recommendations for managing allergic rhinitis and allergic asthma that are relevant.

The following peak professional bodies provide information to patients and carers to assist with self- and clinical-management of hayfever and asthma in general but not specifically in relation to TA.

Asthma Australia and ASCIA updated their patient and carer information sheets on TA in December 2016 based on published evidence and expert knowledge.

Appendix X (Australasian Society of Clinical Immunology and Allergy. 2016) [https://www.allergy.org.au/images/pcc/ASCIA\\_PCC\\_Thunderstorm\\_asthma\\_Dec2016.pdf](https://www.allergy.org.au/images/pcc/ASCIA_PCC_Thunderstorm_asthma_Dec2016.pdf), (Asthma Australia. 2016) <https://www.asthmaaustralia.org.au/nsw/about-asthma/manage-your-asthma/triggers/asthma-and-thunderstorms>

British Society of Allergy and Clinical Immunology devised guidelines displayed at pharmacy counters. Allergen avoidance—Hayfever sufferers can take basic measures to avoid exposure to allergens (Parikh et al. 1997).

- Listen to pollen forecast and plan day accordingly
- Avoid cutting grass, picnics, camping
- If out in countryside, shower and wash hair on return
- Wear wrap-around sunglasses when outside
- Before evening (when pollen descends as air cools), bring in washing, close bedroom windows
- Keep car windows closed, and consider buying an air filter for the car
- Avoid smoking and other irritants such as fresh paint
- Avoid other allergens that affect you.

The Asthma and Allergy Foundation of America recommends “**If your asthma symptoms are caused by allergies, take steps to control known or potential triggers in your environment**”. (<http://asthmaandallergies.org/asthma-allergies/adult-onset-asthma/>)

- Allergy-proof your house for dust, mould, cockroaches, and other common indoor allergens to which you are allergic.
- Reduce your outdoor activities when the pollen count or ozone level is high.
- Choose foods that don’t contribute to your asthma or allergy symptoms.
- Evaluate your workplace for possible allergens and take the necessary steps to reduce your exposure to them.
- In order to determine relevant triggers, you may want to seek consultation with an allergist who can further define these triggers.
- In addition, anyone with asthma should consider getting an annual flu shot. Older adults also should talk with their internist about getting a pneumonia vaccination.”

This Foundation provides more extensive advice for those with ragweed pollen allergy. This advice also refers to steps patients can take to minimise pollen exposure and control asthma if symptoms are triggered by ragweed pollen exposure. However the advice may be pertinent to patients with allergies triggered by exposure to grass pollen in Australia since grass pollen is a dominant aeroallergen making up between 18-23% of total pollen in the air in Victoria and NSW (Ong et al. 1995; Bass et al. 1997).

- **Track the pollen “count” for your area.** The news media often report the pollen levels, especially when high. Check your local newspaper or call the weather information telephone number for your area.
- **Where to find the pollen count.** The National Allergy Bureau™ (NAB™) is the section of the American Academy of Allergy, Asthma, and Immunology’s (AAAAI) Aeroallergen Network that is responsible for reporting current pollen levels to physicians and the public. (American Academy of Allergy Asthma and Immunology.) <http://www.aaaai.org/nab/index.cfm?p=default>
- **Emphasize activities in centrally air-conditioned spaces.** Window units set on “recirculate” or “vent closed” also can help. Various filter units and devices producing ultraviolet (UV) light and ions have unproven value.
- **Keep the pollen off!** Keep windows closed so the pollen cannot easily enter your house or car. Use dryers instead of outside line drying for laundry. Remove outer clothing before entering the house if you’ve been working or playing outside during the pollen season. Take a shower after being outside to remove pollen that collects on your hair and skin.
- **Stay indoors.** Airborne pollen tends to peak between the hours of 10:00 a.m. and 4:00 p.m. Try to take care of outdoor activity when the pollen levels are not at their peak.
- **Get away from high pollen levels.** People living in the eastern and midwestern United States—where ragweed thrives—may get significant relief by going west to the Rocky Mountains and beyond during the peak ragweed season. Traveling abroad in late summer also can greatly reduce your exposure. Be sure to check the areas where you might travel to make sure ragweed is not a problem there as well (parts of central/eastern Europe have a late summer ragweed season.)
- **Should you make a permanent move?** People with severe nasal allergy and asthma symptoms due to ragweed may consider living in a place with less ragweed. Generally the west coast of the U.S. offers the lowest exposures. Although this approach often helps people feel better, these individuals are prone to develop allergies to plants in the new location. What’s a better solution? Develop a well thought out treatment plan to manage your allergies and asthma year-round.
- **Take antihistamines.** These medicines often work well to control symptoms of allergic rhinitis (such as hayfever), regardless of what causes those symptoms. The drowsiness caused by products in the past is less of a problem with antihistamines now on the market. Anti-inflammatory nose sprays also can help and usually have few side effects. Similar medicines, specifically for the eyes, can reduce ocular symptoms. Antihistamines are available without a prescription (over-the-counter) as well as in forms which do not cause drowsiness and are somewhat stronger with a prescription from your physician.

- **Nasal steroid sprays are more effective than antihistamines.** They work best if started before or at the beginning of the season and if they are used every day.
- **Use quick relief or long acting medicines for asthma symptoms.** Ragweed pollen also may trigger various symptoms of asthma, such as cough, wheezing, tightness in the chest or difficulty breathing. Your physician can prescribe medicines that provide immediate relief as well as for long-term control.
- **Consider getting allergy shots.** Also known as immunotherapy, this form of treatment can reduce your allergic response to specific allergens. In order for allergy shots to work, the allergens must be carefully identified with allergy testing. Allergy shots generally are taken over the course of several years, and it can take several months, or even one to two years, to see the full benefit. With proper materials and dosage, you may see major improvements in your symptoms.

(<http://asthmaandallergies.org/asthma-allergies/adult-onset-asthma/>)

The National Asthma Handbook advises in relation to “Allergies as a trigger” that “*Exposure to pollen can worsen asthma symptoms during the pollen seasons. Pollen counts are generally highest on calm, hot, sunny days in spring, early summer or during the dry season in tropical regions.*” <http://www.astmahandbook.org.au/clinical-issues/triggers/avoidable-triggers>

Advice to those at risk to stay indoors “with the windows closed” (D’Amato et al. 2016) when a thunderstorm warning is issued in springtime or on days with a high pollen count is based on observations from thunderstorm epidemics from UK and Australia.

- In Iran after an asthma epidemic affected patients recalled during a questionnaire administered 20 days after a TA episode that they were outdoors before the storm and onset of symptoms (Forouzan et al. 2014).
- Wardman et al., (2002) reported that 59% of patients who experienced TA, were outside during the storm.
- Girgis et al., found that individuals who reported being outside or inside with open windows during the thunderstorm were twice as likely to experience symptoms (Girgis et al. 2000).

Girgis et al. also advised “use of inhaled steroids during spring” for “individuals with history of asthma (wheezers and sneezers) who live in affected areas affected by spring thunderstorms”.

### Outdoor allergen indoors

A confounding influence may be high levels of grass pollen inside the home. Dust sampled within the homes of patients who experienced springtime epidemic of asthma in California had high levels of ryegrass pollen allergen; house dust of homes of 15 patients with springtime asthma with high levels of ryegrass pollen-specific IgE (mostly > 200 units = 20 ng IgE per milliliter) were found to have greater than 10 micrograms of grass pollen allergen (Lol p 1) per gram of dust when sampled within two weeks of ED visit for asthma (Pollart et al. 1988). We are not aware of research measuring the increase in indoor concentrations of grass pollen allergen during springtime thunderstorms or the influence of closing window and doors on indoor allergen content. However, it is plausible to suggest that indoor exposure to outdoor allergen sources would be minimized if outdoor air sources were excluded by keeping doors and windows closed and even by using air conditioners with filters capably or removing pollen particles. A further study of indoor concentrations of pollen and mould spores in Houston found that whilst indoor concentrations of these outdoor allergen sources inside homes were markedly lower than outdoor concentrations, there was considerable variability between homes and indoor values were not correlated with outdoor pollen and spore levels (Stock et al. 1988). A specific search of literature on allergen monitoring may provide further insights.

A recent randomized controlled trial in the setting of south east England, UK general practice involving 20 services showed that tailoring allergen avoidance recommendation to individual children’s SPT compared to usual care resulted in improved rhinitis symptom outcomes (MD -3.14, CI -0.8 to -6.01) and quality of life scores (MD -0.50; CI 0.32-0.68) whilst no significant changes in asthma symptoms, healthcare utilisation or normal activity were observed between groups (Smith et al. 2016). Whilst examples of allergen avoidance were provided; removal of pets from the home,

methods of allergen avoidance were not elaborated on in this publication but those articulated in advice from peak professional bodies (e.g. those listed above) are commonly used. Platts-Mills showed that for adults with house dust mite allergy, prolonged allergen avoidance in a controlled environment reversed bronchial hyperactivity (Platts-Mills et al. 1982). Early controlled trial of dust free bedrooms of asthmatic children indicated that allergen avoidance is beneficial in the context of house dust mite allergy (Murray et al. 1983). Further descriptive studies in adults indicated that allergy testing in non-specialist clinics enabled appropriate allergen avoidance messages. (Sibbald et al. 1997) investigated the potential of SPT in general practice to identify and direct health messaging about allergen avoidance to the specificity of patient’s allergic sensitivities; if messaging was targeted to those with allergic sensitivities planned interventions would have been reduced from 305 to 142 after SPT. However, more recent pragmatic randomized controlled trials for allergy assessments in adults with asthma and rhinitis did not show significant improvements in symptoms and outcomes (Smith et al. 2015). With respect to pollen allergy avoidance the use of nasal filters have been shown to be an effective method of minimizing allergen access to the nose and resulted in significant benefits to patients with reduced symptoms during the pollen season (O’Meara et al. 2005).

It should be noted that the efficacy of allergen avoidance and the ability to implement allergen avoidance effectively remain controversial (Smith et al. 2015).

Of note with respect to avoidance of pollen allergen, the messaging regarding time of day of peak exposure is not clear and should be further considered. It will depend on the timing of release of pollen and the transport of the pollen from rural to the urban areas (see Question 12).

The extensive networks of pollen monitoring elsewhere globally in countries with high burdens of allergic respiratory disease provides a weight of circumstantial evidence for the value in providing hayfever and asthma patients with pollen indexes (see Question 13). Various new methods based on smart phone applications for disseminating pollen information for the use of patients are under development (Bousquet et al. 2015). Remarkably, few studies have been undertaken to demonstrate the utility and public health benefit of the intervention of providing local current pollen information (Guillam et al. 2010).

**(USA) National Heart Lung and Blood Institute Expert Review Report 3 (2007)**

Asthma Expert Panel Report 3 for the diagnosis and management of Asthma: Section 3: Control of Environmental factors and co-morbid conditions that affect asthma. National Heart, Lung and Blood Institute, 2007. Available from: <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report> (McCarter 2008).

The pathway for stepped escalation of asthma management to achieve control states;

- **“Precipitating and/or aggravating factors of asthma** include viral respiratory infections and environmental allergens, indoor (e.g., mold, house-dust mite, cockroach, animal dander or secretory products) and **outdoor (e.g., pollen)**
- Evidence B for **single allergen sensitisation** to house dust mite, animal dander, mould, cockroach and **pollen**; evidence is strongest for allergen specific immunotherapy with single allergens. The influence of allergy on asthma is stronger in children than adults.
- Consider seasonal periods of daily long-term control therapy for patients who have asthma symptoms only in relation to certain seasons (e.g., **seasonal pollens**, allergens, or viral respiratory infections) and who have intermittent asthma the rest of the year. This approach has not been rigorously evaluated; close monitoring for 2–6 weeks after therapy is discontinued is essential to assure sustained asthma control.
- **Check the air quality index** and try not to work or play hard outside when the air pollution or **pollen levels (if you are allergic to the pollen) are high.**
- If possible, **stay indoors with windows closed during the midday and afternoon, if you can. Pollen and some mould spore counts are highest at that time.”**

**Medication use**

Australian asthmatics exhibit poor adherence to prescribed disease modifying medications including inhaled corticosteroids (Reddel et al. 2015). The age group commonly reported to be affected by TA 15-34 year olds as this age group represents the lowest number of ICS inhaler medications are dispensed in Australia (Correll et al. 2015).

In earlier studies many patients affected by TA were not using ICS (Girgis et al. 2000; Bellomo et al. 1992; Wardman et al. 2002). This may be because i) they were patients with rhinitis (hayfever) and did not know they had asthma (no diagnosis of asthma) or ii) they had a history or diagnosis of asthma but had less severe asthma or intermittent asthma for which ICS were considered unnecessary, or iii) they were asthmatics who failed to comply with prescribed use of ICS and were rendered more susceptible to asthma symptoms during the TA event than known asthmatics who used preventative ICS (well controlled asthma). In the study of TA event NSW, patients with asthma on case days were less likely than asthma patients of control days without thunderstorms to be using inhaled corticosteroids (OR 0.43, 95% CI 0.22 – 0.87). Those affected by asthma on case days compared to control days appeared to have less severe disease with significantly fewer recent doctor visit ( $p = 0.001$ ), fewer recent hospital visit ( $p = 0.002$ ), less sleep disturbance ( $p = 0.001$ ) and lower impact on activity ( $p = 0.001$ ) and work ( $p = 0.001$ ) (Girgis et al. 2000). Although it's difficult to determine cause and effect, those most affected on case days with thunderstorms may have had less perceived need for prescription of inhaled corticosteroids due to lower disease severity (Girgis et al. 1999).

The benefit or harm of prescribing preventative therapy for lower airway disease in patients with allergic rhinitis due to grass pollen allergy who may be at risk of TA during the pollen season needs to be carefully considered.

### Public Health messaging

In the Wagga Wagga event, those affected with asthma on case days were also less likely than controls to have an asthma action plan (OR 0.33, 95% CI 0.16 - 0.67; Girgis et al. 2000). Whilst there was not a significant difference between patients with asthma on case and control days, both groups showed low use of the asthma management plans. This highlights the need for more specific health messaging focused on asthma education and quality use of medications. The Charles Sturt University lead by Dr Bruce Graham in partnership with the Murrumbidgee and Southern NSW Local Health District and Asthma Australia have established an excellent local messaging system for alerting health services and providing patients with pollen information ([www.csu.edu.au/asthma](http://www.csu.edu.au/asthma)) which includes an Asthma Register, TA alert and text messaging service.

In regards to inhaled corticosteroid use for those patients with allergic rhinitis at risk of TA, use of budesonide can provide systemic and local nasal effects including reduction of eosinophils in patients with allergic rhinitis (Greiff et al. 1998).

### Minimisation of TA risk through use of allergen specific to immunotherapy

Minimisation of the risks and impact of TA may be achieved by implementation of public health messaging, patient education, quality use of asthma preventative medication, as well as by enhancing clinical management of individuals at risk of TA. Management of rhinitis can ameliorate symptoms of asthma in patients with seasonal allergies (Scadding 1997), providing an opportunity for medical intervention to reduce individual susceptibility to TA. Evidence for the benefit of allergen-specific immunotherapy for treatment of children and adults with allergic rhinitis and or asthma is substantial (reviewed in question 11).

The Australian Society for Clinical Immunology and Allergy Guidelines on immunotherapy (2014) state:

- “Allergen immunotherapy is often recommended for treatment of allergic rhinitis (hayfever) due to pollen or dust mite allergy (and sometimes asthma) when: symptoms are severe
- the cause is difficult to avoid (such as grass pollen)
- medications don't help or cause adverse side effects
- people prefer to avoid medications”

(<https://www.allergy.org.au/patients/allergy-treatment/immunotherapy?highlight=WyJpbW11bm90aGVyYXB5liwiZm9yIiwiaW1tdW5vdGhlcmFweSBmb3liXQ=>)

Currently as few as approximately 200 clinical immunology physicians are actively practicing in Australia which is insufficient to meet the current and grow needs of our population for specialist allergy care (ASCIA et al. 2015). Future workforce planning and training is needed to ensure there is access for patients to suitably trained physicians who can assist with management of grass pollen allergy in patients with allergic rhinitis and in particular those patients who are

at risk of experiencing asthma upon exposure to high concentrations of grass pollen in the air. Notably, it is recommended that initiation of allergen-specific immunotherapy should be managed by allergy specialists.

#### **Key messages**

There is little published information directly focusing on public health messaging for reducing the risk and impact of TA. Targeting allergen avoidance advice to those with known sensitivity may improve the benefit of the intervention.

Identifying those at risk of TA exacerbations is likely to help direct messaging to those in need at the appropriate time during the pollen season.

Management of upper airway disease (hayfever) would improve asthma control and limit susceptibility to TA exacerbation.

Further education is needed to encourage quality use of medication and adherence to asthma management plans.

Allergen-specific immunotherapy for grass pollen in sensitized at risk patients is likely to provide benefits.

#### **Strength of evidence**

A body of evidence indicates that control of rhinitis through medication and immunotherapy would be beneficial.

The evidence that effective grass pollen allergen avoidance can be achieved and provide real protection from TA epidemics is less clear.

#### **Gaps in knowledge**

Broad-based, multifaceted and consistent public health messaging strategy for protection against pollen allergy, including pollen-induced asthma.

Integrated education resource package for allergy, respiratory and emergency medicine physicians, general practitioners, pharmacists, carers and patients to increase awareness of the triggers, symptoms and management of hayfever and asthma in general, particularly during the grass pollen season when the risk of TA is high.

Model for shared care by respiratory and immunology physicians of patients with grass pollen allergies with symptoms of hayfever and allergic asthma exacerbated by pollen exposure.

Sufficient workforce of clinical immunologists available and practicing to meet the growing needs of allergy patients in Australia.

## DISCUSSION AND CONCLUSIONS

The November 2016 event was the most extreme TA epidemic experienced in Australia or elsewhere. Nine people are reported to have died due to this TA epidemic and emergency medical services were unexpectedly strained. This report reviews the published literature on TA events and notes the variations in level of evidence for the conditions contributing to the phenomenon. The reviewed evidence is considered against the framework of the current hypothesis proposed by key opinion leaders.

The evidence from published literature indicated that susceptibility of individuals to TA can be identified by a clinical history of rhinitis, sensitivity to the triggering airborne allergen and exposure to the high pollen levels in the air (associated with the peak ryegrass season in Australia) at the time of arrival of the thunderstorm. The TA phenomenon is described by a combination of thunderstorm activity (including lightning and high wind gusts or outflows), which collect pollen, concentrate it in the air and then deliver allergen particles in downdrafts over populated areas to where it can do most damage to the vulnerable people. This proposed mechanism remains unchallenged in the literature although it has only been clearly exemplified in the context of TA in one Australian investigation and nowhere else. Tables 14 and 15 summarise the cases for each line of evidence for the proposed mechanisms of D’Amato et al. (2016) and Marks and Bush (2007).

**TABLE 14: EVALUATION OF D’AMATO ET AL. (2016) EVIDENCED-BASED COMPONENT CAUSES**

Lines of evidence	Confirmation of evidence
1. There is a close temporal association between the start of the thunderstorm and the onset of asthma epidemics	<ul style="list-style-type: none"> <li>Thunderstorms within 80km occur on 31% of case days with TA.</li> <li>Other UK and US longitudinal studies show that thunderstorm are not evident during all asthma epidemics; thunderstorms alone are insufficient to cause asthma epidemics.</li> </ul>
2. Asthma epidemics related to thunderstorms are limited to pollen (and outdoor mould) seasons	<ul style="list-style-type: none"> <li>Australian TA epidemic events all occurred in spring when grass pollen in the air was at high to extreme levels.</li> <li>TA epidemics elsewhere occurred in spring or summer coinciding with airborne allergen exposure.</li> </ul>
3. There are not high levels of gaseous and particulate components of air pollution during thunderstorm-related asthma outbreaks	<ul style="list-style-type: none"> <li>Elevated ozone (and NO<sub>2</sub>) have been associated with thunderstorms but not with asthma admissions. The lack of influence of air quality factors on TA epidemics in Australia needs confirmation.</li> </ul>
4. Subjects with pollen allergy who stay indoors with the window closed during thunderstorms are not involved	<ul style="list-style-type: none"> <li>Protection from being inside with windows closed reported but this evidence is dependent on patient recall at later date.</li> <li>Detection of outdoor grass pollen allergen inside homes can be high in spring time; being inside may not be a sufficient precaution against TA.</li> </ul>
5. There is a major risk for subjects who are not receiving antiasthma treatment but subjects with allergic rhinitis and without previous asthma can experience severe bronchoconstriction	<ul style="list-style-type: none"> <li>Most affected patients in Australia and elsewhere not taking inhaled corticosteroids, regardless of asthma diagnosis.</li> <li>Those diagnosed only with hayfever would not have prescription for asthma preventer.</li> <li>Those with asthma may have mild or intermittent disease and without prescribed preventer. There appears to be poor adherence to prescribed medication use amongst asthmatics.</li> </ul>
6. Non-allergic subjects are not involved in thunderstorm-related asthma	<ul style="list-style-type: none"> <li>Not all studies assessed sensitivity to suspected allergens but those that did showed high frequency of SPT or sp IgE to the airborne allergen present before thunderstorm (grass pollen and/or mould spores).</li> <li>Control subjects were mostly asthmatics presenting on non-thunderstorm days; non-asthmatic controls from the same population have not been included.</li> </ul>

**TABLE 15: EVALUATION OF MARKS AND BUSH (2007) EVIDENCED-BASED COMPONENT CAUSES**

Lines of evidence	Confirmation of evidence
A key hypothesis discussed in the literature is that thunderstorms occurring during the spring/summer growing season, concentrate pollen grains at ground level which rupture due to osmotic shock and release fine (i.e. respirable) allergenic particles or aeroallergens into the atmosphere	<ul style="list-style-type: none"> <li>• Shown in Australia; TA occurs with high-extreme levels of grass pollen in air.</li> <li>• Mechanism for pollen grain rupture could be due to osmotic shock, electrical or mechanical fragmentation (the latter described for mould spores).</li> <li>• Wind transport of pollen bioaerosols from rural sources to populated urban centres have not been modelled in Australia.</li> </ul>
During the first 20 to 30 minutes of a spring/summer thunderstorm, people with diagnosed asthma and those who have not previously experienced asthma symptoms but have a history of hayfever (i.e. allergic rhinitis) and atopy can experience asthma symptoms.	<ul style="list-style-type: none"> <li>• Insufficient evidence in Australia for the close temporal relationship between thunderstorm onset and symptom onset.</li> <li>• Venables (1994) increased number of calls (hayfever with breathlessness) within 20 minutes.</li> <li>• IGEM thunderstorm passing and emergency calls commenced at 5pm Nov 21 tracking with the arrival of the thunderstorm Melbourne vicinity between 3.30 and 5pm; may depend on context (storm size/geographical area affected/ population density).</li> </ul>
These susceptible groups inhale allergenic materials such as fine starch particles from ryegrass pollen, other micronic pollen fragments or starch granules, or other aeroallergens that are small enough to bypass the nose and throat, and penetrate into the lungs and induce irritation and an allergic inflammation with asthma symptoms that are often severe.	<ul style="list-style-type: none"> <li>• True for Australia;               <ul style="list-style-type: none"> <li>➢ ruptured pollen on exposed microscope slides,</li> <li>➢ patient sensitivity with grass pollen and with ruptured pollen starch granules containing allergen,</li> <li>➢ experimental airway challenge with ruptured pollen starch granules elicited airway inflammation.</li> </ul> </li> </ul>
Epidemic TA events described in Melbourne have almost always occurred in November (peak of spring).	<ul style="list-style-type: none"> <li>• True</li> </ul>

**Limitations of the review**

The required scope of this rapid literature review was extensive and broad. The full extent of information within the grey literature sources, for instance doctoral theses, were not incorporated because the review retained focus on published scientific literature sources. Thousands of publications were identified for each theme via search strategy 1. Adoption of an alternative more focused search strategy was required. Where indicated, responses to some questions present key messages (for examples Questions 4 and 10) from the literature but do not draw on the full extent of academic publications.

To address the fourteen questions within the required scope of the report, there was a need to source and assimilate information from a broad range of article types that assessed different factors contributing to the occurrence of TA epidemics. This limitation was addressed by a multidisciplinary team with capacity to process information on TA from different disciplines relevant to the key themes; meteorological and environmental factors, exposure and bioaerosol triggers, and individual susceptibility factors.

Given the multifactorial nature of TA and the sporadic timing of TA episodes diverse study designs; case-control, case-series, and descriptive, were included in the review to address the scope of questions posed by the Department. This diversity of study design and the time constraints, prevented use of a prescriptive systemic approach to evaluation of findings, strength and weight of evidence in each study.

### Unique aspects of this review

Whilst only 22 TA events have been reported globally and described in 60 primary research articles, commentaries including 42 review articles on the topic are extensive. However, no previous review has collated descriptions and data presented on all TA events globally or considered with such a broad scope aspects of causality, impact and mitigation options. The approach of employing a multidisciplinary team to analyse and synthesise the reported information on TA events is unique. Such an approach has the advantage of allowing a comprehensive review of the complexity of causation and impact of TA. Moreover, whilst Australia has the highest number per nation of TA events previous reviews have not focused the Australian experiences.

### Assumptions that have been challenged

The outcomes of the review challenge the extent and level of evidence available to support the lead theory for TA. The review highlights the lack of clarity on the complexity of meteorological factors associated with TA events. Whilst there is one strong case-control report with evidence for an association between thunderstorm outflows and epidemic days with increased asthma, this type of study has not been replicated in Australia or elsewhere. Notably, the effect size of thunderstorms with outflows on asthma epidemics in that study was incomplete; 33% of days with epidemic levels of asthma presentations (Marks et al., 2001). Whilst other descriptive studies lend support to this hypothesis (Venables et al., 1997; Grundstein et al., 2008), other time series studies do not (Newson et al., 1998). Moreover, this review indicates that other environmental and meteorological factors such as high level of thunderstorm associated lightning (sferics) that interact with the effect of thunderstorm outflows may modify the influence of thunderstorms on asthma presentations, have not been consistently identified.

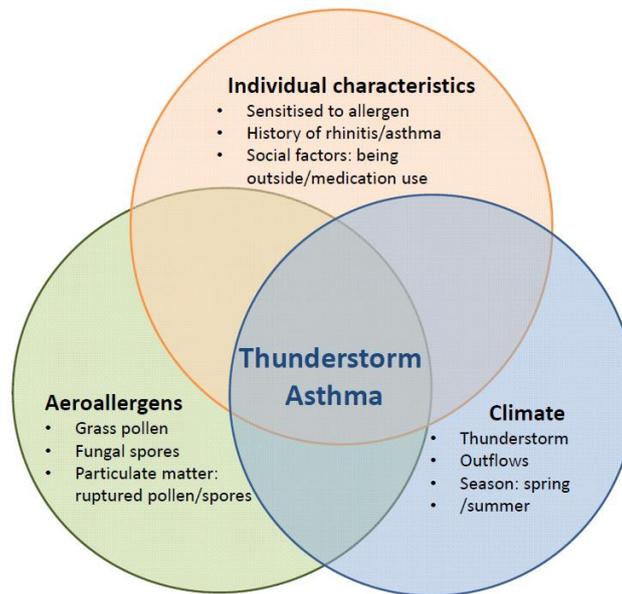
### New understandings

This review provides a model based on synthesis of meteorological, environmental and individual susceptibility factors into a component cause framework where one or more of each of these types of factors is necessary but not individually sufficient for the development of epidemic levels of TA (Figure 3, repeated below). Depending on geographical location, environment and timing, separate circumstances and combinations of factors may conspire to induce TA in susceptible individuals by involvement of particular i) meteorological factors; outflows and/or sferics; ii) high level exposure to allergen sources (specific pollen/spore type), and iii) of patients susceptible to TA (history of hayfever; uncontrolled asthma/undiagnosed asthma with allergy to triggering allergen; being outside). Presence of multiple factors within each category may amplify additively or synergistically the likelihood and/or severity of TA. In temperate regions of Australia, spring time thunderstorms with outflows (and sferics), during the peak of grass pollen season, in a particularly “bad” grass pollen seasons, occurring after multiple (consecutive) days of high to extreme grass pollen levels, may tend to characterize the meteorological and environmental circumstances converging to lead to TA epidemics.

This review provides deeper insights to patient susceptibility factors (Questions 8 and 9), highlighting large gaps in current knowledge in Australia and elsewhere of the demographics (particularly relating to age and gender and disease comorbidities), as well as patterns and levels of allergic sensitivity to grass pollen allergens and the influence of genetic polymorphisms on susceptibility to TA. Further research is proposed to identify characteristics of those patients at highest risk of TA who may be candidates for preventative therapy, better education on medication use and self-managed responses to TA (use of asthma action plans).

As well as considerations for development, implementation and evaluation of targeted public health messages for managing acute epidemics of TA, this review considers other approaches for understanding, predicting and preventing TA. In particular, the review highlights the dissociation between research, understanding and clinical management of asthma primarily by respiratory physicians, and hayfever by clinical immunologists, and the need for developing knowledge transfer between these communities of practice that provide care for patients with asthma and/or hayfever. The review addresses approaches for clinical management of hayfever including citation of meta-analysis of the efficacy of allergen-specific immunotherapy and considerations for medication use for asthma control in patients with hayfever.

There is also a call for partnership and inter-sector engagement to develop capabilities for monitoring and forecasting grass pollen exposure and predicting thunderstorms with features associated with TA events.



**FIGURE 13: THREE TYPES OF CONTRIBUTING CONDITIONS FOR CAUSATION OF THUNDERSTORM ASTHMA.**

The conditions contributing to the development of thunderstorm asthma epidemics have been identified through this review process and grouped into related factors; individual characters conferring vulnerability to TA, weather factors grouped under climate, and environmental exposure to aeroallergen triggers (aeroallergens).

### Considerations arising from this review

This report identifies and highlights the many gaps in knowledge relating to TA events, noting an imperative to fill these gaps because of the scale of the 2016 TA outbreak and the likelihood of such events increasing with climate change. Considerations arising from this review for addressing the gaps in knowledge are provided under the following categories.

#### (a) forecasting and early warning systems

##### Forecasting systems

1. Implement a TA alert system that directly notifies hospital emergency departments and ambulance services of an impending risk of increased presentations for respiratory distress.
2. Establish parameters that predict future TA events; thunderstorm characteristics, grassland cover greenness, grass pollen production and release, wind transport speed and direction, and current local pollen count data collected by standardized methods.

##### Fill knowledge gaps

- geographical influences on risk of TA.
- effect of climate change on storm frequency,
- other storm features associated with TA.

##### Aeroallergen exposure

3. Extend and improve existing pollen monitoring network for Victoria and other affected regions to enhance knowledge of triggers for TA and predictability of future events.
4. Improve the ability to monitor and forecast daily grass pollen levels including ground truthing with automated pollen counters and phenocams.

### Fill knowledge gaps

- specific allergen triggers within airborne allergen sources, and
- effect of climate change on grass growing patterns and grass species distribution

### (b) health and community response; public health messaging and education

5. Education resource package for specialists (immunology and respiratory), general practitioners, pharmacists, carers and patients to increase awareness of the triggers, symptoms and management of hayfever and asthma in general, particularly during the grass pollen season when the risk of TA is high.
6. Develop and implement a targeted and evidenced-based public health message for better clinical- and self-management of pollen allergies and minimisation of TA risk that is delivered by a strategic and well organised process: Key messages might include *“If you sneeze and wheeze, check what’s in the breeze”*.

### Fill knowledge gaps

- epigenetic, genetic and immunological biomarkers of susceptibility,
- benefits of better rhinitis and asthma control,
- preventative benefits of allergen-specific immunotherapy,
- specific allergen triggers within airborne allergen sources, and
- geographical influences on risk of TA.

### (c) clinical-pharmaceutical management; individual characteristics; allergic sensitivity and disease status

#### Clinical care of patients

7. Encourage systems for integrated clinical care of patients with allergic rhinitis and allergic asthma; foster communication and transfer of knowledge between the clinical immunology and respiratory medicine to deliver integrated care
8. Develop and implement appropriate clinical advice with “TA Management Action Plans” to individual patients at risk of grass pollen allergies and TA:
  - **For known asthmatics**, an awareness of seasonal flares, control of allergic rhinitis (see ARIA; Bousquet et al. 2008) prompt asthma management (availability of reliever and spacer, asthma plan, use of preventer according to asthma plan, consideration of using preventer during season), consideration of EpiPen if previous severe episode;
  - **For seasonal allergic rhinitis patients**, promote awareness of asthma (sneeze and wheeze), control of allergic rhinitis (anti-histamines, nasal corticosteroids, allergen-specific immunotherapy), encourage carriage of a reliever (short or long acting beta agonists) during the season, seek advice (pharmacist, GP, specialist);
  - **For both groups**, general advice regarding thunderstorm days; avoidance advice (e.g. stay indoors where possible, car windows closed).

In summary, the necessary conditions for ensuring that services and predictive early warning/forecasting systems respond effectively to reduce the risk of harm to the absolute achievable minimum include the following:

- 1) Establishment of sustainable pollen monitoring capabilities with broad coverage of the key grassland areas that are the source of pollen allergen transported into urban areas. Additional sites in rural areas are needed to supplement knowledge of pollen levels at existing urban collection sites.
- 2) Development of capacity to integrate pollen production data with models of wind transport for establishment of an operational short-term pollen forecasting system. Such pollen forecasts would need to be integrated with other weather predictions; i.e. thunderstorms with particular high risk characteristics, to enable decisions on level of risk of TA events.
- 3) Establishment of communication pathways to transfer alerts/warnings of days with risk of thunderstorm and high pollen levels to emergency services, and healthcare networks (primary and tertiary services and pharmacies) and patients.

## APPENDIX I

### AusPollen Partnership : NHMRC GNT 1116107; 2016-2020

#### AusPollen: Implementation of a standardized national pollen alert system for better management of allergic respiratory health

##### Executive Summary

Allergic rhinitis (hay fever) and episodic asthma attacks triggered by grass pollen regularly affects up to three million Australians. The annual direct medical cost of asthma alone is \$1.1 billion, according to Australasian Society of Clinical Immunology and Allergy's (ASCI) Access Economics Report of 2007. The total societal cost of asthma and allergies was estimated at \$30 billion. Despite the high prevalence, medical and socioeconomic burden of allergic rhinitis and asthma, Australia is one of the few developed countries without a national pollen monitoring program.

##### *Our vision*

The AusPollen project will provide allergy and asthma patients with accurate, relevant, localised information on pollen levels in the air. AusPollen will lead to reduced symptoms and improved quality of life of patients by empowering them to self-manage their condition through making timely decisions about preventative medicine and avoidance strategies.

In this initial phase AusPollen will implement a standardized pollen monitoring network in four major cities through collaboration of public, private and academic partners who bring data, analytical and clinical skills to the project. We will apply innovative smartphone technology and have the means and scale to personally deliver the information to patients, and their clinicians to better and more economically manage their condition. New techniques under development by this team will supersede inaccurate and unsubstantiated pollen forecasts. Importantly, the AusPollen project is designed to test the value of provision of localised pollen information and education resources to individual asthma or allergy sufferers by recruiting participants to a national trial.

##### *Project aims*

1. Inform patients in the community of local grass pollen levels using a standardized pollen count network and smartphone app.
2. Evaluate the components needed to build an innovative validated grass pollen forecast system.
3. Provide public stakeholders with education tools for managing respiratory health in people with pollen allergies and data for future health service planning and policy development.
4. Evaluate the short-term impact of the local pollen alerts on quality of life and how this empowers patients to better manage their own pollen allergy symptoms.

##### *Bridging practice and policy gaps to improve self- and clinical management of allergic disease*

The AusPollen project was co-developed with our partner organisations (Asthma Australia, ASCIA, Bureau of Meteorology, MeteoSwiss (Switzerland), Commonwealth Scientific and Industrial Research Organisation and Stallergenes), who are all key stakeholders in care and education of allergy and asthma patients, and in the establishment of operational forecast systems for airborne pollen.

##### *Value and significance*

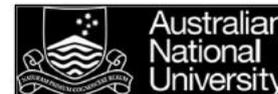
The Australian Pollen Allergen Partnership will establish the inaugural national pollen monitoring program. This study will evaluate for the first time whether providing pollen alert information enables people to better self-manage pollen allergies to improve quality of life and lower the medical and socio-economic burden of the prevalent chronic inflammatory diseases of hay fever and allergic asthma.

It is anticipated that knowledge of local airborne grass pollen levels is needed to empower patients to self-manage symptoms better, as a resource for health professionals in clinical management of patients with allergic respiratory diseases, and for future health service planning.

**Investigative team**

- |   |  |
|---|--|
| Associate Professor Janet Davies (CIA), <i>Queensland University of Technology, Brisbane</i>        | Associate Professor Bircan Erbas, <i>La Trobe University, Melbourne</i>        |
| Professor Constance Katelaris, <i>Campbelltown Hospital &amp; Western Sydney University, Sydney</i> | Associate Professor Ed Newbigin, <i>The University of Melbourne, Melbourne</i> |
| Professor Alfredo Huete, <i>University of Technology Sydney, Sydney</i>                             | Dr Elizabeth Ebert, <i>Bureau of Meteorology, Melbourne</i>                    |
| Dr Rieks van Klinken, <i>Commonwealth Scientific and Industrial Research Organisation, Brisbane</i> | Professor Simon Haberle, <i>The Australian National University, Canberra</i>   |
| Dr Danielle Medek, <i>Waitemata District Hospital, New Zealand</i>                                  | Associate Professor Paul Beggs, <i>Macquarie University, Sydney</i>            |

**Participating Academic Institutions**



**Partner Organisations**

The AusPollen Partnership Project is supported (Sept 2016 – Aug 2020) by NHMRC and matching in kind and cash contributions from partner organisations



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August 22, 2016

## APPENDIX II

### ARC discovery project: DP170101630; 2017-2019

AUSTRALIAN RESEARCH COUNCIL Discovery Project DP170101630; 2017-2019

### Satellite tracking of emerging health threats from grass pollen exposure

**Chief Investigators:**

Prof Alfredo Huete,  
University of Technology, Sydney

A/Prof Janet Davies,  
Queensland University of Technology and Metro North Hospital and Health Service

A/Prof Paul Beggs, Macquarie University Macquarie University, Sydney

**Partner Investigator**

Mr Michel Thibaudon, Réseau National de Surveillance Aerobiologique (France) (The National Network for Monitoring Aerobiological)

**Project summary**

Grass pollens are the key environmental allergen source in Australia and the primary cause of allergic diseases. Pollen exposure has dramatically increased since the 1960's and we don't know why. This Project will investigate and attribute the ecological causes of changing pollen allergen exposures through an innovative integration of 40 years of satellite data, field phenology cameras, and multiple pollen traps that will track grass pollen sources, their evolution, and impact areas. The outcomes will advance our knowledge of environmental drivers and enable more accurate pollen forecasts that will help alleviate the medical and socioeconomic burden costs of allergic diseases, which is estimated at 30 billion dollars.

**Impact Statement**

This research will benefit public health, quality of life, and the economy through knowledge acquired of pollen allergen exposure conditions and their causes. The research outcomes will aid public health management and minimise impacts of allergic diseases and other emerging pollen health threats, thereby reducing economic burden costs associated with allergic diseases in Australia. Satellites can play important roles in environmental health protection and fill key gaps in pollen forecasting.



This project is complementary to and integrated with the AusPollen Partnership



## APPENDIX III

### Submission to Victorian Inspector General of Emergency Management from AusPollen and Australasian Society for Clinical Immunology and Allergy.



Inspector-General for Emergency Management  
GPO Box 4356  
Melbourne VIC 3001

30 January 2017

**Re: Submission to the IGEM Inquiry into the emergency response to the thunderstorm asthma event of 21-22 November 2016**

Dear Sir,

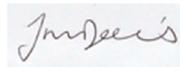
The Australasian Society for Clinical Immunology and Allergy (ASCIA) is the peak medical organisation for clinical immunology and allergy. As such, ASCIA is committed to advancing the science and practice of clinical immunology and allergy, by promoting education and the highest standard of ethical medical practice. ASCIA is closely engaged with the newly established AusPollen Partnership. AusPollen is an NHMRC-funded Partnership project (GNT1116107 2016-2019, led by Davies, QUT) to establish a standardised national airborne pollen monitoring and alert system. The AusPollen project will provide allergy and asthma patients with accurate, relevant, localised information on pollen levels in the air. It is anticipated that the AusPollen project will lead to reduced symptoms and improved quality of life of patients by empowering them to self-manage their condition through making timely decisions about preventative medicine and avoidance strategies. The AusPollen team from eight Australian universities is partnering with ASCIA, Asthma Australia, the Bureau of Meteorology, CSIRO, Stallergenes Australia and MeteoSwiss, the Swiss Federal Institute of Meteorology and Climatology. The Melbourne Pollen Count ([www.melbournepollen.com.au](http://www.melbournepollen.com.au)) is one of four AusPollen monitoring sites.

ASCIA and AusPollen make this joint submission based on our experience of pollen monitoring and understanding of allergic respiratory diseases, including pollen allergy, their causes and options for management.

Yours sincerely,



Professor William Smith MBBS(Hons) FRACP FRCPA PhD  
President,  
Australasian Society Clinical Immunology & Allergy  
Allergy South Australia



Associate Professor Janet Davies BSc PhD MAICD  
Principle Investigator,  
NHMRC AusPollen Partnership  
Queensland University of Technology

#### Authorship Team:

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Dr Jeremy McComish MB BS FRACP FRCPA (ASCIA Area Representative Victoria),  
Dr William Smith (President, ASCIA),  
Prof Connie Katelaris MBBS PhD FRACP (University Western Sydney, Campbelltown Hospital)

### Line of Enquiry 1. Public Health Response Plan

**Comment:**

On Monday 21st November 2016, Melbourne experienced an epidemic of asthma following a thunderstorm that led to the activation of disaster codes within its hospitals. Emergency services were overwhelmed and an unprecedented number of people (nine) died as a result of thunderstorm asthma (TA). Although in scale the event was unprecedented, TA in Melbourne is a regular seasonal occurrence with at least five earlier events reported in scientific literature (1-4). The phenomenon of TA has also been reported elsewhere including rural NSW, Australia and overseas (5, 6)). In Melbourne, all recorded TA events have taken place in November, the peak of the grass pollen season, with perennial ryegrass pollen (*Lolium perenne*), Victoria's most commonly sown pasture grass occupying over 4 million hectares, being repeatedly implicated as a major source of allergens involved in trigger TA.

TA events present a difficult challenge for public health and emergency services due to the rapid onset of symptoms in a large cohort of previously well patients. Although much remains unknown about causative factors for specific events, previous episodes have demonstrated some common features: timing of thunderstorms during late spring, association with high grass pollen counts, pre-existing seasonal allergic rhinitis (but not necessarily known asthma) and in particular sensitisation to grass pollen (ryegrass) in affected individuals, and lack of preventer use in known asthmatics.

The Victorian State Health Emergency Response Plan of 2013 provides well-developed procedures articulating the engagement of multiple sectors in an incident response that includes and relies upon community members, emergency services and hospital incident management teams. Driving concern amongst the community and hospital and health services, is the unknown risk of repeat episodes. Australia has one of the highest asthma mortality rates in the world and with climate change increases in severe weather events (7, 8), the frequency of TA events is likely to grow. Current understanding of biology and immunopathology of allergic asthma, availability and known benefit of grass pollen allergen-specific immunotherapy, and emerging technologies such as AusPollen's Melbourne Pollen Count App ([www.melbournepollen.com.au](http://www.melbournepollen.com.au)) mean that a number of preventive and therapeutic opportunities exist. However, the risk factors at population level for TA remain inadequately defined and biomarkers that could reliably identify individuals at high risk of TA have not been determined.

### Line of Enquiry 2: Coordination of agencies

**Recommendation 2a:**

Develop an integrated education resource package for the community of general practitioners, pharmacists, carers and patients to increase awareness of the triggers, symptoms and management of hay fever and asthma in general, particularly during the grass pollen season when the risk of TA is high.

**Rationale:**

Effective emergency and long-term responses to TA rest on the community at large, especially with the community of people who have hay fever and asthma and those who provide them care. Adequacy of the TA response will depend on community education to increase awareness of the potential health impact of exposure to the eliciting allergen source, as well as knowledge of and use of appropriate preventer and reliever medications (antihistamines, nasal corticosteroids, inhaled corticosteroids,  $\beta$ -agonists) during the allergy season and specifically at the time of an acute attack of respiratory allergy or asthma. Education of the wider community, patients and carers will require a coordinated effort between peak professional bodies such as ASCIA and the Thoracic Society of Australia and New Zealand (TSANZ). The involvement of non-government organisations who provide support and education materials to asthma patients and carers including Asthma Australia and the National Asthma Council is especially important.

ASCIA provides a centralised allergy patient and carer information resource on its website, and could expand this to incorporate further meteorological, aerobiological and clinical information. The ASCIA website is well

known by the patient community with a wide reach. To update the ASCIA pollen calendars, the AusPollen Partnership team (as the ACEAS Australian Aerobiology Working Group) analysed and synthesised available evidence of grass pollen seasonality, regional and seasonal variation and historical grass distributions (9-12). However, given the year to year, place to place, and daily fluctuations in airborne pollen concentration, current local pollen monitoring by standardized methods is essential to underpin any short-term predictive models of pollen levels (13). In December 2016, ASCIA and Asthma Australia worked together with members of AusPollen to provide revised and consistent information on TA; ([https://www.allergy.org.au/images/pcc/ASCIA\\_PCC\\_Thunderstorm\\_asthma\\_Dec2016.pdf](https://www.allergy.org.au/images/pcc/ASCIA_PCC_Thunderstorm_asthma_Dec2016.pdf), <https://www.asthmaaustralia.org.au/nsw/about-asthma/manage-your-asthma/triggers/asthma-and-thunderstorms>)

**Recommendation 2b:**

Foster communication and transfer of knowledge between the disciplines of clinical immunology and respiratory medicine to enable delivery of integrated clinical care of patients with allergic rhinitis and allergic asthma.

**Rationale:**

At a national level, greater sharing of clinical knowledge of immunopathology, triggers, diagnosis and management of asthma and respiratory allergies between clinical immunology and respiratory medicine physicians would help the immediate and long-term management of patients with allergic asthma triggered by pollen allergen exposure. This interdisciplinary knowledge base should be transferred from the tertiary hospital and health services to the primary healthcare networks and allied health practitioners including pharmacists. Regular joint symposia of peak professional bodies (ASCIA and TSANZ) as well as workshops and education sessions for specialists and general practitioners could be useful formats to facilitate this knowledge transfer.

**Recommendation 2c:**

At a national level, increase support and build collaboration between agencies who contribute to air quality monitoring, including monitoring of airborne allergenic bioaerosols, the Bureau of Meteorology and academic institutes with expert knowledge of pollen allergy and pollen aerobiology.

**Rationale:**

In future monitoring of airborne allergenic bioaerosols including grass pollen and fungal spores (*see recommendation 3e*) could be incorporated into air quality monitoring systems and networks that measure ambient daily levels of other types of airborne particles. The ability to integrate pollen count datasets, with data on other ambient air pollutants, measures of grassland greenness and meteorological variables that inform an operational forecast system for pollen aerobiology and TA (*see Recommendation 3f*) will require high level coordination between a number of departments from multiple states and the federal Bureau of Meteorology. As grassland production of pollen and wind transport patterns cross state borders, national coordination will be essential to understand, predict and effectively manage the yearly seasonal incidences of pollen-induced allergic asthma as well as severe TA events that affect large numbers of people in Victoria and other parts of Australia.

**Line of Enquiry 3: Public warnings and information**

**Recommendation 3a:**

Implement a TA alert system that directly notifies hospital emergency departments and ambulance services of an impending risk of increased presentations for respiratory distress.

**Rationale:**

The ability to forecast TA events is yet to be developed and implemented (see Recommendation 3f and 4b). Part of the appropriate response to minimise the impact of TA is early warning to the emergency services and hospital emergency departments to enable resources to be marshalled to manage increased presentations and admissions.

**Recommendation 3b:**

Develop and implement a targeted and evidenced-based public health message for better clinical- and self-management of pollen allergies and minimisation of TA risk that is delivered by a strategic and well organised process.

**Rationale:**

Each year at the start of spring, various media outlets run stories on seasonal allergies. However, these media-initiated stories are generally focussed on hay fever *per se* and their potency depends on a newsworthy angle. Broad-based, multifaceted and consistent public health messaging for protection against pollen allergy, including pollen-induced asthma, has not been developed. Targeted messages or slogans similar to the ‘slip, slap, slop’ campaign that encouraged people to protect against skin cancer by reducing their sun exposure, may be useful tools to raise community awareness and encourage behaviour change (e.g. staying indoors, closing windows, quality use of appropriate medications). Moreover, current ad hoc messages are mostly provided at the start of the ‘hay fever’ season and don’t cover the period of greatest risk for TA in mid to late November and early December. Important messages for the public include alerts regarding the coincidence of particular storm weather patterns and high grass pollen counts, and messages for those with seasonal allergies and grass pollen sensitivity who “wheeze and sneeze”. For example “If you sneeze and wheeze, check what’s in the breeze..... do something about it”.

The public health messaging program will need to ensure that the information is well qualified, targeted and evidence-based. The harm of inducing elevated levels of anxiety in the community will need to be prevented by ensuring that all the key ecological and meteorological risk factors of TA are well understood (Recommendation 3f) and specific clinical factors that confer risk for individuals are identified (Recommendation 4c). Further research is required to fully inform and predict which thunderstorms during the pollen season are likely to elicit increased incidences of asthma and or epidemics of TA.

**Recommendation 3c:**

Develop a mobile phone number register of those at risk of TA using smart phone technology.

**Rationale:**

Registration of phone numbers enables text messages to be distributed directly to self-registered at-risk people in the community in the event of a predicted TA episode. Similar database registries are utilized by Councils and the Bureau of Meteorology to provide to registered users alerts for impending events for example flood, storms or bushfires. Text messaging to smart phones provides an alert message directly to susceptible individuals who may be empowered to implement a TA action plan.

**Recommendation 3d:**

Develop and implement appropriate clinical advice with “TA Management Action Plans” relevant for individual patients at risk of grass pollen allergies and TA;

- a. Known asthmatics- an awareness of seasonal flares, control of allergic rhinitis (see ARIA; allergic rhinitis impact on asthma International Consensus (14)), asthma management (availability of reliever and spacer, asthma plan, use of preventer according to asthma plan, consideration of using preventer during season), consideration of EpiPen if previous severe episode
- b. Seasonal allergic rhinitis patients- promote awareness of asthma (sneeze and wheeze), control of allergic rhinitis (anti-histamines, nasal corticosteroids, allergen-specific immunotherapy), encourage carriage of a reliever (short or long acting beta agonists) during the season, seek advice (pharmacist, GP, specialist)
- c. General advice relevant to both groups- advice regarding thunderstorm days, avoidance advice (e.g. stay indoors where possible, car windows closed).

**Rationale:**

During previous Australian TA events around one third of patients had not previously been diagnosed with asthma (2, 3, 5), with preliminary data from the most recent event in Melbourne appearing to support this. Thus information targeting susceptible individuals (those with asthma and/or seasonal pollen allergies) should be addressed specifically to each group. Asthma Management Plans developed by Asthma Australia are helpful reference tools for patients with asthma guiding regular preventer use and response when symptoms worsen. Specific action plans for those at risk of TA would provide clear actions to undertake in response to TA alerts. Research from the Woolcock Institutes highlights the need for better asthma control in Australian patients with asthma (15). However, in previous reports on TA in Melbourne and Wagga Wagga up to 40 % of cases did not have a diagnosis of asthma. Notably, there is little evidence for the benefit of recommending asthma medication to hay fever patients without a diagnosis of asthma.

**Recommendation 3e:**

Extend and improve the existing pollen monitoring network for Victoria and other affected regions interstate to enhance knowledge of triggers for TA and predictability of future events.

**Rationale:**

Grass pollen is a major cause of seasonal allergies and is likely an important trigger for TA. In Melbourne, TA occurs in November and past events have occurred on days with high levels of airborne grass pollen. Standardized monitoring of airborne grass pollen levels will be important to forecasting future TA events.

Late spring and early summer in Melbourne are also when respiratory allergies are at their worst, with the rate of hospital admissions for asthma at this time correlated with ambient grass pollen levels (NHMRC MAPCAH study (16)). Although Melbourne appears to be a hot spot for TA, regional Victoria could also be affected; studies in the 1990s indicated pollen-associated TA frequently occurs in rural NSW (5, 17). AusPollen has established pollen collection and counting sites in Sydney, Brisbane, Canberra and Melbourne.

Currently pollen monitoring in Victoria is restricted to the AusPollen site at the University of Melbourne and two independent sites at Burwood and Geelong run by Deakin University. For the AusPollen sites, pollen counts and 7-day forecast are distributed daily free-of-charge to traditional media outlets with the information also available online through dedicated webpages, via twitter (@melbournepollen) and from free apps that can be downloaded from iTunes or Google play. The Melbourne pollen count app and the other AusPollen pollen count apps include a quick survey that lets respondents assess their hay fever symptoms on a daily basis. Between October 1 and December 31 2016, over 44,000 survey responses were received from 9,000 devices located within Melbourne. Average daily survey symptom scores are highly correlated with grass pollen levels and serve as a good indicator of the level of pollen-related allergy in the community.

Although the Melbourne AusPollen site is well-established having been in operation for over 25 years, it and other pollen count sites nationally receive only a limited budget and has several points of weakness that can

affect service delivery. It is also important that the methods of monitoring pollen across all sites nationally are standardised, that reporting and recording pollen data are robust and secure, and that any AusPollen messaging provided through its network or to media outlets is consistent with those provided by public health services.

**Recommendation 3f:**

Establish parameters that predict future TA events; these could include thunderstorm characteristics, grassland cover greenness, grass pollen production and release, wind transport speed and direction, and current local pollen count data collected by standardized methods.

**Rationale:**

Although grass pollen is the major outdoor aeroallergen source in Australia, our ability to reliably predict the onset, size, peak and duration of the grass pollen season is limited. Evidenced-based short-term forecasting of TA would require new systems for real-time integration of information from several sources including AusPollen Partners (*see Recommendation 4b*) who provide local pollen counts, the Bureau of Meteorology and remote sensing of grass land cover and grass land phenology to inform grass biomass, greenness and pollen release. Research is currently underway by members of the AusPollen team (ARC Discovery DP170101630 Huete (UTS), Davies (QUT) and Beggs (Macquarie University)) to improve understanding of the ecological drivers of regional and temporal variation in grass pollen sources and wind transport.

Operational predictive models that can forecast i) grass pollen season severity, ii) grass pollen season start, peak and duration as well as iii) daily grass pollen concentrations and iv) risk of TA need to be developed and evaluated via a collaborative multi-disciplinary partnership that is adequately resourced to gather the prerequisite datasets and undertake the modelling and forecast development. The AusPollen team has established the necessary effective and productive working relationships and is well capable of undertaking the forecast development, but an operational forecast system that is required to predict TA is beyond the current project scope and resources.

**Line of Enquiry 4 Other relevant matters and opportunities for improvement**

**Recommendation 4a:**

Work with primary health care network and general practitioners to encourage patients to register for eHealth records and incorporate allergy status information of patients who have attended primary health care clinics for consultation on allergies and or respiratory conditions.

**Rationale:**

Knowledge and clinical history of risk factors including pollen allergy, allergic rhinitis and asthma status may be of assistance in providing clinical care to patients experiencing respiratory symptoms. It would be necessary to evaluate whether such information was helpful in understanding the precipitating trigger for or management of patients presenting with respiratory distress during a TA episode.

**Recommendation 4b:**

Improve the ability to monitor and forecast daily grass pollen levels by testing of automated pollen counters.

**Rationale:**

Pollen monitoring relies on experienced and skilled pollen counters trained to identify and quantify by light microscopy the presence and level of grass pollen in air samples. The AusPollen Partnership was funded to support one pollen trap per state. A sustainable pollen monitoring network requires sufficient resources to allow for contingency planning in the case of operator absence due to illness or instrument failure. Notably, one pollen collection site represents the grass pollen concentrations and daily fluctuations over broad area of between 30- 100 km diameter (13, 18, 19). Whilst the timing of peaks in daily grass pollen levels is consistent

between sites, grass pollen levels increase with distance from the coast (20). Remote sensing can indicate regional grassland greenness and pollen levels with broad synoptic coverage (13, 21) increasing the capacity to predict grass pollen concentrations over a wider area including at risk regional centres.

The ARC Discovery project seeks to incorporate data from multiple pollen collection sites (in Sydney and Brisbane), phenocams that record grassland greenness, integrated with remote sensing of grassland coverage and meteorological factors to inform components for development of a real-time validated pollen forecast system. In addition to remote sensing and phenocam monitoring of grassland greenness and phenology, citizen science networks eg the Grassland Curing (Victorian CFA) group that monitor grassland browning to mitigate risk of bushfires, could be recruited to monitor grassland greenness, a key factor that precedes flower and pollen production.

A number of automated real-time pollen monitor prototypes, which are based on a variety of technologies, are under development (22, 23). There are no systems currently in production and the available prototypes are expensive, have low accuracy at low pollen concentrations and may not function well in Australian environmental conditions. However, if such devices were evaluated, appropriately adapted to Australian conditions, then these could complement remote sensing data and a central manual pollen count site to provide a wider ground-truthing of grass pollen levels across Australia and contribute to a broad pollen aerobiology data network. AusPollen will be trialling the Plair automated pollen count instrument (Meterology Switzerland) as part of its research program. This and other existing automated instruments should be tested for their utility and accuracy in monitoring pollen in Australia. The devices would need to be robust for our environment, produced by a company with a sustainable business model capable of providing long-term technical support and software upgrades and sensitive and specific for grass pollen at concentrations that occur in Australia. Alternatively, prototype devices could be developed in collaboration with existing experts from overseas companies or independently in Australia.

**Recommendation 4c:**

Special and timely support for clinical and scientific research targeting knowledge gaps relating to allergy and asthma disease status and risk factors for TA.

**Rationale:**

Investigation of this recent episode of TA, if properly conducted, has potential to reveal fundamental information on the role allergies in asthma mortality and provide insights for improved emergency and public health management of future threats of TA episodes. There are a number of outstanding gaps in our knowledge relating to the individual clinical risk profiles of patients who are susceptible to TA in the community. A special initiative funding scheme may provide researchers collaborating from clinical and scientific disciplines the opportunity to immediately follow up patients affected by the recent event to identify the contributing causative factors. These knowledge gaps include but are not limited to factors associated with individual patient susceptibility, benefits of better rhinitis and asthma control and in particular the preventative benefits of allergen-specific immunotherapy, knowledge of the specific allergen triggers within airborne allergen sources, epigenetic, genetic and immunological biomarkers of susceptibility, and geographical influences on risk of TA.

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APPENDIX IV

DEVADAS poster EAACI 2016 (Devadas et al. 2016)

### Remote sensing of phenology; a dynamic tool to inform allergenic grass pollen aerobiology

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**INTRODUCTION**

- Grass pollen is a major aeroallergen globally.
- Exposure is expected to intensify with climate change.
- Accurate assessments of the sources, timing, and duration of grassland pollination are critical for improved management of allergic rhinitis.
- Conventional methods for monitoring airborne pollen are labour intensive, site-specific, and hampered by a sparsity of sampling sites.
- Satellite remote sensing offers an alternative method with synoptic coverage and repeatability of measurements.
- Satellite remote sensing is useful for mapping land cover and tracking vegetation condition & phenology.

**AIM**

We aim to test the predictive capabilities of satellite remote sensing to inform grass pollen aerobiology in five contrasting urban environments in both Northern Hemisphere (France) and Southern Hemisphere (Australia).

**METHOD**

Land cover classes as well as satellite observations of greenness as an index of grass phenology were used to predict grass pollen concentrations in five contrasting urban environments in both Northern Hemisphere (France) and Southern Hemisphere (Australia). The satellite-based enhanced vegetation index (EVI) phenology profiles over a 16 day window were related with in situ grass pollen count datasets spanning five to 13 years to assess the predictive capabilities of the satellite remote sensing for airborne pollen forecasting.

**RESULTS**

**CONCLUSIONS**

- Local GAMs have predictive capabilities for forecasting grass pollen release for both Australian and French sites.
- GAMs were useful at sites dominated by temperate species as well as the Australian Sydney site with multiple peaks in airborne grass pollen correlating with the presence of subtropical, summer-flowering grasses.
- Remote sensing of phenology revealed vital information on pollen sources for forecasting grass pollen aerobiology to aid management of public health risk.
- The contribution of other parameters (wind, temperature and precipitation) to EVI-informed, daily pollen forecast models need to be evaluated.

**ACKNOWLEDGEMENTS**

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## APPENDIX V

### Qualifications and experience of key project staff

Name	Associate Professor Janet Davies
Title/office held	Head Allergy Research, QUT Principle Investigator NHMRC AusPollen Partnership
Qualifications	Doctor of Philosophy, Bachelor of Science, Biological and Environmental Science
Previous experience	<p>Associate Prof Davies leads the Allergy Research Group at QUT and the NHMRC funded AusPollen Partnership (2016-2019). She led the Australian Aerobiology Working Group forerunner projects synthesising pollen exposure data across Australasia and beyond (ACEAS 2015-2016 and AIFA 2013-2014). Her research has been published in over 50 peer reviewed papers in quality field-leading journals and has been awarded multiple prizes from European Academy of Allergy and Clinical Immunology and Australian Society of Clinical Immunology and Allergy. She is frequently called to present her work at national (30) and international (15) meetings and for the Australian Society for Clinical Immunology and Allergy (10) and the Asthma Australia (5) and its state level Foundations. Associate Professor Davies serves as Vice Chair of the World Health Organisation IUIS Allergen Nomenclature Committee, the European Academy of Allergy and Clinical Immunology Interest Group on Aerobiology and Air Pollution and the Immunotherapy Working Party of the Australian Society of Clinical Immunology and Allergy. She was appointed to an international Task Force on Component Resolved Diagnosis in 2015 and has contributed multiple chapters on pollen allergy for several global position papers and texts for example the Global Atlas of Allergy (2014) and the Molecular Allergology User’s Guide (2016). She is an inventor of a patent granted in Australia and three patent applications that underpin more specific immunodiagnosis and treatment for subtropical grass pollen allergy. Her recent research is supported by grants of \$2.5 million from NHMRC, ARC, The Asthma Foundation of Queensland and National Foundation of Medical Research Innovation as well as over \$1 million in partner contributions. Associate Professor Davies is employed part time with QUT and holds a position with the Metro North Hospital and Health Service as the Assistant Director of Research.</p>

Name	David Fagan
Title/office held	Director, Corporate Transition; Real World Future
Qualifications	Bachelor of the Arts, Journalism Graduate of the Australian Institute of Company Directors
Previous experience	David Fagan is QUT's Director of Corporate Transition and is a journalist and editor with decades of experience in informing the public on complex subjects. He is a former deputy editor and night editor of The Australian (1997-2002), editor and editor-in-chief of Queensland's major newspaper, The Courier-Mail (2002-2012) and Queensland editorial director of News Corporation 2012-2013. He has worked on publishing and digital strategy for News Corporation and general and digital strategy for QUT since 2014 when he joined the university, reporting to the Vice-Chancellor. He has led multiple product launches, overseen complex journalistic investigations and has reported on a wide range of issues, particularly in the areas of business and politics. At QUT, his responsibilities include the Real World Futures program which explores the impact of technology disruption on future working, living and thinking. A key element of this has been the use of digital applications for better health outcomes.

Name	Mr Marko Simunovic
Title/office held	Researcher in Public Health and Epidemiology
Qualifications	Master of Public Health (Epidemiology), Bachelor of Biomedical Science
Previous experience	Marko Suminovic completed a Bachelor of Biomedical Science in 2011 and a Masters degree in Public Health in 2016 at the Queensland University of Technology. He has expertise in public health research including his Masters report on climatic influences on outbreaks of Ross River Virus in Queensland. He has a strong understanding of methodological designs for quantitative studies including criteria for data, logistic regression analysis, interpreting and reporting the outcomes in the field of epidemiological investigations. He has previously worked as a laboratory technician at ALS coal and Symbio Alliance with accountability for efficiency, accuracy and consistency. Marko is currently employed as a research assistant at QUT involved in undertaking systematic reviews for public health applications.

Name	Dr Anđelija Milic
Title/office held	Researcher in Meteorology and Environment
Qualifications	Doctor of Philosophy, Air quality and Health Masters of Science, Environmental Chemistry Bachelor of Science, Environmental Chemistry
Previous experience	<p>Anđelija Milic is an environmental chemist with laboratory, research and teaching experience. Before her doctoral studies with the Australian Atmospheric Research Group at QUT, Anđelija completed Bachelor and Masters studies at the University of Belgrade in Serbia in environmental chemistry. She recently finalised her PhD (through Queensland University of Technology) in the International Laboratory for Air Quality and Health, studying the ambient atmospheric aerosols in Australia. Her research focused on chemical characterisation and constraint of the impact of biomass burning aerosols in both urban and remote Australia. As a part of the large, diverse, international research group, Anđelija has been involved in field studies collaborating with atmospheric chemists/physicists/biologists from common-field institutes. Anđelija is skilled in data collection, data analysis, use of aerosol measurement instrumentation and comprehensive statistical analytical packages. Anđelija is experienced in writing research proposals, reports and journal articles with ten peer-reviewed publications. Her work includes a recent literature review on biomass burning aerosol in China that provides a comprehensive database for biomass burning emissions and impact on air quality, health and climate.</p>

Name	Dr Jane Al Kouba
Title/office held	Researcher in Immunology and Disease Status
Qualifications	Doctor of Philosophy, Immunology Master of Science, Biology, Bachelor of Sciences (Dean's Honour List)
Previous experience	<p>Dr Al Kouba completed her PhD at the University of Queensland and obtained Masters from the University of Balamand in Lebanon with High Distinction. Her PhD project focussed on therapeutic approaches for reversing allergen-induced airway inflammation in asthma. She has extensive knowledge of the disciplines of immunology, molecular biology and cell biology relating to asthma and research skills in models of allergic airway inflammation. Upon completion of her doctorate in 2015, Dr Al Kouba joined Associate Professor Janet Davies Allergy Research Laboratory, to work on pollen allergy and aerobiology projects. She has demonstrated the ability to critically assess and analyse data and effective communication including preparation of primary research and literature review publications in the fields of asthma and immunology.</p>

**External Co-author**

Name	Associate Professor Bircan Erbas,
Qualifications	PhD MSc Public Health and Epidemiology
Institution	LaTrobe University
Relevant Experience	<p>Associate Professor Bircan Erbas is a leading pollen epidemiologist, biostatistician in the field of environmental determinants of health and respiratory epidemiology. She led the successful NHMRC project grant (ID 541934) which established the link between grass pollen and childhood asthma exacerbations as a major clinical and public health issue in Australia. Outcomes of her work are relevant for local advocacy and government groups and she has presented the implications of her work for clinical practice and health service to the board of the Asthma Foundation of Victoria and at the National Asthma Conference (2011). Pollen related allergic respiratory disease is a major community health issue and Erbas has engaged international with diverse communities and geographical regions to translate her research to socially and culturally diverse communities.</p> <p>Assoc. Prof. Erbas was invited to be part of the Australian Aerobiology Working Group to develop the first national pollen monitoring, synthesizing and forecasting group in Australasia funded by the Australian Centre for Ecological Analysis and Synthesis (ACEAS). This resulted in an NHMRC funded AusPollen partnership with Erbas as a key chief investigator. She has received a number of international awards, grants and travel stipends for her work on pollen epidemiology and applications of statistical models for the analysis of longitudinal data. Erbas has attracted research funding of nearly \$1 million as Principal Investigator and over \$3.5 million as key co-investigator. A/Prof Erbas has co-authored over 80 refereed academic publications quality international journals. She has supervised 5 PhD students to completion and currently supervises 7 PhD students and 3 Master of Public Health students. Erbas is on the statistical editorial board of <i>Respirology</i> and regional editor of <i>International Journal of Environmental Health Research</i>.</p>

## APPENDIX VI

### Search strategy 1 (24/01/2017)

**TABLE 16: CINAHL (VIA EBSCO HOST) SEARCH STRATEGY; PUBLIC HEALTH AND EPIDEMIOLOGY THEME**

Search terms used	Items found
<p>Line 1: aria OR Rhinoconjunctivitis OR Sinusitis OR (MH "sinusitis+") OR airways OR Rhinitis OR (MH "Rhinitis") OR (hay-fever OR hayfever) OR asthma* OR (MH "Asthma+/EP/ET/MO/PC")</p> <p>AND</p> <p>Line 2: (MH "Pollen") OR Pollen* OR aeroallergen* OR (MH "Air Pollution+") OR (MH "Environmental Pollution+") OR Pollution OR bioaerosol OR grass* OR (MH "Fungi+") OR Fung* OR mold OR mould OR (MH "Environment+") OR Environ* OR (MH "Hypersensitivity+") OR (MH "Allergens+") OR allerg* OR (MH "Dust") OR Dust OR trigger*</p> <p>AND</p> <p>Line 3: (MH "Weather+") OR Weather OR thunderstorms OR (MH "Rain") OR Rain OR (MH "Climate+") OR Climate OR (MH "Seasons") OR Season*</p> <p>AND</p> <p>Line 4: (MH "Hospitalisation+") OR Hospital* OR (MH "Severity of Illness") OR Severe OR severity OR (MH "Emergency Service+") OR Emergency OR (MH "Symptoms+") OR Symptom*</p>	<b>830</b>
<b>When filter is set to publications from 2007-2017</b>	<b>459</b>

**TABLE 17: PUBMED SEARCH STRATEGY; PUBLIC HEALTH AND EPIDEMIOLOGY THEME**

Search terms used	Items found
<p><u>Line 1:</u> aria OR Rhinoconjunctivitis OR sinusitis OR airways OR Rhinitis OR hay-fever OR hayfever OR asthma* OR "Sinusitis"[Mesh] OR "Asthma"[Mesh] OR "Rhinitis"[Mesh]</p> <p>AND</p> <p><u>Line 2:</u> "Pollen"[Mesh] OR "Air Pollution"[Mesh] OR "Environmental Pollution"[Mesh] OR "Fungi"[Mesh] OR "Environment"[Mesh] OR "Hypersensitivity"[Mesh] OR "Allergens"[Mesh] OR "Dust"[Mesh] OR Pollen* OR aeroallergen* OR Pollution OR bioaerosol OR grass* OR fung* OR mold OR mould OR Environ* OR allerg* OR Dust OR trigger*</p> <p>AND</p> <p><u>Line 3:</u> weather OR rain OR climate OR seasons OR thunderstorm OR "Weather"[Mesh] OR "Rain"[Mesh] OR "Climate"[Mesh] OR "Seasons"[Mesh]</p> <p>AND</p> <p><u>Line 4:</u> hospital* OR severe OR Severity OR emergency OR symptom* OR "Hospitalisation"[Mesh] OR "Severity of Illness Index"[Mesh] OR "Emergencies"[Mesh] OR "Signs and Symptoms"[Mesh]</p>	<b>2,979</b>
<b>When filter is set to publications from 2007- 2017</b>	<b>1,100</b>

**TABLE 18: EMBASE (INCLUDING MEDLINE) SEARCH STRATEGY; IMMUNOLOGY AND DISEASE STATUS THEME**

Search terms used	Items found
#28: #23 AND #27	9,111
#27: #24 OR #25 OR #26	488,806
#26 'prick test'/exp OR 'prick test'	18,906
#25 'immunoglobulin e'/exp OR immunoglobilin AND e OR ige	87,493
#24 'allergy'/exp OR allerg*	463,947
#23: #14 AND #22	10,110
#22: #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	997,086
#21 'allergen'/exp OR allergen	73,345
#20 'airborne particle'/exp OR particle OR trigger	330,673
#19 'dust'/exp OR dust	55,664
#18 'aerosol'/exp OR aerosol OR bioaerosol OR aeroallergen	68,523
#17 'pollen'/exp OR pollen	42,113
#16 'fungus spore'/exp OR spore	35,262
#15 'fungus'/exp OR fungus OR mold OR mould	482,817
#14: #8 AND #13	21,939
#13: #9 OR #10 OR #11 OR #12	575,185
#12 'season'/exp OR season* OR spring OR summer	453,170
#11 'meteorology'/exp OR meteorolog*	21,616
#10 'weather'/exp OR weather	49,353
#9 'climate'/exp OR climate OR thunderstorm OR storm	106,402
#8: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	453,097
#7 aria OR 'airway* disease'	17,541
#6 'rhinoconjunctivitis'/exp OR rhinoconjunctivitis	4,919
#5 'sinusitis'/exp OR sinusitis	40,785
#4 'pollen allergy'/exp OR 'pollen allergy' OR hayfever OR 'hayfever'	17,220
#3 'rhinitis'/exp OR rhinitis	85,628
#2 'respiratory disease*' OR 'respiratory allerg*' OR 'respiratory tract disease'	124,411
#1 'asthma'/exp OR asthma	267,446
#28: #23 AND #27 :When filter is set to publications from 2007-2017	4,859

**TABLE 19: SCOPUS DATABASE SEARCH STRATEGY; METEOROLOGY AND ENVIRONMENT THEME**

Search terms used	Items found
<p><b>TITLE-ABS-KEY:</b> airways OR rhinitis OR hay-fever OR hayfever OR asthma OR respiratory</p> <p><u>Search within results:</u> allergen OR aeroallergen OR pollen OR grass OR grass AND pollen OR rye AND grass OR fungus OR fungi OR fungal OR mold OR mould OR pollen OR trigger OR bioaerosol OR aerosol OR particle</p> <p><u>Search within results:</u> weather OR thunderstorms OR storms OR rain OR rainfall OR climate OR season OR seasonal OR meteorological OR meteorology OR spring OR summer OR wind OR lightning OR humidity OR temperature OR model</p> <p><u>Search within results:</u> hospitalisation OR hospital OR severity AND of AND illness OR severe OR severity OR emergency AND service OR emergency AND department OR emergency OR symptom OR intensive AND care</p>	<b>1600</b>
<b>When filter is set to publications from 2007-2017 (limit to 2007-2017)</b>	<b>1017</b>

**TABLE 20: WEB OF SCIENCE DATABASE SEARCH STRATEGY; METEOROLOGY AND ENVIRONMENT THEME**

Search terms used	Items found
<p><b>TOPIC:</b> (airways) OR <b>TOPIC:</b> (rhinitis) OR <b>TOPIC:</b> (hay-fever) OR <b>TOPIC:</b> (hayfever) OR <b>TOPIC:</b> (asthma) OR <b>TOPIC:</b> (respiratory)</p> <p><u>Search within results:</u> <b>TOPIC:</b> (allergen OR aeroallergen OR pollen OR grass OR grass AND pollen OR rye AND grass OR fungus OR fungi OR fungal OR mold OR mould OR pollen OR trigger OR bioaerosol OR aerosol OR particle)</p> <p><u>Search within results:</u> <b>TOPIC:</b> (weather OR thunderstorms OR storms OR rain OR rainfall OR climate OR season OR seasonal OR meteorological OR meteorology OR spring OR summer OR wind OR lightning OR humidity OR temperature OR model)</p> <p><u>Search within results:</u> <b>TOPIC:</b> (hospitalisation OR hospital OR severity AND of AND illness OR severe OR severity OR emergency AND service OR emergency AND department OR emergency OR symptom OR intensive AND care)</p>	<b>5904</b>
<b>When filter is set to publications from 2007-2017 (limit to 2007-2017)</b>	<b>3373</b>

## Grey literature search strategy

Grey literature sources that were searched included the following;

**ProQuest Dissertations and Theses Global:**

thunderstorm\* N/5 (asthma\* OR rhinitis OR "hayfever" OR hayfever)  
Limited to English Language  
46 hits

**Google:**

allintitle:thunderstorm\* asthma\* filetype:pdf  
81 hits  
Removing the pdf limit finds 9660 hits

**Factiva (all dates i.e. since 1992, and all sources):**

thunderstorm\* near3 asthma\*  
1133 (i.e. 2,496 total that includes 1362 duplicates detected by Factiva) although the actual number of unique articles may actually be around 756, or perhaps as many as 823. The exact number of articles is not precise because some articles are syndicated across many newspapers – Factiva can filter some out when exporting but EndNote does not reliably detect duplicate articles in different newspapers from the imported Factiva records. Also, some records overlap with the Australia & New Zealand News stream search results.

**Australia & New Zealand News stream:**

thunderstorm\* N/3 asthma\*  
329 hits (some overlap with Factiva results)

## Secondary “thunderstorm” and “asthma” search outcomes by database

**TABLE 21: SECONDARY SEARCH RESULTS**

Database search strategy	Endnote running total
<b>PubMed</b> ("Asthma"[Mesh] OR ("asthma"[MeSH Terms] OR "asthma"[All Fields])) AND thunderstorm [All Fields]  Publication date: no restrictions n= 53	<b>53</b>
<b>EBSCOhost (Cinahl)</b> (thunderstorm) AND (MH "Asthma+" OR asthma)  Publication date: no restrictions n = 11	<b>+11 = 64</b>
<b>Embase (including Medline)</b> Thunderstorm/exp OR Thunderstorm AND asthma/exp OR asthma  Publication date: no restrictions n=78	<b>+78 =142</b>
<b>Scopus</b> <b>(Keywords, Abstract, Title)</b> Thunderstorm and Asthma  Publication date: no restrictions n=106	<b>+106 = 248</b>
<b>Web of Science</b> <b>(Topic)</b> Thunderstorm and Asthma  Publication date: 1900-2017 (Default setting) n=138	<b>+138 = 386</b>

## APPENDIX VII

### National Thunderstorm Asthma events

TABLE 22: TIMELINE OF THUNDERSTORM ASTHMA EPIDEMICS (AUSTRALIA)

Location	Date	Time of event	Season	Hospital presentations	Allergen trigger
<b>Melbourne</b> (Egan 1985)	11 Nov 1984	Early morning	Spring	85 attended 16 admitted	Not specified
<b>Melbourne</b> (Bellomo et al. 1992)	Nov 8 1987	Afternoon/evening	Spring	154 attended 26 admitted 1 ICU, 1 Death	Grass pollen
<b>Melbourne</b> (Bellomo et al. 1992)	Nov 29 1989	Evening	Spring	277 attended 47 admitted, 3 ICU	Grass pollen
<b>Wagga Wagga</b> (Girgis et al. 2000)	30 Oct 1997	20:00h -12:00h	Spring	183 attended	Grass pollen
<b>Newcastle</b> (Wark et al. 2002)	27 Oct 1998	Evening	Spring	6 attended	Grass pollen
<b>Melbourne</b> (Erbas et al. 2012)	19/20 Nov 2003	12:40h	Spring	70 attended	Grasp pollen
<b>Melbourne</b> (Howden et al. 2011)	25 Nov 2010	Evening	Spring	36 attended	Grass pollen
<b>Melbourne</b> (Murnane 2011; Beggs et al. 2015)	8 Nov 2011	03:30-06:30h	Spring	30 attended	Grass pollen
<b>Canberra</b> (Colley 2014)	27 Oct, 2014	Not specified	Spring	15 attended	Grass pollen
<b>Melbourne</b> (Inspector-General for Emergency Management 2017)	21 Nov 2016	17:00h	Spring	4,000 attended, 30 ICU	Grass pollen

## International Thunderstorm Asthma events

TABLE 23: TIMELINE OF THUNDERSTORM ASTHMA EPIDEMICS (INTERNATIONAL)

Location	Date	Time of event	Season	Hospital/general practice presentations	Allergen trigger
<b>Birmingham, UK</b> (Packe et al. 1985;1986)	6/7 Jul 1983	19:50-21:30h	Summer	106 attended 32 admitted	<i>Didymella exitialis</i>  <i>Sporobolomyces</i>
<b>Nottingham, UK</b> (Alderman et al. 1986)	20 Jun 1984	17:00-17:30h	Summer	19 attended	<i>Didymella Excitialis</i>
<b>Leicester, UK</b> (Allitt et al. 1997)	22 Jul 1989	17:00-19:00h	Summer	32 admitted	<i>Didymella ascospores</i>
<b>Midlands to South East England, UK</b> (Venables et al. 1997; Allitt 2000; Celenza et al. 1996; Hajat S 1997; Higham 1994; Higham et al. 1997; Davidson et al. 1996; Campbell-Hewson et al. 1994; Murray et al. 1994; Sutherland et al. 1994)	24 Jun 1994	18.00–22.45h	Summer	488 asthma calls in affected areas +640 (104 admitted, 5 ICU 1 death) Note: suspect that there are repeated events	Grass pollen
<b>Calgary, Canada</b> (Wardman et al. 2002)	31 Jul 2000	Evening	Summer	157 attended	<i>Amaranthaceae</i> Protist: <i>Myxomycetes</i> , Fungi: <i>Stemphyllium</i> , <i>Helicomycetes</i> , <i>Ustilaginales</i>
<b>Cambridge, UK</b> (Pulimood et al. 2007)	29/30 Jul 2002	20:00h	Summer	57 admitted patients 3 ICU 1 death	<i>Alternaria</i>
<b>Al-Khobar, Saudi Arabia</b> (Al-Rubaish 2007)	2 Nov 2002	No specified	Autumn	No specified	No specified
<b>Naples, Italy</b> (D'Amato et al. 2008)	4 Jun 2004	01:30-02:00h	Summer	7 attended 7 admitted 1 ICU	<i>Parietaria</i>
<b>South-East England, UK</b> (Levy et al. 2007)	24 Jun 2005	Evening	Summer	400% increase calls: difficulty breathing. 50% increase GP out-of- hours emergency patient attendance	Not specified
<b>Barletta, Italy</b> (Losappio et al. 2011; Losappio et al. 2012)	27 May 2010	Afternoon	Spring	20 attended	Olive tree pollen
<b>London, UK</b> (Elliot et al. 2014)	23 Jul 2013	04:00–5:00h	Summer	40 attended	Not specified
<b>Ahvaz, Iran</b> (Shoushtari et al. 2016; Forouzan et al. 2014)	2 Nov 2013	Evening	Autumn	443 patients 37 admitted 3 ICU	Not specified

**Abbreviations:** Jun: June, Jul: July, Dec: December, Jan: January, Nov: November, Oct: October, h: hour.

## APPENDIX VIII

### Major fungal aeroallergens

TABLE 24: MAJOR AEROALLERGENS IN FUNGAL SPORES

Fungal species:	<i>Alternaria alternata</i>	<i>Cladosporium</i>	<i>Penicillium</i>	<i>Aspergillus</i>
Biochemical name				
Unknown*	Alt a 1*	Cla h 2	Pen ch 33	Asp f 2,4,7,9,15,16,17
60S acidic ribosomal phosphoprotein P1			Pen cr 26	
Acid ribosomal protein P1	Alt a 12	Cla h 12	Pen b 26	
Acid ribosomal protein P2		Cla h 5		
Aldehyde dehydrogenase	Alt a 10	Cla h 10		
Alkaline serine protease			Pen b 13; Pen ch 13; Pen c 13	Asp fl 13; Asp f 13; Asp o 13
Aspartate protease				Asp f 10
Beta-xylosidase				Asp n 14
Calreticulin			Pen ch 31	
Catalase			Pen c 30	
Cyclophilin				Asp f 27
Disulfide isomerase	Alt a 4			
Elongation factor 1 beta			Pen c 24	
Enolase	Alt a 6	Cla h 6	Pen c 22	Asp f 22
Extracellular alkaline serine protease				Asp v 13
Glutathione-S-transferase	Alt a 13			
Heat shock protein 70	Alt a 3		Pen c 19	
Heat shock protein 90				Asp f 12
L3 ribosomal protein				Asp f 23
Manganese superoxide dismutase	Alt a 14			
Mannitol dehydrogenase	Alt a 8	Cla h 8		
metalloprotease				Asp f 5
Mitogillin famiy				Asp f 1
Mn superoxide dismutase				Asp f 6
N-acetyl-glucosaminidase			Pen ch 20	
Pectate lyase			Pen c 32	
Peptidyl-prolyl isomerase				Asp f 11
Peroxisomal membrane protein			Pen c 3	Asp f 3
PhiA cell wall protein				Asp f 34
Ribosomal protein P2	Alt a 5			Asp f 8
Serine protease	Alt a 15			
TAKA-amylase A				Asp o 21
Thioredoxin				Asp f 28,29
Transaldolase		Cla c 14	Pen ch 35	
Vacuolar serine protease		Cla c 9; Cla h 9	Pen ch 18; Pen o 18	Asp f 18; Asp n 18
YCP4 protein	Alt a 7	Cla h 7		
3-Phytase B				Asp n 25 <sup>1</sup>

<sup>1</sup> The source of the allergens in this table is the WHO/ IUIS allergen nomenclature website.

\* Alt a 1 is the only commercially available allergen.

Cla c , *Cladosporium cladosporioides* ; Cla h , *C. herbarum*.

Pen b , *Penicillium brevicompactum*; Pen ch , *P. chrysogenum*; Pen c , *P. citrinum*; Pen cr , *P. crustosum*; Pen o , *P. oxalicum*

Asp f , *Aspergillus fumigatus*; Asp fl , *A. flavus*; Asp n , *A. niger*; Asp o , *A. oryzae*; Asp v , *A. versicolor*

## APPENDIX IX

### Level of identity between group 1 and group 5 allergens

Lol p 1 (IUIS: Lol p 1.0103; Beckmann et al. 1998) vs Phl p 1(IUIS: Phl p 1.0102; Laffer et al. 1994)

unnamed protein product

Sequence ID: Query\_201447 Length: 263 Number of Matches: 1

Range 1: 19 to 263 [Graphics](#) ▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
465 bits(1196) 7e-173 Compositional matrix adjust. 223/245(91%) 234/245(95%) 0/245(0%)					
Query	19	GSAHGIAKVPPGPNITAEYGDKWLD	AKSTWYGKPTGAGPKDNGGACGYKD	VDKAPFNGMT	78
Sbjct	19	GSA+GI KVPPGPNITA YGDKWLD	AKSTWYGKPTGAGPKDNGGACGYKD	VDK PF+GMT	78
Query	79	GCGNTPIFKDRGRCGSCFEIKCTK	PESCSGEAVITITDDNEEPIAPYH	FDLSGHAFGSM	138
Sbjct	79	GCGNTPIFK GRGCGSCFEIKCTK	PE+CSGE V V ITDDNEEPIAPYH	FDLSGHAFG+M	138
Query	139	AKKGEEQKLR	SAGELELQFRRVKCKYPDGTKPT	FHVEKASNPNYLAILVKYVDGD	DVVA 198
Sbjct	139	AKKG+EQKLR	SAGELELQFRRVKCKYP+GTK	IFHVEK SNPNYLA+LVKYV+GD	DVVA 198
Query	199	VDIKEKGKDKWIELKESWGAV	WRIDTPDKLTGPFTVRYTTEGGTK	SEVEDVIPEGWKADT	258
Sbjct	199	VDIKEKGKDKWIELKESWGA+WR	IDTPDKLTGPFTVRYTTEGGTK+E	EDVIPEGWKADT	258
Query	259	SYSK 263			
Sbjct	259	SY +K 263			

FIGURE 14: ALIGNMENT OF THE PROTEIN SEQUENCE OF GROUP 1 BETA EXPANSIN ALLERGENS LOL P 1 AND PHL P 1 OF TEMPERATE RYEGRASS AND TIMOTHY GRASS RESPECTIVELY

Lol p 5 (IUIS: Lol p 5.0102; Griffith et al. 1991) vs Phl p 5 (IUIS: Phl p 5.0101; Dolecek et al. 1993)

unnamed protein product

Sequence ID: Query\_197447 Length: 308 Number of Matches: 1

Range 1: 109 to 277 [Graphics](#) ▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
119 bits(299)	3e-36	Compositional matrix adjust.	97/173(56%)	111/173(64%)	6/173(3%)
Query 125	LTSKLDAAAYKLAYKTAEGATPEAKYDAYVATLSEALRIIAGTLEVHAVKPAEEVKV--I				182
	L KLD AY +AYK AE A P +		+LR+IAG LEVHAVKPA EEV I		
Sbjct 109	LIPKLDIAYDVAYKAAE-AHPRGQVRRRLRHCPHRSLRVIAGALEVHAVKPATEEVLAAKI				167
Query 183	PAGELQVIEKVDAAFKVAATAANAAPANDKFTVFEEAFNDAIKASTGGAYESYKFIPALE				242
	P GELQ+++K+DAAFK+AATAANAAP NDKFTVFE+AFN A+ TGGA P				
Sbjct 168	PTGELQIVDKIDAAFKIAATAANAAPTNDKFTVFESAFNKALNECTGGAMRPTSSSPPSR				227
Query 243	AAVKQAYAATVATAPEVKYTVFETALKKAITAMSEAQKAAPAAAATATATAA				295
	+ APEVKY VFE AL KAITAM++AQKA KPAAAA AA				
Sbjct 228	PRSSRPTPPSPAAPEVKYAVFEAALTKAITAMTQAQKAGKPAAAAAT---AA				277

FIGURE 15: ALIGNMENT OF THE PROTEIN SEQUENCE OF GROUP 5 ALLERGENS LOL P 5 VS PHL P 5 OF TEMPERATE RYEGRASS AND TIMOTHY GRASS RESPECTIVELY

## APPENDIX X

### ASCIA: Thunderstorm asthma information



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[www.allergy.org.au](http://www.allergy.org.au)

# Information

FOR PATIENTS, CONSUMERS AND CARERS



## Thunderstorm asthma

It seems reasonable to think that rain would relieve allergic rhinitis (hay fever) and asthma triggered by pollen, by washing pollen out of the air. However, rain from some thunderstorms can make some people's symptoms worse. Epidemics of thunderstorm asthma in Australia have occurred in Melbourne and Wagga Wagga.

**Around 1 in 4 people with allergic rhinitis also have asthma**

It is important to recognize that pollen can trigger asthma as well as hay fever symptoms. Many people with hay fever due to grass pollen allergy can get wheeze or chest tightness in the spring and summer season when they also have hay fever. This is likely to be asthma triggered by grass pollen allergy.

**Grass pollen can be wind-blown for long distances**

Grasses rely on the wind to distribute their pollen. A single hectare of ryegrass pasture, for example, will release hundreds of kilograms of pollen per season. The concentration of pollen will be highest nearest its source, but high speed winds can distribute pollen grains over long distances.

Intact pollen grains (generally 12-60 micrometre diameter) are usually trapped in the upper airways and do not reach the lungs. Other allergen carrying particles including atmospheric pollutants (as small as 0.1 micrometre diameter) can carry grass and tree pollen allergens. Unlike intact pollen, these smaller particles are capable of reaching the small airways of the lung and triggering asthma attacks.

**Thunderstorms and weather changes can trigger asthma attacks**

Thunderstorm asthma is thought to be triggered by massive loads of small pollen allergen particles being released into the air during some thunderstorms that have rapid changes in wind, temperature and humidity.

A single pollen grain contains up to 700 starch granules and some grass pollen allergens are located in these starch granules. When it rains or is humid, pollen grains can absorb moisture and burst open, releasing hundreds of small pollen allergen particles that can penetrate deep into the small airways of the lung.

Not everyone affected by Australian thunderstorm asthma epidemics has had thunderstorm asthma before. However, they have usually had severe hay fever and have been found to be allergic to ryegrass pollen.

It is important to note that:

- Not all thunderstorms, even on days with high pollen counts, trigger thunderstorm asthma
- Other weather factors are involved in thunderstorm asthma
- It is not only people with pollen allergy who may be affected by thunderstorm asthma
- Other allergens such as fungal spores, massive humidity and temperature changes over a short period can also affect some people with asthma and other respiratory diseases during a thunderstorm

**Pollen asthma can be treated effectively**

If you wheeze during Spring or have severe hay fever, see your doctor for appropriate advice.

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### ASCIA INFORMATION FOR PATIENTS, CONSUMERS AND CARERS

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If your asthma is triggered by pollens, and is worse in the spring and summer when hay fever is active, then it is important that you have a current asthma action plan and that you regularly use a preventer medication, especially during this time.

Allergen immunotherapy (desensitisation) reduces pollen allergy and has been shown to be beneficial for hay fever (allergic rhinitis) and allergic asthma.

#### What can I do to protect myself from thunderstorm asthma?

Firstly see your doctor to make sure that your hay fever due to grass pollen is well treated. Regular use of nasal corticosteroid sprays is more effective than antihistamine tablets for severe hay fever, and both treatments can be used together.

If you experience any symptoms of asthma such as chest tightness, wheeze, shortness of breath, cough, waking with breathing symptoms then see your doctor for assessment and get a plan to manage asthma.

You should have access to a preventer medication and make sure to use it every day, particularly if high pollen counts and or thunderstorms are predicted.

Thunderstorms are common in spring so if you have bad hay fever try to avoid being outside on high pollen days, particularly during windy days and thunderstorms.

#### Further information

Allergic Rhinitis: <http://allergy.org.au/patients/allergic-rhinitis-hay-fever-and-sinusitis>  
AusPollen pollen monitoring network: [www.pollenforecast.com.au](http://www.pollenforecast.com.au)  
Sydney, Melbourne, Canberra and Brisbane pollen count websites and apps are available at:  
[www.sydneypollen.com.au](http://www.sydneypollen.com.au)  
[www.melbournepollen.com.au](http://www.melbournepollen.com.au)  
[www.canberrapollen.com.au](http://www.canberrapollen.com.au)  
[www.brisbanepollen.com.au](http://www.brisbanepollen.com.au)

Asthma Australia: [www.asthmaaustralia.org.au/](http://www.asthmaaustralia.org.au/)  
National Asthma Council: [www.nationalasthma.org.au](http://www.nationalasthma.org.au)

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Content last updated December 2016

## APPENDIX XI

### Abstracts

1. (2001). "Thunderstorms and asthma." Jama-Journal of the American Medical Association **285**(22): 2847-2847.
2. (2001). "Thunderstorms and asthma exacerbations." Medicine Today **2**(7): 10.
3. (2003). "RN news watch: clinical highlights. Study confirms link between thunderstorms and asthma attacks." RN **66**(6): 20-81.
4. (2006). "Thunderstorm advice." Practice Nurse **31**(12): 7-7.
5. (2010). "Ask the experts. Thunderstorms and your health." AMT Events **27**(3): 167-179.
6. (2010). "Storm's a-comin'." Harvard Health Letter **35**(10): 1-3.
  - a. Summer thunderstorms can be exciting, but they also have some health effects you may not know about.
7. (2014). "Thunderstorm asthma." Emerg Nurse **22**(6): 13.
  - a. AN ASSOCIATION between asthma and thunderstorms based on retrospective data has been noted in several papers. This study, however, draws on almost-real-time, anonymised attendance data from 35 emergency departments (EDs) in the UK, and lightning-strike plots from the Met Office.
8. Abou Chakra, O., et al. (2011). "Ability of Pollen Cytoplasmic Granules to Induce Biased Allergic Responses in a Rat Model." International Archives of Allergy and Immunology **154**(2): 128-136.
  - a. Background: Grass pollen is one of the most important aeroallergens in Europe. It highly contributes to respiratory allergic diseases, mainly allergic rhinitis. In contact to water or airborne pollutants, pollen grains can release pollen cytoplasmic granules (PCGs) containing allergens. Because of their size (< 5 µm), PCGs may penetrate deeper into the lungs to induce higher allergic responses, such as asthma. They have been associated with thunderstorm-related asthma. The aim of this study was to evaluate, with Brown Norway rats, the allergenic potential of isolated PCGs and to compare it with the allergenicity of whole timothy grass pollen. Methods: Rats were sensitized (day 0) and challenged (day 21), in controlled comparative conditions, with pollen grains (0.5 mg) or PCGs (4.5 x 10(7) and 0.5 mg). At day 25, blood samples, bronchoalveolar lavage fluid (BALF) and bronchial lymph node were collected. IgE and IgG1 levels in sera were assessed by ELISA. Alveolar cells, protein and cytokine concentrations were quantified in BALF. T cell proliferation, in response to pollen or granules, was performed by lymph node assay. Results: The results showed that proliferative responses of lymph node cells were similar in PCG- and pollen-sensitized rats. IgE and IgG1 levels were higher in pollen-than in PCG-sensitized rats. However, eosinophils, lymphocytes and pro-allergy cytokines in BALF were higher in PCG- than in pollen-sensitized rats. Conclusions: Thus, PCGs, able to deeply penetrate in the respiratory tract, induced local and strong allergic and inflammatory responses more linked with asthma-than rhinitis-related allergic symptoms. Copyright (C) 2010 S. Karger AG, Basel
9. Abou Chakra, O., et al. (2009). "Towards an identification of water soluble and water-insoluble allergens of pollen cytoplasmic granules." Allergy: European Journal of Allergy and Clinical Immunology **64**: 108.
  - a. Background: Grass pollen is one of the most important aeroallergens in Europe. It highly contributes to respiratory allergic diseases such as asthma or allergic rhinitis. In contact to water or airborne pollutants, pollen grains can release microparticles called 'pollen cytoplasmic granules' or PCG. Because of their small size (<5 µm), PCG may penetrate deeper than pollen grains into the lungs. They could induce higher allergic responses and are already associated with thunderstorm asthma. PCG allergens have been poorly studied. The goal of this study was to identify the water-soluble and water-insoluble allergens of the PCG and to compare them to those of whole pollen grains. Methods: PCG were isolated from timothy pollen by osmotic shock in water, following by filtration and centrifugation. For water-insoluble extracts, PCG and whole pollen grains were suspended in mixture of thiourea (2M), urea (7M) and CHAPS (5% w/v). Water-insoluble proteins were separated by immobilized pH gradient following by SDS-PAGE. The separation of water-soluble proteins was performed by isoelectric focusing following by 2D SDS-PAGE. Allergen contents were analyzed by immunoblotting using a set of grass pollensensitive patient sera. Results: In the water-soluble extract of PCG, most of the proteins had small relative molecular masses (Mr <40 kDa) and isoelectric points (pI) comprised between 4.45 and 8.2. In comparison to water-soluble extract of whole pollen grains, several water-soluble allergens such as Phl p 1, Phl p 5 and Phl p 6 were present on whole pollen grains and PCG, but other allergens such as Phl p 4 and Phl p13 were present only in whole pollen grains. However, immunoblotting of water soluble extract of PCG showed different specific spots for these microparticles: (23.4 kDa; 5.85), (24.1 kDa; 7.05) and (73 kDa; 2.5). In the other hand, the immunoblot of water-insoluble extract of PCG revealed that the majority of proteins had a Mr ranged between 30 and 45 kDa and a pI between 4.45 and 7.5. In comparison to water-insoluble extract of pollen grains, most waterinsoluble allergens present in PCG were common to those of pollen grains except two specific spots: (15.7 kDa; 4.85) and (16.4 kDa; 4.7). Conclusions: In water soluble and waterinsoluble extracts, whole pollen grains presented a greater spectrum of proteins than PCG. Moreover, although the majority of allergens were common to PCG and whole pollen grains, other allergens seem to be associated only with PCG.
10. Alderman, P. M., et al. (1986). "Asthma and thunderstorms." Archives of Emergency Medicine **3**(4): 260-262.
11. Alifano, M., et al. (2007). "Atmospheric pressure influences the risk of pneumothorax - Beware of the storm!" Chest **131**(6): 1877-1882.
  - a. Background: idiopathic spontaneous pneumothorax (ISP) results from rupture of blebs, bullas, or diseased alveolar walls. Initiating mechanisms may relate to increased transpulmonary pressure. The possible impact of changes in atmospheric pressure (Patm) on the occurrence of ISP remains uncertain. Methods: We

studied the relationship between the occurrence of ISP and meteorological conditions during a 4-year period in the urban area of Bologna, Italy, in which all cases of pneumothorax can be exhaustively identified. For each day of the study period, Patm and ambient temperature were obtained from the local meteorological institute. A cluster was defined as the admission of at least two patients with pneumothorax within 3 days of each other. Results: There were 294 episodes of ISP; 247 (84%) occurred in 76 clusters. Clusters were significantly associated with wider differences in Patm between the index day (ie, the first day of the cluster) and the previous day (ie, the difference in mean  $\pm$  SEM] Patm,  $-1.23 \pm 0.45$  vs  $+0.04 \pm 0.12$  mm Hg, respectively;  $p = 0.01$  [analysis of variance]). Similarly, pneumothorax and storms (but not temperature) were significantly associated ( $p < 0.0001$  [X-2 test]). Conclusions: This large-scale study shows that patients with ISP are hospitalized in clusters and suggests that important variations in Patm may be involved. The knowledge of this relationship may help to understand the pathophysiology of the disease.

12. Allitt, U. (2000). "Airborne fungal spores and the thunderstorm of 24 June 1994." *Aerobiologia* **16**(3-4): 397-406.
  - a. On the evening of 24 June 1994 there were thunderstorms which passed from the south to the north over large areas of England, followed by an extensive and initially alarming episode of 'thunderstorm asthma'. It was eventually concluded that the probable cause of this episode was the release of allergenic particles from wetted grass pollen. As part of the investigation of this episode changes in the fungal air spora were investigated at several sites. The fungal spores present varied from site to site. At London, Addlestone and Leicester there were very marked transient peaks of smut ustilospores, (and to a much smaller extent at Cambridge), particularly those of *Ustilago segetum* (Bull.) Roussel. At many sites there were transient peaks of *Cladosporium* conidia. The possible causes of the transient peaks are discussed. At most of the other sites except London there were high concentrations of ascospores after the rain. Typically, *Didymella* ascospores occur after rain, but on this occasion they occurred at low concentrations at all sites, because of dry weather in the previous month. Instead, there were high concentrations of ascospores which normally occur in far lower numbers, viz. ascospores of *Phaeosphaeria nigrans* and *Diatrypaceous* ascospores. The reasons for this were related to increased rainfall in the previous thirteen months. There were site to site differences in the ascospore composition of the air spora, and this was related to habitat differences, where this was known.
13. Allitt, U. and M. A. Stern (1997). *Asthma and Didymella ascospores following a thunderstorm in Leicester (England)*.
  - a. In the late afternoon of 2 July 1989 there was a thunderstorm in Leicester (England). During the evening, after the rain had stopped, there were many cases of acute asthma. A microscopic examination was made of the Burkard spore trap trace for the relevant period. This showed that although there were many changes in the air-spores after the storm, the most significant change was the occurrence of high concentrations of *Didymella* ascospores. The hourly concentration was approximately 60,000 m<sup>-3</sup> air at 22.00, 23.00 and 00.00 hrs GMT. During this period, *Didymella* ascospores occurred in clumps of less than eight which were interpreted as part-octads. After this period, *Didymella* concentrations declined, and those of *Sporobolomyces* rose. Spore numbers were compared with meteorological factors, particularly rain.
14. Almaguer, M., et al. (2014). "Airborne basidiospores of *Coprinus* and *Ganoderma* in a Caribbean region." *Aerobiologia* **30**(2): 197-204.
  - a. The present study sought to examine *Coprinus* and *Ganoderma* airborne spore counts, analysing seasonal variations, the influence of meteorological variables and intraday behaviour with a view to charting the aerobiological dynamics of both genera in Havana (Cuba) during a 2-year period (November 2010-October 2012). A Hirst-type volumetric air sampler was used as sampling methodology. The spores registered in the air were identified and counted following the model proposed by the Spanish Aerobiological Network based on two longitudinal transects along the slides. *Coprinus* spores outnumbered those of the *Ganoderma* (28,468 annual total spores vs. 1,921 spores). Moreover, both genera were recorded in the atmosphere on a large number of days over the two-year study period, with daily maximum concentrations in the rainy months. The daily maximum value for *Coprinus* was 880 spores/m<sup>3</sup> (30 September 2011), whereas for *Ganoderma* 44 spores/m<sup>3</sup> (4 September 2011). The analysis of the Spearman correlation coefficient showed a significant positive correlation of the airborne *Coprinus* and *Ganoderma* spores with the temperature, relative humidity and rainfall, whereas the degree of association is negative with the wind speed. Regarding the intraday behaviour, both basidiospores were more abundant in the atmosphere during the night, with a maximum peak at 5-6 a.m.
15. Al-Rubaish, A. M. (2007). "Thunderstorm-associated bronchial asthma: a forgotten but very present epidemic." *J Family Community Med* **14**(2): 47-51.
  - a. Acute episodes of bronchial asthma are associated with specific etiological factors such as air pollutants and meteorological conditions including thunderstorms. Evidence suggests that thunderstorm-associated asthma (TAA) may be a distinct subset of asthmatics, and, epidemics have been reported, but none from Saudi Arabia. The trigger for this review was the TAA epidemic in November 2002, Eastern Saudi Arabia. The bulk of patients were seen in the King Fahd Hospital of the University, Al-Khobar. The steady influx of acute cases were managed effectively and involved all neighboring hospitals, without evoking any "Major Incident Plan". THREE GROUPS OF FACTORS ARE IMPLICATED AS CAUSES OF TAA: pollutants (aerobiologic or chemical) and meteorological conditions. Aerobiological pollutants include air-borne allergens: pollen and spores of molds. Their asthma-inducing effect is augmented during thunderstorms. Chemical pollutants include greenhouse gases, heavy metals, ozone, nitrogen dioxide, sulfur dioxide, fumes from engines and particulate matter. Their relation to rain-associated asthma is mediated by sulfuric and nitric acid. Outbreaks of non-epidemic asthma are associated with high rainfall, drop in maximum air temperature and pressure, lightning strikes and increased humidity. Thunderstorm can cause all of these and it seems to be related to the onset of asthma epidemic. Patients in epidemics of TAA are usually young atopic adults not on prophylaxis steroid inhalers. The epidemic is usually their first known attack. These features are consistent with the hypothesis that TAA is related to both aero-allergens and weather effects. Subjects allergic to pollen who are in the path of thunderstorm can inhale air loaded with pollen allergen and so have acute asthmatic response. TAA runs a benign course. Doctors should be aware of this phenomenon and the potential outbreak of asthma during heavy rains. A & E departments and ICU should be alert for possible rush of asthmatic admissions and reinforce ventilators and requirements of cardio-pulmonary resuscitation. Scientific approach should be adopted to investigate such outbreaks in the future and must include meteorological, bioaerosol pollutants and chemical pollutant assessment. Regional team work is mandatory.
16. Anderson, W., et al. (2001). "Asthma admissions and thunderstorms: A study of pollen, fungal spores, rainfall, and ozone." *QJM - Monthly Journal of the Association of Physicians* **94**(8): 429-433.

17. Anto, J. M. (1995). "ASTHMA OUTBREAKS - AN OPPORTUNITY FOR RESEARCH." *Thorax* **50**(3): 220-222.
18. Anto, J. M. and J. Sunyer (1997). "Thunderstorms: A risk factor for asthma attacks." *Thorax* **52**(8): 669-670.
19. Atkinson, R. W. and D. P. Strachan (2004). "Role of outdoor aeroallergens in asthma exacerbations: epidemiological evidence." *Thorax* **59**(4): 277-278.
  - a. Confounding factors complicate the interpretation of time series studies in examining the role of outdoor aeroallergens in asthma exacerbations.
20. Atkinson, R. W., et al. (2006). "Temporal associations between daily counts of fungal spores and asthma exacerbations." *Occupational and Environmental Medicine* **63**(9): 580-590.
  - a. Background: Outdoor aeroallergens are one of a number of environmental factors thought to precipitate asthma exacerbations. Aims: To investigate the short term associations between daily fungal spore concentrations and indicators of daily asthma exacerbations in a large urban population. Methods: Daily counts of visit for asthma to family physicians and hospital accident and emergency (A&E) departments and emergency hospital admissions in London 1992-93 were compiled. Daily concentrations of fungal spores (30 species), daily average temperature, humidity, and concentrations of pollen and outdoor air pollution were also compiled. The analysis was restricted to the period when fungal spores were most prevalent (June to mid-October). Non-parametric regression time series methods were used to assess associations controlling for seasonality, day of week, and meteorological factors. The sensitivity of the findings to the inclusion of pollen and air pollution into the models was also assessed. Results: In children aged 0-14 years the relative risks for increases in the number of A&E visit and hospital admissions associated with changes in fungal spore concentrations from the lower to upper quartiles were 1.06 (95% CI 0.94 to 1.18) and 1.07 (0.97 to 1.19) respectively. The addition of pollen or air pollutants had little impact on the observed associations. A number of individual spore taxa, in particular *Alternaria*, *Epicoccum*, *Agrocybe*, *Mildews*, and both coloured and colourless Basidiospores and Ascospores, were associated with increases in the number of emergency visit and hospital admissions for asthma, although the precision of these estimates were low. No evidence was found for associations in adults. Conclusions: Fungal spore concentrations may provoke or exacerbate asthma attacks in children resulting in visit to A&E departments and emergency hospital admissions. These findings were unlikely to be due to confounding by other environmental factors. The associations were comparable to those observed for ambient air pollution from similarly designed studies.
21. Badorrek, P., et al. (2012). "Pollen starch granules in bronchial inflammation." *Annals of Allergy Asthma & Immunology* **109**(3): 208-+.
  - a. Background: Pollen grains with a diameter of more than 10  $\mu$ m preferentially deposit in the upper airways. Their contribution to lower airway inflammation is unclear. One hypothesis is that lower airway inflammation is mainly caused by allergen containing pollen starch granules, which are released from the pollen grains and can easily enter the peripheral airways because of their smaller size. Objective: To investigate the differential effect of pollen grains and pollen starch granules on nasal symptoms and lower airway inflammation. Methods: In a 2-period crossover design, 30 patients with allergic rhinitis and mild intermittent asthma underwent 2 allergen challenges on consecutive days in an environmental challenge chamber with either a mixture of pollen grains plus starch granules or starch granules only. End points were the total nasal symptom score (TNSS), nasal secretion weight, nasal flow, spirometry, and exhaled nitric oxide (eNO). Results: The presence of pollen grains had a significant and considerable effect on increase in TNSS and secretion weight and on decrease in nasal flow. Starch granules alone only had minimal effects on nasal symptoms. Challenges with starch granules significantly increased eNO. Pollen had no effect on eNO. Conclusion: Pollen grains cause nasal symptoms but do not augment lower airway inflammation, whereas starch granules trigger lower airway inflammation but hardly induce nasal symptoms. (C) 2012 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.
22. Balbus, J. M. (1999). *Asthma and global climate change*.
  - a. Global climate change is expected to result in direct and indirect changes in factors that are associated with asthma exacerbation. These factors include the weather (e.g., thunderstorms, sudden temperature or pressure changes), outdoor air pollutants (e.g., ozone, sulfur oxides, nitrogen oxides), and outdoor aeroallergens. Global climate change will manifest as highly variable climate change between regions, prohibiting generalisations about future changes in weather variables. A more active hydrologic cycle may produce more frequent and severe thunderstorms and cooling episodes. Warmer temperatures are associated with higher ozone concentrations. Lastly, pervasive climate changes are likely to alter dominant vegetation in specific regions, with secondary changes in aeroallergen timing and intensity. Whether some or all of these changes will have an impact on overall asthma incidence is highly uncertain. Indoor allergens and infection-related shifts in T-helper responses, which appear to play significant roles in the pathogenesis of asthma, are less likely to be affected by global climate change.
23. Barker, J. and G. Brear (2006). The critically ill asthmatic. *Handbook of ICU Therapy, Second Edition*: 381-391.
24. Barnig, C. and A. Casset (2012). "Respiratory allergens and asthma exacerbation." *Revue Des Maladies Respiratoires* **29**(6): 810-819.
  - a. Introduction. - Asthma exacerbations are characterized by a progressive aggravation of respiratory symptoms such as dyspnea, cough, wheezing or chest tightness. Background. - The relationship between allergy and asthma exacerbations has been evaluated by epidemiological studies based on various criteria such as oral corticosteroid requirement, emergency room visit and hospital admission for asthma. Many studies have observed that deteriorating asthma can be related to increased exposure to allergens, particularly allergens from house dust mite, cockroach, cat, rodent, mold or pollen. Several studies have demonstrated that sensitisation to respiratory allergens and allergen exposure increases the risk of exacerbation of asthma. When asthma exacerbations are work-related, occupational allergens may be implicated. Conclusions and perspectives. - Most studies provide evidence that allergen exposure contributes to the risk of asthma exacerbations, but other precipitating factors, such as viruses, can interact and increase the risk. (C) 2012 SPLF. Published by Elsevier Masson SAS. All rights reserved.
25. Bauman, A. (1996). "Asthma associated with thunderstorms." *Bmj* **312**(7031): 590-591.

26. Baxi, S. N., et al. (2016). "Exposure and Health Effects of Fungi on Humans." Journal of Allergy and Clinical Immunology: In Practice **4**(3): 396-404.
27. Beggs, P. J. (2012). Impacts of climate change on aeroallergens and allergic respiratory diseases in children in rural areas. Respiratory Diseases: Causes, Treatment and Prevention: 111-124.
28. Beggs, P. J. (2017). "Allergen aerosol from pollen-nucleated precipitation: A novel thunderstorm asthma trigger." Atmospheric Environment **152**: 455-457.
29. Bellomo, R. (1992). "thunderstorm ASSOCIATED EPIDEMICS OF ASTHMA - REPLY." Medical Journal of Australia **157**(5): 352-353.
30. Bellomo, R., et al. (1992). "Two consecutive thunderstorm associated epidemics of asthma in the city of Melbourne. The possible role of rye grass pollen." Medical Journal of Australia **156**(12): 834-837.
  - a. Objective: To document the clinical impact and identify the meteorological and environmental circumstances surrounding two epidemics of asthma exacerbations associated with thunderstorms in the city of Melbourne and to find a possible aetiology for these events. Design: Collection of meteorological and environmental data from the Victorian Bureau of Meteorology and the Environment Protection Authority; collection of clinical data from metropolitan emergency departments and the Victorian Ambulance Service; and study of a cohort of affected patients with asthma and a control group of asthmatics who were not affected by the storms. Setting: Tertiary institution. Patients: Twelve storm-affected patients with asthma and 16 asthmatics not affected by the storms. Intervention: Administration of a questionnaire, medical interview, pulmonary function tests and skin prick tests with common allergens. Main outcome and results: Both epidemics caused a major increase in the number of hospital attendances and admissions because of asthma exacerbation (five to ten fold rise). These events could not be related to atmospheric pollution or specific meteorological features of the storms. Patients affected by the second storm were significantly more likely to suffer from hayfever ( $P < 0.05$ ), rye grass pollen allergy ( $P < 0.05$ ) and allergy to rainfall released rye grass starch granules ( $P < 0.025$ ). Conclusions: Late spring thunderstorms in the city of Melbourne can trigger epidemics of asthma attacks. The seasonal nature of the phenomenon and the pattern of allergic responses found in affected patients suggest a possible aetiological role for rye grass pollen.
31. Bentham, G., et al. (1996). "Effect of ozone, thunderstorms and other weather conditions on the respiratory function of asthmatics." Thorax **51**(SUPPL. 3).
32. Bergmann, K. C. (2013). "Climate change and allergic asthma." Atemwegs- und Lungenkrankheiten **39**(11): 451-460.
  - a. Climate change is characterized by raised temperatures, CO<sub>2</sub>, ultraviolet rays and ozone. Asthmatics are at a higher risk in suffering more from the results of climate change due to non-specific and allergen-specific bronchial hyperreactivity. Climate change effects the formation, distribution and number of allergenic pollen. Tree pollen appear earlier in the year and in higher numbers, grass pollen have a decreasing trend and mugwort pollen have a longer season. It is possible that in few years, an all-year round pollen load will exist. In cities the combination of pollen and air pollution leads to special problems for pollen asthmatics. Similarly, thunderstorm periods are also a special risk. The influence of climate change on molds has been less examined. In indoor areas, it could cause changes (increase) to the mite populations through warmer winters and as a result of reduced heating. The German Governments "Adaptation Program" is an attempt to limit the health-threatening results of climate change. © 2013 Dustri-Verlag Dr. Karl Feistle.
33. Bergmann, K. C. (2016). "Weather conditions and climate change have an effect on allergies." Allergo Journal **25**(5): 33-39.
34. Bopaka, R. G., et al. (2015). "Correlation between control of asthma and skin sensitisation to mold." Revue Francaise D Allergologie **55**(8): 517-520.
  - a. The aim of this study was to evaluate the control of symptoms in asthmatic patients and its relation to sensitisation to molds. This retrospective study, which took place between September 2011 and July 2013, included 219 asthmatic patients which we divided into two groups: group 1 was composed of the 44 patients (20% of the patients, of which 71% were females), who were sensitized to at least one mold and group 2 was composed of the 175 patients (62% females), who were not sensitized to molds, this diagnosis having been established by prick-tests for allergic sensitivity to airborne molds. We used the Global Initiative for Asthma (GINA) as the basis for the evaluation of asthma control. We found that asthma was "partially controlled" in 68% of group 1 patients but "partially controlled" in only 31% of group 2 patients ( $P < 0.001$ ). In contrast, asthma was "controlled" in only 25% of group 1 patients compared to 57% in group 2 who were "controlled" ( $P < 0.001$ ). As a result of this study, we point out that sensitisation to molds is not rare in Morocco and constitutes a risk factor for poor control of asthma, and we recommend that sensitisation to molds should be considered in all patients with poorly controlled asthma. (C) 2015 Elsevier Masson SAS. All rights reserved.
35. Bousquet, J., et al. (2003). "Links between rhinitis and asthma." Allergy **58**(8): 691-706.
  - a. There is compelling evidence of a close relationship between the upper and lower airways in asthma and rhinitis. Rhinitis is present in the majority of patients with asthma, and a significant minority of patients with rhinitis have concomitant asthma. Similarities between the two conditions occur in the nature of the inflammation present in the target tissues. A common initiating step in the inflammatory process of allergic airways disease is the presence of immunoglobulin E providing an adaptor molecule between the offending allergen and inflammatory cell activation and mediator release. Differences in the two conditions arise largely from the structural differences between the nose and the lungs. In an asthmatic, concomitant allergic rhinitis increases healthcare costs and further impairs quality of life. The presence of rhinitis should always be investigated in children and young adults with asthma. Subjects with allergic rhinitis have an increased risk of developing asthma and may form a suitable population for secondary intervention to interrupt the 'allergic march'.
36. Burch, M. and E. Levetin (2002). "Effects of meteorological conditions on spore plumes." International Journal of Biometeorology **46**(3): 107-117.
37. Burge, H. A. (2002). "An update on pollen and fungal spore aerobiology." Journal of Allergy and Clinical Immunology **110**(4): 544-552.

- a. Changes in climate are altering pollen distribution. Predictive modelling can be used to forecast long- and short-term changes in pollen concentrations. Increasing evidence confirms the presence of pollen allergens on small, respirable particles in the air, explaining the occurrence of pollen-season increases in asthma. Like pollens, above ground indoor fungal aerosols primarily reflect outdoor concentrations. Basement spore concentrations might be higher and reflective of local sources. Fungal presence in the indoor or outdoor air can be monitored on an area basis or with personal monitors. The samples can be analyzed by means of microscopy, culture, DNA probes, HPLC, or immunodetection. Total fungal biomass can be estimated on the basis of measurements of ergosterol or glucan in environmental samples. Unfortunately, there are no generally accepted standards for interpretation of fungal levels in indoor or outdoor air. At present, the best approach to indoor fungal control is moisture control in the indoor environment. This will essentially prevent fungal growth, except from extraordinary events.
38. Buters, J., et al. (2015). "Variation of the group 5 grass pollen allergen content of airborne pollen in relation to geographic location and time in season." *Journal of Allergy and Clinical Immunology* **136**(1): 87-U179.
- a. Background: Allergies to grass pollen are the number one cause of outdoor hayfever. The human immune system reacts with symptoms to allergen from pollen. Objective: We investigated the natural variability in release of the major group 5 allergen from grass pollen across Europe. Methods: Airborne pollen and allergens were simultaneously collected daily with a volumetric spore trap and a high-volume cascade impactor at 10 sites across Europe for 3 consecutive years. Group 5 allergen levels were determined with a Phl p 5-specific ELISA in 2 fractions of ambient air: particulate matter of greater than 10  $\mu\text{m}$  in diameter and particulate matter greater than 2.5  $\mu\text{m}$  and less than 10  $\mu\text{m}$  in diameter. Mediator release by ambient air was determined in Fc epsilon RI-humanized basophils. The origin of pollen was modeled and condensed to pollen potency maps. Results: On average, grass pollen released 2.3  $\mu\text{g}$  of Phl p 5 per pollen. Allergen release per pollen (potency) varied substantially, ranging from less than 1 to 9  $\mu\text{g}$  of Phl p 5 per pollen (5% to 95% percentile). The main variation was locally day to day. Average potency maps across Europe varied between years. Mediator release from basophilic granulocytes correlated better with allergen levels per cubic meter ( $r(2) = 0.80, P < .001$ ) than with pollen grains per cubic meter ( $r(2) = 0.61, P < .001$ ). In addition, pollen released different amounts of allergen in the non-pollen bearing fraction of ambient air, depending on humidity. Conclusion: Across Europe, the same amount of pollen released substantially different amounts of group 5 grass pollen allergen. This variation in allergen release is in addition to variations in pollen counts. Molecular aerobiology (ie, determining allergen in ambient air) might be a valuable addition to pollen counting.
39. Buters, J. T. M. (2015). "Pollen, allergens, mould and bacteria in ambient air." *Allergologie* **38**(12): 590-596.
- a. Allergic diseases are on the rise since decades. Despite many years of research it is still unclear which environmental factors are mainly responsible for this continuous increasing incidence of allergic sensitisations. There is evidence on a protective role of biological components in a selected group of farm children with barn contact. Besides this, the effects of biological exposure on allergic diseases in comparison to chemical exposure are poorly investigated. This is partly due to the fact that biological components in ambient air are insufficiently monitored. Pollen in ambient air is monitored, but the amount of allergen released per pollen varies 10-fold, from grass pollen even 20-fold. In addition, free, non-pollen bound allergens are detected. Bacteria in ambient air are not (or seldom) monitored, and molds to a limited extend. The monitoring of pollen and the allergic symptoms they provoke have progressed in recent years. Online symptom diaries, downloaded as apps, are available and make it possible to use allergic individuals as biological monitors for allergic symptoms and provide other allergic individuals with this information online. Online pollen monitors that provide close to real-time pollen concentrations are currently being tested. The monitoring of biological components in ambient air, like pollen and molds is mostly performed by volunteers. To guarantee continuity, homogeneity and completeness of data it would be preferable that pollen monitoring becomes a publically funded activity. Without a correct monitoring of biological exposure a primary prophylaxes of allergic diseases is not possible. To stop the allergy-epidemic this approach should be preferred.
40. Caillaud, D., et al. (2005). "Asthma and thunderstorms." *Revue Francaise d'Allergologie et d'Immunologie Clinique* **45**(1): 29-32.
41. Canário, P., et al. (2014). "Environmental conditions and childhood asthma in LISBON. An exploratory analysis for autumn thunderstorms." *Finisterra* **49**(98): 179-196.
42. Cecchi, L., et al. (2010). "Projections of the effects of climate change on allergic asthma: the contribution of aerobiology." *Allergy* **65**(9): 1073-1081.
- a. Climate change is unequivocal and represents a possible threat for patients affected by allergic conditions. It has already had an impact on living organisms, including plants and fungi with current scenarios projecting further effects by the end of the century. Over the last three decades, studies have shown changes in production, dispersion and allergen content of pollen and spores, which may be region- and species-specific. In addition, these changes may have been influenced by urban air pollutants interacting directly with pollen. Data suggest an increasing effect of aeroallergens on allergic patients over this period, which may also imply a greater likelihood of the development of an allergic respiratory disease in sensitized subjects and exacerbation of symptomatic patients. There are a number of limitations that make predictions uncertain, and further and specifically designed studies are needed to clarify current effects and future scenarios. We recommend: More stress on pollen/spore exposure in the diagnosis and treatment guidelines of respiratory and allergic diseases; collection of aerobiological data in a structured way at the European level; creation, promotion and support of multidisciplinary research teams in this area; lobbying the European Union and other funders to finance this research.
43. Celenza, A., et al. (1996). "Thunderstorm associated asthma: A detailed analysis of environmental factors." *British Medical Journal* **312**(7031): 604-607.
- a. Objectives - To meteorological pollutants or pollen, and an asthma epidemic which occurred in London on 21 and 29 June 1994 after a thunderstorm. Design- Retrospective study of patients' accident and emergency department records, with bivariate and multivariate analysis of environmental factors and data collection for the two months surrounding the epidemic. Setting - The accident and emergency department of St Mary's Hospital in west central London, Subjects - 148 patients presenting with asthma between 1 June and 31 July 1991, of whom 40 presented in the 24 hours after the storm. Results - The asthma epidemic was significantly associated with a drop in air temperature six hours previously and a high grass pollen concentration nine hours previously. Non-epidemic asthma was significantly associated with lightning strikes, increase in humidity or sulphur dioxide concentration, a drop in temperature or high rainfall

the previous day, and a decrease in maximum air pressure or changes in grass pollen counts over the previous two days. Conclusions - New episodes of asthma during the epidemic on 21 and 25 June 1994 were associated with a fall in air temperature and a rise in grass pollen concentration. Non-epidemic asthma was significantly associated with a greater number of environmental changes. This may indicate that the patients with thunderstorm associated asthma were a separate population, sensitive to different environmental stimuli.

44. Colquhoun, J. R. and G. B. Marks (2003). "Thunderstorm related asthma in South-Eastern Australia - Recent findings and asthma epidemic forecasting possibilities." Journal of Meteorology **28**(283): 350-353.
45. Corbett, S. W. (1996). "Asthma exacerbations during Santa Ana winds in southern California." Wilderness & Environmental Medicine **7**(4): 304-311.
  - a. This study investigated the relationship between Santa Ana wind conditions and visit for asthma at a southern California emergency department. Visits to the emergency department for asthma were analyzed retrospectively to determine whether the incidence increased during Santa Ana wind conditions. These northeasterly winds are common during fall and winter in southern California and belong to a class known as Foehn winds. They are characterized by gusty winds, decreased relative humidity, warm temperatures, and decreased levels of airborne pollutants. During a 4-year period, we noted that emergency department visit for asthma increased (3.12 vs. 2.16 visit per day,  $P < 0.0001$ ) during Santa Ana winds compared with other weather conditions. Asthmatics presenting during Santa Ana winds appeared to be more ill, as judged by higher admission rates (21.9 vs. 18.7%,  $P < 0.05$ ). These winds were also associated with reduced particulate matter ( $PM_{10}$ ) counts ( $P < 0.0001$ ). Although the magnitude of the increase in emergency department visit was small, it occurred at a time when typical inciters of respiratory disease should be minimal. An as yet unidentified factor associated with these winds may be a stimulant for some asthmatics. Similar wind patterns in other localities might affect respiratory disease as well.
46. Dabrera, G., et al. (2013). "Thunderstorm asthma: an overview of the evidence base and implications for public health advice." QJM : monthly journal of the Association of Physicians **106**(3): 207-217.
  - a. Thunderstorm asthma is a term used to describe an observed increase in acute bronchospasm cases following the occurrence of thunderstorms in the local vicinity. The roles of accompanying meteorological features and aeroallergens, such as pollen grains and fungal spores, have been studied in an effort to explain why thunderstorm asthma does not accompany all thunderstorms. Despite published evidence being limited and highly variable in quality due to thunderstorm asthma being a rare event, this article reviews this evidence in relation to the role of aeroallergens, meteorological features and the impact of thunderstorm asthma on health services. This review has found that several thunderstorm asthma events have had significant impacts on individuals' health and health services with a range of different aeroallergens identified. This review also makes recommendations for future public health advice relating to thunderstorm asthma on the basis of this identified evidence.
47. Dales, R. E., et al. (2003). "The role of fungal spores in thunderstorm asthma." Chest **123**(3): 745-750.
  - a. Study objectives: To document the existence and investigate the etiology of "thunderstorm asthma," which has been reported sporadically over the past 20 years. Design: We assessed the relationship between thunderstorms, air pollutants, aeroallergens, and asthma admissions to a children's hospital emergency department over a 6-year period. Results: During thunderstorm days ( $n = 151$  days) compared to days without thunderstorms ( $n = 919$  days), daily asthma visit increased from 8.6 to 10 ( $p < 0.05$ ), and air concentrations of fungal spores doubled (from 1,512 to 2,749/m<sup>3</sup>), with relatively smaller changes in pollens and air pollutants. Daily time-series analyses across the 6 years of observation, irrespective of the presence or absence of thunderstorms, demonstrated that an increase in total spores, equivalent to its seasonal mean, was associated with a 2.2% (0.9% SE) increase in asthma visit. Conclusions: Our results support a relationship between thunderstorms and asthma, and suggest that the mechanism may be through increases in spores that exacerbate asthma. Replication in other climates is suggested to determine whether these findings can be generalized to other aeroallergen mixes.
48. D'Amato, G. (2009). Outdoor Air Pollution and Allergic Airway Disease. Allergy and Allergic Diseases, Second Edition. **2**: 1266-1278.
49. D'Amato, G. (2011). "Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma." Multidisciplinary Respiratory Medicine **6**(1): 28-37.
  - a. Over the past two decades there has been increasing interest in studies regarding effects on human health of climate changes and urban air pollution. Climate change induced by anthropogenic warming of the earth's atmosphere is a daunting problem and there are several observations about the role of urbanisation, with its high levels of vehicle emissions and other pollutants, and westernized lifestyle with respect to the rising frequency of respiratory allergic diseases observed in most industrialized countries. There is also evidence that asthmatic subjects are at increased risk of developing exacerbations of bronchial obstruction with exposure to gaseous (ozone, nitrogen dioxide, sulfur dioxide) and particulate inhalable components of air pollution. A change in the genetic predisposition is an unlikely cause of the increasing frequency in allergic diseases because genetic changes in a population require several generations. Consequently, environmental factors such as climate change and indoor and outdoor air pollution may contribute to explain the increasing frequency of respiratory allergy and asthma. Since concentrations of airborne allergens and air pollutants are frequently increased contemporaneously, an enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of allergic respiratory diseases and bronchial asthma. Scientific societies such as the European Academy of Allergy and Clinical Immunology, European Respiratory Society and the World Allergy Organisation have set up committees and task forces to produce documents to focalize attention on this topic, calling for prevention measures.
50. D'Amato, G. (2016). "Climate change, pollen allergy and extreme events leading to increasing prevalence of allergic respiratory diseases." Toxicology Letters **259**: S27.
  - a. Evidence suggests that major changes involving the atmosphere and the climate, including global warming induced by human activity, have impact on the biosphere and human environment. Current knowledge on the worldwide effects of climate change on respiratory allergic diseases is provided by epidemiological and experimental studies on the relationship between asthma and environmental factors, like meteorological variables, airborne allergens and

air pollution. Epidemiologic studies demonstrate that urbanisation, high levels of vehicle emissions and westernized lifestyle are correlated to an increase in the frequency of pollen-induced respiratory allergy. Studies on plant responses to elevated CO<sub>2</sub> levels indicate that plant exhibit enhanced photosynthesis and produce more pollen. Meteorological factors (temperature, wind speed, humidity, thunderstorms etc.) along with their climatic regimes (warm or cold anomalies and dry or wet periods, etc.), can affect both biological and chemical components of this interaction. In addition, by inducing airway inflammation, air pollution overcomes mucosal barrier priming allergen-induced responses. There are observations that thunderstorms occurring during pollen season can induce severe asthma attacks in pollinosis patients. The hypotheses for thunderstorm-related asthma are linked with bioaerosols, and involve the role of rainwater in promoting the release of respirable particulate matter. After hydration and rupture by osmotic shock during the beginning of a thunderstorm, pollen grains may release in atmosphere part of their cytoplasmic content, including inhalable, allergen-carrying paucimicronic particles such as starch granules and other cytoplasmic components. The so called "thunderstorm asthma" is characterized by asthma outbreaks possibly caused by the dispersion of more respirable allergenic particles derived from pollen and spores by osmotic rupture. Since the first report of this phenomenon in the UK in 1985, further episodes (increase in emergency room visit and hospital admissions by asthma) have been reported in several parts of the world. However, although thunderstorm-associated asthma outbreaks are not frequent, it is possible to observe in clinical practice single cases of patients with deterioration of the allergic respiratory symptoms during a thunderstorm.

51. D'Amato, G., et al. (2013). "Climate change, air pollution and extreme events leading to increasing prevalence of allergic respiratory diseases." Multidisciplinary Respiratory Medicine **8**(2).
52. D'Amato, G. and L. Cecchi (2008). Climate change air pollution and respiratory diseases.
53. D'Amato, G., et al. (2012). "A trans-disciplinary overview of case reports of thunderstorm-related asthma outbreaks and relapse." European Respiratory Review **21**(124): 82-87.
54. D'Amato, G., et al. (2007). "Allergenic pollen and pollen allergy in Europe." Allergy: European Journal of Allergy and Clinical Immunology **62**(9): 976-990.
55. D'Amato, G., et al. (2008). "Thunderstorm-related asthma: Not only grass pollen and spores." Journal of Allergy and Clinical Immunology **121**(2): 537-538.
56. D'Amato, G., et al. (2013). "Climate Change and Allergic Respiratory Diseases." Allergy, Asthma & Immunophysiology: From Basic Science to Clinical Management: 25-31.
57. D'Amato, G., et al. (2012). "Thunderstorms and near fatal asthma." Rassegna di Patologia dell'Apparato Respiratorio **27**(6): 326-332.
  - a. An increasing body of evidence shows the occurrence of severe asthma epidemics during thunderstorm in the pollen season. We describe, other than an update on the "Thunderstorm-asthma", the first case of relapse of near fatal thunderstorm-asthma occurred in a 36 years old, 20 weeks pregnant woman affected by seasonal asthma and sensitized to Parietaria (pellitory of the wall) pollen. She was involved in the 2005 epidemics in Naples and had a relapse of severe asthma in 2011. The 28th of May 2012, she experienced a severe dyspnoea about two hours after being outdoor during a thunderstorm. She was admitted at the ER and unsuccessfully treated with adrenaline (1 ml i.m.), high dose steroids (2 gr methylprednisolone i.v.); then she was intubated and transferred to the intensive unit. Despite a four days full systemic therapy with oxygen (FiO<sub>2</sub>:0.60), methylprednisolone (1 gr/die i.v.), albuterol (1 fl i.v.), pCO<sub>2</sub> increased to 103 mmHg. Theophylline (240 mg in continuous infusion) was added, resulting in a pCO<sub>2</sub> reduction to 90 mmHg. Clinical picture dramatically improved only after two infusions of magnesium sulfate (2 gr i.v.), with a normalisation of arterial blood gas parameters. At day 8, patient was extubated, steroids slowly tapered and magnesium sulfate infused for 2 days more; fluticasone spray aerosol was given at 500 mcg/twice. Clinical and ultrasound checks did not show any foetal distress. Patient could be discharged with inhalers (1000 mcg fluticasone/die) and oral prednisone (25 mg/die). Also in the previous two episodes, in this patient symptoms appeared after a thunderstorm occurred during the Parietaria pollen season. In the case described here, clinical picture markedly improved after infusion of magnesium sulfate, with classic acute asthma treatments resulting unsuccessful. The present case confirms that a small subgroup of asthmatics is at risk of severe exacerbations, when exposed to a thunderstorm during pollen season.
58. D'Amato, G., et al. (2013). "A relapse of near-fatal thunderstorm-asthma in pregnancy." European Annals of Allergy and Clinical Immunology **45**(3): 116-117.
  - a. Thunderstorm-related asthma is a dramatic example of the allergenic potential of pollen antigens. Pollen allergic patients who encounter the allergenic cloud of pollen during a thunderstorm are at higher risk of having an asthma attack. Relapse is also possible and we describe here the first case of relapse of near fatal thunderstorm-asthma occurred in a 36 years old, 20 weeks pregnant woman affected by seasonal asthma and sensitized to allergens released by Parietaria pollen. Patients suffering from pollen allergy should be alerted of the danger of being outdoors during a thunderstorm in the pollen season and if they experienced an episode of severe thunderstorm-related asthma could be at risk of a relapse during a heavy precipitation event.
59. D'Amato, G., et al. (2015). "Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organisation." World Allergy Organisation Journal **8**.
  - a. The prevalence of allergic airway diseases such as asthma and rhinitis has increased dramatically to epidemic proportions worldwide. Besides air pollution from industry derived emissions and motor vehicles, the rising trend can only be explained by gross changes in the environments where we live. The world economy has been transformed over the last 25 years with developing countries being at the core of these changes. Around the planet, in both developed and developing countries, environments are undergoing profound changes. Many of these changes are considered to have negative effects on respiratory health and to enhance the frequency and severity of respiratory diseases such as asthma in the general population. Increased concentrations of greenhouse gases, and especially carbon dioxide (CO<sub>2</sub>), in the atmosphere have already warmed the planet substantially, causing more severe and prolonged heat waves, variability in temperature, increased air pollution, forest fires, droughts, and floods - all of which can put the respiratory health of the public at risk. These changes in climate

and air quality have a measurable impact not only on the morbidity but also the mortality of patients with asthma and other respiratory diseases. The massive increase in emissions of air pollutants due to economic and industrial growth in the last century has made air quality an environmental problem of the first order in a large number of regions of the world. A body of evidence suggests that major changes to our world are occurring and involve the atmosphere and its associated climate. These changes, including global warming induced by human activity, have an impact on the biosphere, biodiversity, and the human environment. Mitigating this huge health impact and reversing the effects of these changes are major challenges. This statement of the World Allergy Organisation (WAO) raises the importance of this health hazard and highlights the facts on climate-related health impacts, including: deaths and acute morbidity due to heat waves and extreme meteorological events; increased frequency of acute cardio-respiratory events due to higher concentrations of ground level ozone; changes in the frequency of respiratory diseases due to trans-boundary particle pollution; altered spatial and temporal distribution of allergens (pollens, molds, and mites); and some infectious disease vectors. According to this report, these impacts will not only affect those with current asthma but also increase the incidence and prevalence of allergic respiratory conditions and of asthma. The effects of climate change on respiratory allergy are still not well defined, and more studies addressing this topic are needed. Global warming is expected to affect the start, duration, and intensity of the pollen season on the one hand, and the rate of asthma exacerbations due to air pollution, respiratory infections, and/or cold air inhalation, and other conditions on the other hand.

60. D'Amato, G., et al. (2002). "Outdoor air pollution, climatic changes and allergic bronchial asthma." *European Respiratory Journal* **20**(3): 763-776.
- a. Both the prevalence and severity of respiratory allergic diseases such as bronchial asthma have increased in recent years. Among the factors implicated in this "epidemic" are indoor and outdoor airborne pollutants. Urbanisation with its high levels of vehicle emissions and Westernised lifestyle parallels the increase in respiratory allergy in most industrialised countries, and people who live in urban areas tend to be more affected by the disease than those of rural areas. In atopic subjects, exposure to air pollution increases airway responsiveness to aeroallergens. Pollen is a good model with which to study the interrelationship between air pollution and respiratory allergic diseases. Biological aerosols carrying antigenic proteins, such as pollen grains or plant-derived paucimicronic components, can produce allergic symptoms. By adhering to the surface of these airborne allergenic agents, air pollutants could modify their antigenic properties. Several factors influence this interaction, i.e., type of air pollutant, plant species, nutrient balance, climatic factors, degree of airway sensitisation and hyperresponsiveness of exposed subjects. However, the airway mucosal damage and the impaired mucociliary clearance induced by air pollution may facilitate the penetration and the access of inhaled allergens to the cells of the immune system, and so promote airway sensitisation. As a consequence, an enhanced immunoglobulin E-mediated response to aeroallergens and enhanced airway inflammation favoured by air pollution could account for the increasing prevalence of allergic respiratory diseases in urban areas.
61. D'Amato, G., et al. (2005). "Environmental risk factors and allergic bronchial asthma." *Clinical and Experimental Allergy* **35**(9): 1113-1124.
- a. The prevalence of allergic respiratory diseases such as bronchial asthma has increased in recent years, especially in industrialized countries. A change in the genetic predisposition is an unlikely cause of the increase in allergic diseases because genetic changes in a population require several generations. Consequently, this increase may be explained by changes in environmental factors, including indoor and outdoor air pollution. Over the past two decades, there has been increasing interest in studies of air pollution and its effects on human health. Although the role played by outdoor pollutants in allergic sensitisation of the airways has yet to be clarified, a body of evidence suggests that urbanisation, with its high levels of vehicle emissions, and a westernized lifestyle are linked to the rising frequency of respiratory allergic diseases observed in most industrialized countries, and there is considerable evidence that asthmatic persons are at increased risk of developing asthma exacerbations with exposure to ozone, nitrogen dioxide, sulphur dioxide and inhalable particulate matter. However, it is not easy to evaluate the impact of air pollution on the timing of asthma exacerbations and on the prevalence of asthma in general. As concentrations of airborne allergens and air pollutants are frequently increased contemporaneously, an enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of allergic respiratory allergy and bronchial asthma. Pollinosis is frequently used to study the interrelationship between air pollution and respiratory allergy. Climatic factors (temperature, wind speed, humidity, thunderstorms, etc) can affect both components (biological and chemical) of this interaction. By attaching to the surface of pollen grains and of plant-derived particles of paucimicronic size, pollutants could modify not only the morphology of these antigen-carrying agents but also their allergenic potential. In addition, by inducing airway inflammation, which increases airway permeability, pollutants overcome the mucosal barrier and could be able to 'prime' allergen-induced responses. There are also observations that a thunderstorm occurring during pollen season can induce severe asthma attacks in pollinosis patients. After rupture by thunderstorm, pollen grains may release part of their cytoplasmic content, including inhalable, allergen-carrying paucimicronic particles. © 2005 Blackwell Publishing Ltd.
62. D'Amato, G., et al. (2007). "Thunderstorm-asthma and pollen allergy." *Allergy: European Journal of Allergy and Clinical Immunology* **62**(1): 11-16.
- a. Thunderstorms have been linked to asthma epidemics, especially during the pollen seasons, and there are descriptions of asthma outbreaks associated with thunderstorms, which occurred in several cities, prevalently in Europe (Birmingham and London in the UK and Napoli in Italy) and Australia (Melbourne and Wagga Wagga). Pollen grains can be carried by thunderstorm at ground level, where pollen rupture would be increased with release of allergenic biological aerosols of paucimicronic size, derived from the cytoplasm and which can penetrate deep into lower airways. In other words, there is evidence that under wet conditions or during thunderstorms, pollen grains may, after rupture by osmotic shock, release into the atmosphere part of their content, including respirable, allergen-carrying cytoplasmic starch granules (0.5-2.5 µm) or other paucimicronic components that can reach lower airways inducing asthma reactions in pollinosis patients. The thunderstorm-asthma outbreaks are characterized, at the beginning of thunderstorms by a rapid increase of visit for asthma in general practitioner or hospital emergency departments. Subjects without asthma symptoms, but affected by seasonal rhinitis can experience an asthma attack. No unusual levels of air pollution were noted at the time of the epidemics, but there was a strong association with high atmospheric concentrations of pollen grains such as grasses or other allergenic plant species. However, subjects affected by pollen allergy should be informed about a possible risk of asthma attack at the beginning of a thunderstorm during pollen season. © 2007 The Authors.
63. D'Amato, G., et al. (2016). "Climate change and air pollution: Effects on respiratory allergy." *Allergy, Asthma and Immunology Research* **8**(5): 391-395.
64. D'Amato, G., et al. (2016). "Thunderstorm-related asthma: What happens and why." *Clinical and Experimental Allergy* **46**(3): 390-396.

- a. The fifth report issued by the Intergovernmental Panel on Climate Change forecasts that greenhouse gases will increase the global temperature as well as the frequency of extreme weather phenomena. An increasing body of evidence shows the occurrence of severe asthma epidemics during thunderstorms in the pollen season, in various geographical zones. The main hypotheses explaining association between thunderstorms and asthma claim that thunderstorms can concentrate pollen grains at ground level which may then release allergenic particles of respirable size in the atmosphere after their rupture by osmotic shock. During the first 20-30 min of a thunderstorm, patients suffering from pollen allergies may inhale a high concentration of the allergenic material that is dispersed into the atmosphere, which in turn can induce asthmatic reactions, often severe. Subjects without asthma symptoms, but affected by seasonal rhinitis can also experience an asthma attack. All subjects affected by pollen allergy should be alerted to the danger of being outdoors during a thunderstorm in the pollen season, as such events may be an important cause of severe exacerbations. In light of these observations, it is useful to predict thunderstorms and thus minimize thunderstorm-related events.
65. D'Amato, G., et al. (2015). "Effects on asthma and respiratory allergy of Climate change and air pollution." Multidisciplinary Respiratory Medicine **10**(1).
- a. The major changes to our world are those involving the atmosphere and the climate, including global warming induced by anthropogenic factors, with impact on the biosphere and human environment. Studies on the effects of climate changes on respiratory allergy are still lacking and current knowledge is provided by epidemiological and experimental studies on the relationship between allergic respiratory diseases, asthma and environmental factors, like meteorological variables, airborne allergens and air pollution. Epidemiologic studies have demonstrated that urbanisation, high levels of vehicle emissions and westernized lifestyle are correlated with an increased frequency of respiratory allergy, mainly in people who live in urban areas in comparison with people living in rural areas. However, it is not easy to evaluate the impact of climate changes and air pollution on the prevalence of asthma in general and on the timing of asthma exacerbations, although the global rise in asthma prevalence and severity could be also considered an effect of air pollution and climate changes. Since airborne allergens and air pollutants are frequently increased contemporaneously in the atmosphere, enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of respiratory allergy and asthma in atopic subjects in the last five decades. Pollen allergy is frequently used to study the interrelationship between air pollution and respiratory allergic diseases such as rhinitis and bronchial asthma. Climatic factors (temperature, wind speed, humidity, thunderstorms, etc) can affect both components (biological and chemical) of this interaction. Scientific societies should be involved in advocacy activities, such as those realized by the Global Alliance against chronic Respiratory Diseases (GARD).
66. D'Amato, G., et al. (2016). "Climate change, air pollution, and allergic respiratory diseases: An update." Current Opinion in Allergy and Clinical Immunology **16**(5): 434-440.
- a. Purpose of review The rising trend in prevalence of allergic respiratory disease and bronchial asthma, observed over the last decades, can be explained by changes occurring in the environment, with increasing presence of biologic, such as allergens, and chemical atmospheric trigger factors able to stimulate the sensitisation and symptoms of these diseases. Recent findings Many studies have shown changes in production, dispersion, and allergen content of pollen and spores because of climate change with an increasing effect of aeroallergens on allergic patients. Summary Over the last 50 years, global earth's temperature has markedly risen likely because of growing emission of anthropogenic greenhouse gas concentrations. Major changes involving the atmosphere and the climate, including global warming induced by human activity, have a major impact on the biosphere and human environment. Urbanisation and high levels of vehicle emissions are correlated to an increase in the frequency of pollen induced respiratory allergy prevalent in people who live in urban areas compared with those who live in rural areas. Measures of mitigation need to be applied for reducing future impacts of climate change on our planet, but until global emissions continue to rise, adaptation to the impacts of future climate variability will also be required.
67. D'Amato, M., et al. (2016). "Climate change, extreme meteorological events and respiratory allergy." Allergy, Asthma & Immunophysiology: Innovative Technologies: 91-95.
- a. Epidemiologic studies have demonstrated that urbanisation, high levels of vehicle emissions and westernized lifestyle are correlated with an increased frequency of respiratory allergy, mainly in people who live in urban areas in comparison with people living in rural areas. The major changes to our world are those involving the atmosphere and the climate, including global warming induced by anthropogenic factors, with impact on the biosphere and human environment. Studies on the effects of climate changes on respiratory allergy are still lacking and current knowledge is provided by epidemiological and experimental studies on the relationship between allergic respiratory diseases, asthma and environmental factors, like meteorological variables, airborne allergens and air pollution. Pollen allergy is frequently used to study the interrelationship between air pollution and respiratory allergic diseases such as rhinitis and bronchial asthma. Climatic factors (temperature, wind speed, humidity, thunderstorms, etc) can affect both components (biological and chemical) of this interaction. An increasing body of evidence shows the occurrence of severe asthma epidemics during thunderstorm in the pollen season, several epidemics of asthma have been reported following thunderstorms in various geographical zones.
68. D'Amato, M., et al. (2014). "Update on Effects of Climate Changes on Respiratory Allergy." Allergy, Asthma & Immunophysiology: From Genes to Clinical Management: 45-52.
- a. A body of evidence suggests that major changes involving the atmosphere and the climate, including global warming induced by human activity, have impact on the biosphere and human environment. Studies on the effects of climate changes on respiratory allergy are still lacking and current knowledge is provided by epidemiological and experimental studies on the relationship between asthma and environmental factors, like meteorological variables, airborne allergens and air pollution. However, urbanisation, with its high levels of vehicle emissions and a westernized lifestyle are linked to the rising frequency of respiratory allergic diseases and bronchial asthma observed over recent decades in most industrialized countries. There is also considerable evidence that subjects affected by asthma are at increased risk of developing obstructive airway exacerbations with exposure to gaseous and particulate components of air pollution. However, it is not easy to evaluate the impact of climate changes and air pollution on the prevalence of asthma in general and on the timing of asthma exacerbations, although the global rise in asthma prevalence and severity could be also an effect of air pollution and climate changes. Since airborne allergens and air pollutants are frequently increased contemporaneously in the atmosphere, an enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of allergic respiratory allergy and bronchial asthma in atopic subjects in the last thirty years. Pollen allergy is frequently

used to study the interrelationship between air pollution and respiratory allergic diseases such as rhinitis and bronchial asthma. Epidemiologic studies have demonstrated that urbanisation, high levels of vehicle emissions and westernized lifestyle are correlated with an increased frequency of pollen-induced respiratory allergy prevalently in people who live in urban areas in comparison with people living in rural areas. Climatic factors (temperature, wind speed, humidity, thunderstorms, etc) can affect both components (biological and chemical) of this interaction. In addition, by inducing airway inflammation, which increases airway permeability, pollutants overcome the mucosal barrier and could be able to "prime" allergen-induced responses

69. Dapul-Hidalgo, G. and L. Bielory (2012). "Climate change and allergic diseases." Annals of Allergy Asthma & Immunology **109**(3): 166-172.
70. Davidson, A. C., et al. (1996). "A major outbreak of asthma associated with a thunderstorm: Experience of accident and emergency departments and patients' characteristics." British Medical Journal **312**(7031): 601-604.
  - a. Objective - To investigate the time course of an epidemic of asthma after a thunderstorm, characteristics of patients affected, and the demand on emergency medical resources. Design - Study of registers and records in accident and emergency departments and questionnaire to staff Setting - London area. Subjects - All patients presenting at 12 accident and emergency departments with asthma or other airways disease. Main outcome measures-Numbers of patients, clinical features, information on shortage of resources-equipment, drugs, and staff. Results - The epidemic had a sudden onset on 24 June 1994; 640 patients with asthma or other airways disease attended during 30 hours from 1800 on 24 June, nearly 10 times the expected number. Over half (365) the patients were aged 21 to 30 years. A history of hayfever was recorded in 403 patients; for 283 patients this was the first known attack of asthma; a history of chronic obstructive airways disease was recorded in 12 patients. In all, 104 patients were admitted (including five to an intensive care unit). Several departments ran out of equipment or drugs, caned in additional doctors, or both. Conclusions - This study supports the view that this epidemic was larger than previously reported epidemics and the hypothesis that 'thunderstorm associated asthma' is related to aeroallergens. Demands on resources were considerable; a larger proportion of patients needing intensive care would have caused greater problems
71. Davies, J. M., et al. (2015). "Trans-disciplinary research in synthesis of grass pollen aerobiology and its importance for respiratory health in Australasia." Science of the Total Environment **534**: 85-96.
  - a. Grass pollen is a major trigger for allergic rhinitis and asthma, yet little is known about the timing and levels of human exposure to airborne grass pollen across Australasian urban environments. The relationships between environmental aeroallergen exposure and allergic respiratory disease bridge the fields of ecology, aerobiology, geospatial science and public health. The Australian Aerobiology Working Group comprised of experts in botany, palynology, biogeography, climate change science, plant genetics, biostatistics, ecology, pollen allergy, public and environmental health, and medicine, was established to systematically source, collate and analyse atmospheric pollen concentration data from 11 Australian and six New Zealand sites. Following two week-long workshops, post-workshop evaluations were conducted to reflect upon the utility of this analysis and synthesis approach to address complex multidisciplinary questions. This Working Group described i) a biogeographically dependent variation in airborne pollen diversity, ii) a latitudinal gradient in the timing, duration and number of peaks of the grass pollen season, and iii) the emergence of new methodologies based on trans-disciplinary synthesis of aerobiology and remote sensing data. Challenges included resolving methodological variations between pollen monitoring sites and temporal variations in pollen datasets. Other challenges included "marrying" ecosystem and health sciences and reconciling divergent expert opinion. The Australian Aerobiology Working Group facilitated knowledge transfer between diverse scientific disciplines, mentored students and early career scientists, and provided an uninterrupted collaborative opportunity to focus on a unifying problem globally. The Working Group provided a platform to optimise the value of large existing ecological datasets that have importance for human respiratory health and ecosystems research. Compilation of current knowledge of Australasian pollen aerobiology is a critical first step towards the management of exposure to pollen in patients with allergic disease and provides a basis from which the future impacts of climate change on pollen distribution can be assessed and monitored. Crown Copyright (C) 2015 Published by Elsevier B.V. All rights reserved.
72. Davila, F. D., et al. (2013). "Effects of weather types on hospital admissions for respiratory diseases in Castilla-La Mancha, Spain." Atmosfera **26**(1): 95-107.
  - a. The aim of this study is to evaluate the relationship between the risk of hospital admission for respiratory diseases (RD) and the daily weather types during the period 2000-2006. A synoptic climatological approach is used to investigate links between air-mass types (weather situations) and all respiratory hospital admissions in the Castilla-La Mancha (CLM) area in Spain. This afforded the main circulation weather types (CWThunderstorm) for the winter and spring periods (since respiratory hospital admissions reached their maximum during these seasons) and the frequency distributions of these types were analyzed. A summary of the main characteristics of the hospital admission series and their distribution over the seven years studied, together with the frequency distributions of the admissions classified by sex and ages, for season, month and for each day of the week, is reported. In addition, a comparison between air-mass classification and hospital admissions is made using an admission index (AI). The results reveal different responses of respiratory admission rates to the eight air-mass types identified in winter and in spring. In winter, three air masses southwesterly (SW), anti-cyclonic (A) and hybrid anti-cyclonic southwesterly (HASW), are associated with values 1.5 times higher than the respective average admission rates, while in spring no significant differences are seen.
73. de Weger, L. A. and P. S. Hiemstra (2009). "The effect of climate change on pollen allergy in the Netherlands." Nederlands tijdschrift voor geneeskunde **153**.
74. Demoly, P. (2006). "The links between rhinitis and asthma: what level of evidence?" Revue Francaise D Allergologie Et D Immunologie Clinique **46**: S9-S13.
  - a. The links between rhinitis and asthma are strong and demonstrated by numerous epidemiological, pathophysiological and clinical studies. Epidemiological studies have shown that most asthmatics suffer from rhinitis and that being a rhinitic is a risk factor for being or becoming asthmatic. Histological data demonstrate that nasal inflammation resembles bronchial inflammation. Recent progresses in cellular and molecular biology confirm that the same mechanisms, inflammatory cells and mediators participate to the pathophysiology of both diseases. As the final proof, it is now demonstrated that treating symptomatic rhinitis leads to a better control of asthma. Thus, the guidelines urging to assess rhinitis in the presence of asthma and asthma in the presence of rhinitis and to treat both diseases simultaneously is fully justified. (c) 2006 Elsevier-Masson SAS. Tons droits reserves.

75. Deng, Q. F., et al. (2003). "A preliminary study on the relation between thunderstorms and mortality of in-patients." *Journal of Public Health Medicine* **25**(3): 246-248.
- a. Background The aim of this study was to investigate the association between thunderstorms and mortality of in-patients. Methods Data for in-patients and deaths in internal medicine departments from four hospitals in Shanghai were collected and grouped according to meteorological conditions. Results Weekly mortality of in-patients was significantly higher on days with thunderstorms than on fine days. This effect was significant for patients in respiratory, cardiovascular and neurology wards but not in the wards of other specialties.
76. Denning, D. W., et al. (2006). "The link between fungi and severe asthma: a summary of the evidence." *European Respiratory Journal* **27**(3): 615-626.
- a. There is current evidence to demonstrate a close association between fungal sensitisation and asthma severity. Whether such an association is causal remains to be confirmed, but this is explored by means of a detailed literature review. There is evidence from two randomised controlled trials that, in the example of allergic bronchopulmonary aspergillosis (ABPA), treatment with systemic antifungal therapy can offer a therapeutic benefit to similar to 60% of patients. ABPA is only diagnosed if a combination of clinical and immunological criteria is achieved. It is not known whether such cases are a discrete clinical entity or part of a spectrum of the pulmonary allergic response to fungi or fungal products. This paper describes the epidemiological evidence that associates severity of asthma with fungi and discusses possible pathogenetic mechanisms. Many airborne fungi are involved including species of *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium*, and exposure may be indoors, outdoors or both. The potential for a therapeutic role of antifungal agents for patients with severe asthma and fungal sensitisation is also explored. Not only are many patients with severe asthma desperately disabled by their disease, but, in the UK alone, asthma accounts for 1,500 deaths per yr. The healthcare costs of these patients are enormous and any treatment option merits close scrutiny. Within this report, the case for the consideration of a new term related to this association is put forward. The current authors propose the term "severe asthma with fungal sensitisation". However, it is recognised that enhanced and precise definition of fungal sensitisation will require improvements in diagnostic testing.
77. Dossey, L. (2001). "Weather and health." *Alternative Therapies in Health and Medicine* **7**(5): 12-+.
78. Elliot, A. J., et al. (2014). "Using real-time syndromic surveillance to assess the health impact of the 2013 heatwave in England." *Environmental Research* **135**: 31-36.
- a. Heatwaves are a seasonal threat to public health. During July 2013 England experienced a heatwave; we used a suite of syndromic surveillance systems to monitor the impact of the heatwave. Significant increases in heatstroke and sunstroke were observed during 7-10 July 2013. Syndromic surveillance provided an innovative and effective service, supporting heatwave planning and providing early warning of the impact of extreme heat thereby improving the public health response to heatwaves. Crown Copyright (C) 2014 Published by Elsevier Inc. All rights reserved.
79. Elliot, A. J., et al. (2014). "The impact of thunderstorm asthma on emergency department attendances across London during July 2013." *Emergency Medicine Journal* **31**(8): 675-678.
- a. Background: This study illustrates the potential of using emergency department attendance data, routinely accessed as part of a national syndromic surveillance system, to monitor the impact of thunderstorm asthma. Methods: The Emergency Department Syndromic Surveillance System (EDSSS) routinely monitors anonymised attendance data on a daily basis across a sentinel network of 35 emergency departments. Attendance data for asthma, wheeze and difficulty breathing are analysed on a daily basis. Results: A statistically significant spike in asthma attendances in two EDSSS emergency departments in London was detected on 23 July 2013, coinciding with a series of large violent thunderstorms across southern England. There was also an increase in the reported severity of these attendances. Conclusions: This preliminary report illustrates the potential of the EDSSS to monitor the impact of thunderstorms on emergency department asthma attendances. Further work will focus on how this system can be used to quantify the impact on emergency departments, thus potentially improving resource planning and also adding to the thunderstorm asthma evidence-base.
80. Erbas, B., et al. (2012). "The role of seasonal grass pollen on childhood asthma emergency department presentations." *Clinical and Experimental Allergy* **42**(5): 799-805.
- a. Background: Few studies have focused on the role of grass pollen on asthma emergency department (ED) presentations among children. None have examined whether a dose-response effect exists between grass pollen levels and these asthma exacerbations. Objectives: To examine the association between increasing ambient levels of grass pollen and asthma ED presentations in children. To determine whether these associations are seen only after a thunderstorm, or whether grass pollen levels have a consistent influence on childhood asthma ED visit during the season. Methods: A short time series ecological study was conducted for asthma presentations to ED among children in Melbourne, Victoria, and grass pollen, meteorological and air quality measurements recorded during the selected 2003 period. A semi-parametric Poisson regression model was used to examine dose-response associations between daily grass pollen levels and mean daily ED attendance for asthma. Results: A smoothed plot suggested a dose-response association. As ambient grass pollen increased to about 19 grains/m<sup>3</sup>, the same day risk of childhood ED presentations also increased linearly ( $P < 0.001$ ). Grass pollen levels were also associated with an increased risk in asthma ED presentations on the following day (lag 1,  $P < 0.001$ ). Conclusion: This is the first study to establish a clear relationship between increased risk of childhood asthma ED attendance and levels of ambient grass pollen below 20 grains/m<sup>3</sup>, independent of any impact of thunderstorm-associated asthma. These findings have important implications for patient care, such as asthma management programs that notify the general public regarding periods of high grass pollen exposure, as well as defining the timing of initiation of pollen immunotherapy. © 2012 Blackwell Publishing Ltd.
81. Fedeyko, H. J. and M. C. White (1998). "Thunderstorms and pollen as risk factors for elevated daily counts of emergency room visit for pediatric asthma in Atlanta, Georgia." *American Journal of Epidemiology* **147**(11): S31-S31.
82. Feli, M., et al. (2015). "Emergency medicine's role in the management of a respiratory illness multiple casualty incident." *Asian Journal of Epidemiology* **8**(3): 72-77.

- a. This cross-sectional retrospective descriptive study was performed to determine the role of the emergency medicine in the management of thunderstorms associated asthma Multiple Casualty Incident (MCI) and to give an overview of affected patient characteristics. Eligible participants were all patients presented to the ED with acute bronchospasm, between 2nd-7th November, 2013. Not only available medical records of all patients were gathered and analyzed, retrospectively but also the effectiveness of the MCI plan designed by emergency medicine was reviewed. There was no gender priority in the studied population (201 male, 242 female). The majority of affected patients were aged between 20-40 (278 out of 443). Only 40 patients of all 443 were admitted (37 in the pulmonary ward and 3 in the ICU). No mortality in the ED was reported. Over 50% of patients had a positive history of asthma, allergies have been treated at least once for shortness of breath or asthma previously. Our findings illustrate that described respiratory illness MCI seems to have a benign course, since the majority of patients discharged home. Besides, the designed protocol for treatment of patients and managing the MCI were obviously effective.
83. Forouzan, A., et al. (2014). "An overview of thunderstorm-associated asthma outbreak in Southwest of Iran." Journal of Environmental and Public Health **2014**.
- a. The aim of this study was to report the characteristics and treatment strategies of all patients with acute bronchospasm who were presented to the emergency departments of Ahvaz, Iran, following the occurrence of a thunderstorm on November 2, 2013. A total of 2000 patients presenting with asthma attacks triggered by thunderstorm were interviewed and an initial questionnaire was completed for each individual. After twenty days, patients were asked to complete a supplementary questionnaire, but only 800 of them accepted to do so. The majority of subjects was aged 20-40 years (60.5%) and had no history of asthma in most cases (60.0%). The symptoms had started outdoors for 60.0% of the participants. In most patients, the onset of the condition was on November 2. Short-acting  $\beta_2$ -agonist (salbutamol) and aminophylline were the most commonly prescribed medications in the emergency department. Upon the second interview, 85.3% of the patients were still symptomatic. Overall, 63.6% did not have a follow-up visit after hospital discharge, although all of them were referred to the specialist. The findings of the present study suggest that thunderstorm-associated asthma could affect young adults with no gender priority, with or without asthma history, which put a strain on emergency medical services. © 2014 Arash Forouzan et al.
84. Friedlander, J. L., et al. (2014). "Asthma and Allergens." Clinical Asthma: Theory and Practice: 93-99.
85. Gennaro, D., et al. (2011). "Climatic Change and Urban air pollution on the rising trends of Respiratory Allergy and Asthma." Allergy, Asthma and Immunology: From Genes to Clinical Application: Proceedings of the Iv World Asthma and Copd Forum and Xvi International Congress on Rehabilitation in Medicine and Immunorehabilitation: 15-31.
- a. Over the past two decades there is increasing interest in studies regarding effects on human health of climate changes and urban air pollution. Climate change induced by anthropogenic warming of the earth's atmosphere is a daunting problem and there are several observations about the role of urbanisation, with its high levels of vehicle emissions and other pollutants, and a westernized lifestyle in the rising frequency of respiratory allergic diseases observed in most industrialized countries. There is also evidence that asthmatic subjects are at increased risk of developing exacerbations of bronchial obstruction with exposure to gaseous (ozone, nitrogen dioxide, sulfur dioxide) and particulate inhalable components (PM) of air pollution. A change in the genetic predisposition is an unlikely cause of the increasing frequency in allergic diseases because genetic changes in a population require several generations. Consequently, environmental factors such as climate change and indoor and outdoor air pollution may contribute to explain the increasing frequency of respiratory allergy and asthma. Since concentrations of airborne allergens and air pollutants are frequently increased contemporaneously, an enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of allergic respiratory allergy and bronchial asthma. Scientific societies such as European Academy of Allergy and Clinical Immunology, European Respiratory Society and World Allergy Organisation have organized committees and task forces to produce documents to focalize this topic, asking for prevention measures.
86. Gibson, P. G., et al. (1993). "EPIDEMIC ASTHMA AFTER A thunderstorm - CLINICAL AND CYTOLOGICAL FEATURES OF NEW ONSET ASTHMA." American Review of Respiratory Disease **147**(4): A560-A560.
87. Girgis, S., et al. (1999). "Does inhaled steroid prevent asthma exacerbation during a thunderstorm?" Respirology **4**(SUPPL. 1).
88. Girgis, S. T., et al. (2000). "Thunderstorm-associated asthma in an inland town in south-eastern Australia. Who is at risk?" European Respiratory Journal **16**(1): 3-8.
- a. The aim of the study was to characterize patients at risk of asthma exacerbation during spring thunderstorms and identify potential measures to ameliorate the impact of those events. A case-control study was conducted among patients aged 7-60 yrs, who attended Wagga Hospital (NSW, Australia) for asthma during the period of 1 June 1997 to 31 October 1997. One hundred and eighty-three patients who attended on 30 and 31 October 1997 were the cases and the remaining 121 patients were the controls. Questionnaire data were obtained from 148 (81%) cases and 91 (75%) controls. One hundred and thirty-eight (95%) cases who attended during the thunderstorm gave a history of hayfever prior to the event compared to 66 (74%) controls who attended at other times (odds ratio (OR) 6.01, 95% confidence interval (CI) 2.55-14.15); 111 (96%) cases were allergic to rye grass pollen compared to 47 (64%) controls (OR 23.6, 95% CI 6.6-84.3). Among subjects with a prior diagnosis of asthma (64% cases and 82% controls), controls (56%) were more likely to be taking inhaled steroids at time of the thunderstorm than cases (27%, OR 0.3, 95% CI 0.16-0.57). History of hayfever and allergy to rye grass are strong predictors for asthma exacerbation during thunderstorms in spring. The lower rate of inhaled steroid use in thunderstorm cases suggests that this treatment may be effective in preventing severe attacks during thunderstorms. (C)ERS Journals Ltd 2000.
89. Glovsky, M. M., et al. (1997). "Particulate air pollution: Possible relevance in asthma." Allergy and Asthma Proceedings **18**(3): 163-166.
- a. The relative importance of air pollution in the pathogenesis of bronchial asthma has been of interest for several decades. Numerous studies on the role of gaseous air pollution containing ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide have been published. Very little attention has been focused on the role of respirable particles in the causation of asthma. In this article we summarize some of our ongoing investigations into the sources and composition of airborne particles in the Los Angeles and Pasadena atmosphere, including the search for biologically active particles that may induce asthma attacks. It is found

that the urban atmosphere contains not only combustion-derived particles from diesel engine exhaust and gasoline-powered motor vehicle exhaust, but also particles formed from biological starting materials including plant debris, cigarette smoke, wood smoke, and meat smoke as well as tire debris containing some natural rubber and paved road dust. Paved road dust is a very complex mixture of particles including garden soil, tire dust, plant fragments, redeposited atmospheric particles of all types, and pollen fragments presumably ground up by passing traffic. We have shown previously that latex allergen can be extracted from tire dust, from roadside dust, and from front respirable air samples taken at Los Angeles and Long Beach. At present, work is underway to identify the larger range of allergens that may be contributed by the entrainment of paved road dust into the atmosphere. The possible importance of pollen fragments present in paved road dust in very small particle sizes is discussed as well as their potential relevance in asthma.

90. Grinn-Gofron, A. and A. Strzelczak (2013). "Changes in concentration of Alternaria and Cladosporium spores during summer storms." *Int J Biometeorol* **57**(5): 759-768.
  - a. Fungal spores are known to cause allergic sensitisation. Recent studies reported a strong association between asthma symptoms and thunderstorms that could be explained by an increase in airborne fungal spore concentrations. Just before and during thunderstorms the values of meteorological parameters rapidly change. Therefore, the goal of this study was to create a predictive model for hourly concentrations of atmospheric Alternaria and Cladosporium spores on days with summer storms in Szczecin (Poland) based on meteorological conditions. For this study we have chosen all days of June, July and August (2004-2009) with convective thunderstorms. There were statistically significant relationships between spore concentration and meteorological parameters: positive for air temperature and ozone content while negative for relative humidity. In general, before a thunderstorm, air temperature and ozone concentration increased, which was accompanied by a considerable increase in spore concentration. During and after a storm, relative humidity increased while both air temperature and ozone concentration along with spore concentrations decreased. Artificial neural networks (ANN) were used to assess forecasting possibilities. Good performance of ANN models in this study suggest that it is possible to predict spore concentrations from meteorological variables 2 h in advance and, thus, warn people with spore-related asthma symptoms about the increasing abundance of airborne fungi on days with storms.
91. Grote, M., et al. (2000). "Expulsion of allergen-containing materials from hydrated rye grass (*Lolium perenne*) pollen revealed by using immunogold field emission scanning and transmission electron microscopy." *Journal of Allergy and Clinical Immunology* **105**(6 I): 1140-1145.
  - a. Background: Several studies demonstrated episodes of grass pollen-induced allergic asthma after heavy rainfalls. It has been hypothesized that these asthma attacks might be due to the release of respirable allergen-bearing particles from pollen cytoplasm. Objective: In this study we investigated the release mechanism of the most potent and frequently recognized grass pollen allergens, group 1 and group 5, from freshly harvested and subsequently hydrated rye grass pollen at the ultrastructural level. Methods: Rabbit antisera against purified recombinant group 1 and group 5 allergens were used to investigate, by using field emission scanning and transmission immunogold electron microscopy, the allergen release from rye grass pollen grains into isotonic aqueous solutions or water. Results: Pollen grains exposed to isotonic aqueous solutions remained intact and released allergens by means of diffusion. However, pollen grains hydrated in distilled water or rainwater expelled starch grains and cytoplasmic debris of respirable size. Group 1 and group 5 allergens were observed on and within these materials. Conclusions: Exposure of rye grass pollen to water leads to an expulsion of subcellular allergen-containing pollen components of respirable size. Our ultrastructural data thus support the idea that this release of allergen-containing respirable pollen materials may be a cause of asthma attacks after heavy rainfalls.
92. Grundstein, A. and S. E. Sarnat (2009). "Meteorological mechanisms explaining thunderstorm-related asthma." *Geography Compass* **3**(1): 45-63.
93. Grundstein, A., et al. (2008). "Thunderstorm associated asthma in Atlanta, Georgia." *Thorax* **63**(7): 659-660.
94. Guillemin, M. T. and C. Segala (2008). "Pollen and health effects: Synthesis of epidemiological studies." *Revue Francaise D Allergologie Et D Immunologie Clinique* **48**(1): 14-19.
  - a. Allergic rhinitis grew up by threefold in French population in the last 25 years. In this context, we conducted a review on the relationships between pollens and health effects. Three fields are discussed: assessment of exposure in epidemiological studies, relationships between pollens and health effects, finally the results of the retained studies are presented. In epidemiological studies, population exposure to pollens is always done by outdoor stationary measurement. Relationships between aeroallergen concentrations and clinical effects are difficult to study because some factors as individual susceptibility, differences in the potential noxious effect of each allergen; lag between pollen and clinical effects, concentration limit that start up clinical effects and concentration limit for maximal effect; the successive productions and emissions of the different kinds of pollens; and multi-sensibility. Studying these relationships needs also to take into account several confounding factors such as: meteorological parameters, fungal aeroallergens concentrations; chemical air pollutants concentrations. Most of the epidemiological studies analyse the relationship between daily variations in pollen counts and daily variations in health effects quantified at individual levels in specific populations (panel study) or quantified at population levels (time-series). A review was already realised on studies published between 1978 and 1995 that examined the relationship between pollens and allergic rhinoconjunctivitis. Only 16 of the published studies had been retained (15 panels and one time-series). The conclusion of this work was that these studies showed associations between pollen counts and allergic rhinoconjunctivitis. But these associations could not be quantified and the dose-response curves could not be characterised because of inappropriate statistical methods and not taking into account confounding factors. In our review, nine studies that examined the short-term effect of pollen were retained for their good methodology (two of them are panels). Their results confirm associations between pollen counts and health effects and some of them succeeded in quantifying the short-term effect of pollens on allergic rhinitis, allergic conjunctivitis and also asthma. (C) 2007 Elsevier Masson SAS. Tous droits reserves.
95. Gupta, P., et al. (2012). "Effect of Dust Aerosol in Patients with Asthma." *Journal of Asthma* **49**(2): 134-138.
  - a. Objective. Sandstorms frequently cause adverse health effects especially in patients with asthma. The aim of our research was to explore the mechanism of sandstorm-induced asthmatic exacerbation by administering dust aerosol through an environmentally controlled exposure chamber. Methods. Four samples of soil (Ganganagar clay, Bikaner sand, Jaipur sand, and Ganganagar sand) were collected from three sandstorm-prone areas of Rajasthan, the desert state of India.

Twenty patients with asthma, who had stable disease with a forced expiratory volume in first second (FEV1) more than 70% of predicted, volunteered to participate in this randomized single-blind placebo-controlled crossover study. The four samples of dust and placebo were administered randomly on 5 study days. FEV1 was measured for the next 60 minutes and the maximal decline in FEV1 (Delta FEV1) from baseline was measured. The samples of dust were also analyzed for particle size and adhesiveness. Results. The maximal decline in FEV1 was observed 15 minutes post-exposure with all dust samples. Mean Delta FEV1 was 0.69 +/- 0.08 liters for Ganganagar clay, 0.52 +/- 0.06 liters for Bikaner sand, 0.39 +/- 0.07 liters for Jaipur sand, and 0.32 +/- 0.04 liters for Ganganagar sand dust aerosol samples. Decline in FEV1 correlated with volume of dust particles with size < 10 mu m (PM<sub>10</sub>) and adhesiveness of the dust particles. Conclusion. Smaller-size sandstorm dust particles with higher adhesive properties have a greater potential of aggravating asthma.

96. Hajat S, S. (1997). "Thunderstorm-associated asthma: The effect on GP consultations." *British Journal of General Practice* **47**(423): 639-641.
- a. Evidence shows that asthma attacks can be brought on by adverse weather conditions such as those experienced during a thunderstorm; a prime example of such an occasion being a thunderstorm episode on 24 June 1994, which resulted in a well-documented increase in medical attendances made by those suffering with asthma and respiratory disorders. However, most of these studies have concerned admissions to accident and emergency departments. The aim of this paper was to ascertain whether a similar increase in consultations was observed in the primary care setting.
97. Harries, M. G., et al. (1985). "DIDYMELLA EXITALIS AND LATE SUMMER ASTHMA." *The Lancet* **325**(8437): 1063-1066.
98. Higham, J., et al. (1997). "Asthma and thunderstorms: Description of an epidemic in general practice in Britain using data from a doctors' deputising service in the UK." *Journal of Epidemiology and Community Health* **51**(3): 233-238.
- a. Objective - To describe the areas affected and the scale of an epidemic of thunderstorm associated asthma on the night of 24/25 June 1994 and to explore the spatial and temporal relationship between the thunderstorm and the associated epidemic. Setting - The 29 offices of a deputising service for general practitioners (GP) out of hours calls (Healthcall). At the time of the storm the deputising service provided out of hours cover for about 8500 out of about 30,000 GPs in England, Scotland, and Wales. Methods - Patients who phoned the Healthcall offices to request a home visit were categorised as 'asthma' or 'other causes' based on their presenting complaint. The number of calls on the night of 24/25 June 1994 was compared in areas affected by thunderstorms and areas not affected by thunderstorms and with the night of 17/18 June 1994, when there were no thunderstorms. Results - A large area of the south and east of England was affected by an epidemic of asthma closely related both temporally and spatially with the thunderstorms on 24/25 June 1994. The pooled Mantel-Haenszel estimate for the risk of asthma in thunderstorm affected areas compared with the control night was 6.36 (95% confidence interval 4.97, 8.32) compared with a value of 1.01 (0.80, 1.27) for those not exposed. Extrapolation suggests about 1500 extra patients were likely to have requested a visit from a GP that night because of epidemic asthma. Conclusions - Under certain circumstances thunderstorms are associated with asthma and can affect many patients. Deputising services are a useful source of data for the investigation of epidemics in primary care.
99. Higham, J. H. (1994). "Asthma trends. Thunderstorm peak in Luton [5]." *British Medical Journal* **309**(6954): 604.
100. Horner, W. E., et al. (1992). "BASIDIOSPORE AEROALLERGENS." *Clinical Reviews in Allergy* **10**(3): 191-211.
101. Horvath, A., et al. (2011). "Quantification of airway deposition of intact and fragmented pollens." *International Journal of Environmental Health Research* **21**(6): 427-440.
- a. Although pollen is one of the most widespread agents that can cause allergy, its airway transport and deposition is far from being fully explored. The objective of this study was to characterize the airway deposition of pollens and to contribute to the debate related to the increasing number of asthma attacks registered after thunderstorms. For the quantification of the deposition of inhaled pollens in the airways computer simulations were performed. Our results demonstrated that smaller and fragmented pollens may penetrate into the thoracic airways and deposit there, supporting the theory that fragmented pollen particles are responsible for the increasing incidence of asthma attacks following thunderstorms. Pollen deposition results also suggest that children are the most exposed to the allergic effects of pollens. Finally, pollens between 0.5 and 20 mu m deposit more efficiently in the lung of asthmatics than in the healthy lung, especially in the bronchial region.
102. Howden, M. L., et al. (2011). "Thunderstorm asthma--a timely reminder." *Med J Aust* **195**(9): 512-513.
103. Huffman, J. A., et al. (2013). "High concentrations of biological aerosol particles and ice nuclei during and after rain." *Atmospheric Chemistry and Physics* **13**(13): 6151-6164.
- a. Bioaerosols are relevant for public health and may play an important role in the climate system, but their atmospheric abundance, properties, and sources are not well understood. Here we show that the concentration of airborne biological particles in a North American forest ecosystem increases significantly during rain and that bioparticles are closely correlated with atmospheric ice nuclei (IN). The greatest increase of bioparticles and IN occurred in the size range of 2-6 mu m, which is characteristic for bacterial aggregates and fungal spores. By DNA analysis we found high diversities of airborne bacteria and fungi, including groups containing human and plant pathogens (mildew, smut and rust fungi, molds, Enterobacteriaceae, Pseudomonadaceae). In addition to detecting known bacterial and fungal IN (*Pseudomonas* sp., *Fusarium sporotrichioides*), we discovered two species of IN-active fungi that were not previously known as biological ice nucleators (*Isaria farinosa* and *Acremonium implicatum*). Our findings suggest that atmospheric bioaerosols, IN, and rainfall are more tightly coupled than previously assumed.
104. Ilias, I., et al. (1998). "Eight year retrospective study of thunderstorm-associated asthma attacks in Athens Greece." *International Journal of Environmental Health Research* **8**(4): 335-337.

- a. Reports of short duration studies have been made on the influence of thunderstorms on asthma. In order to evaluate the impact of such weather phenomena over longer time periods in temperate climates the authors compared the daily number of emergency room attendances by people aged 15 to 44 for asthma attacks in Athens' largest chest diseases hospital on 74 thunderstorm and matching control days (91 and 107 attendances respectively) during an eight year period. No statistically significant difference was noted between the studied pairs of days, using the Kruskal-Wallis test. This study showed no actual influence of thunderstorms on asthma attacks. Since daily pollen counts are not available for the city the authors believe that further research into other environmental factors is needed in order to better evaluate the effects of the environment on the exacerbations of bronchial asthma.
105. Jamason, P. F., et al. (1997). "A synoptic evaluation of asthma hospital admissions in New York City." American Journal of Respiratory and Critical Care Medicine **156**(6): 1781-1788.
- a. An evaluation of weather/asthma relationships in the New York City Standard Metropolitan Statistical Area (SMSA) is developed using a synoptic climatological methodology. This procedure isolates "air masses," or bodies of air that are homogeneous in meteorological character, and relates them to daily counts of overnight asthma hospital admissions. The synoptic procedure used here, known as the temporal synoptic index (thunderstorm), can identify air masses in automated fashion for every day over many years. It is apparent that certain air masses are related to statistically significant increases in asthma hospital admissions. The impact varies seasonally, with weather having a particularly important impact on asthma admissions during fall and winter. It appears that air pollution has little impact on asthma during these two seasons, and the air masses associated with the highest admissions are not distinguished by high concentrations of pollutants. However, during spring and summer, the air masses associated with highest admissions are among those with high pollution concentrations. There is a strong interseasonal differential response to weather and air pollution by asthmatics in New York City. If these results can be replicated at other locations in future studies, it may be possible to develop an asthma/weather watch-warning system, based on the expected arrival of high-admissions air masses.
106. Jin, H. J., et al. (2011). "Impacts of climate change on aeroallergens." Journal of the Korean Medical Association **54**(2): 156-160.
- a. Climatic changes are key environmental issues affecting allergic diseases. Temperature and CO<sub>2</sub> content have been found to be increasing together with climate changes, which could increase pollen production, extend the pollination period, and augment the allergenic components of major pollens. Changes in the distribution of major trees and weeds have been noted. Severe weather events such as thunderstorm winds and precipitation could increasingly cause pollen grains to burst, releasing allergenic particles and leading to extensive mold growth. Air pollutants can increase the concentration of allergen released from pollen grains and allow for easier penetration into airway mucosa. Future studies will be essential to investigate the mechanisms by which allergenic contents can be changed in response to climate change. A better understanding of how aeroallergens interact with air pollutants is needed. Climate change has a significant impact on aeroallergen levels and content in ways which may accelerate the development of allergic diseases. Future strategies will be crucial in preventing the allergic diseases associated with climate changes.
107. Kilic, M., et al. (2010). "The effects of meteorological factors and Alternaria spore concentrations on children sensitised to Alternaria." Allergologia Et Immunopathologia **38**(3): 122-128.
- a. Background: Alternaria is the most important fungal species belonging to the class Deuteromycetes which causes allergic respiratory diseases. The fungus pattern often shows a pronounced seasonal periodicity and with fluctuations related to meteorological conditions. In this study, we aimed to investigate the effect of outdoor Alternaria spore concentrations on monthly lung function tests, symptoms, and medication scores in children sensitised only to Alternaria. Additionally, we planned to determine the Alternaria spores of the outdoor environment in Adana, with special respect to their relationships with meteorological conditions and their seasonal changes. Methods: Twenty-five patients with a clinical diagnosis of asthma and/or rhinitis sensitised only to Alternaria were enrolled in the prospective study. Meteorological data and outdoor samples of airborne fungi were obtained between November 2006 and October 2007. Results: The outdoor Alternaria spore concentrations were significantly correlated with the monthly average temperature ( $r=0.626$ ,  $p=0.03$ ) and monthly average barometric pressure ( $r=-0.613$ ,  $p=0.03$ ). Similarly, the outdoor Alternaria spore concentrations were significantly correlated with mean monthly asthma medication score ( $r=0.599$ ,  $p=0.04$ ), value monthly PEF ( $r=-0.737$ ,  $p=0.006$ ), value monthly FEF<sub>25-75%</sub> ( $r=-0.914$ ,  $p=0.0001$ ) and, variation in PEF ( $r=0.901$ ,  $p=0.0001$ ). Conclusions: The atmospheric concentration of Alternaria spores are markedly affected by meteorological factors such as air temperatures and barometric pressures. In hypersensitive patients, Alternaria spores can induce decreases in respiratory functions and development of allergic symptoms between May and September, being especially more influential in August. (C) 2009 SEICAP. Published by Elsevier Espana, S.L. All rights reserved.
108. Kim, H. K., et al. (2014). "Innate type 2 response to Alternaria extract enhances ryegrass-induced lung inflammation." International Archives of Allergy and Immunology **163**(2): 92-105.
- a. Background: Exposure to the fungal allergen Alternaria alternata as well as ryegrass pollen has been implicated in severe asthma symptoms during thunderstorms. We have previously shown that Alternaria extract induces innate type 2 lung inflammation in mice. We hypothesized that the innate eosinophilic response to Alternaria extract may enhance lung inflammation induced by ryegrass. Methods: Mice were sensitized to ryegrass allergen and administered a single challenge with A. alternata extract before or after final ryegrass challenges. Levels of eosinophils, neutrophils, Th2 cells, innate lymphoid cells (ILC2), interleukin (IL)-5 and IL-13 in bronchoalveolar lavage (BAL) as well as inflammation and mucus were assessed. Results: Mice receiving ryegrass sensitisation and challenge developed an eosinophilic lung response. A single challenge with Alternaria extract given 3 days before or 3 days after ryegrass challenges resulted in increased eosinophils, peribronchial inflammation and mucus production in the airways compared with ryegrass-only challenges. Type 2 ILC2 and Th2 cell recruitment to the airways was increased after Alternaria extract exposure in ryegrass-challenged mice. Innate immune challenges with Alternaria extract induced BAL eosinophilia, Th2 cell recruitment as well as ILC2 expansion and proliferation. Conclusions: A single exposure to Alternaria extract in ryegrass-sensitized and -challenged mice enhances the type 2 lung inflammatory response, including airway eosinophilia, peribronchial infiltrate, and mucus production, possibly through Th2 cell recruitment and ILC2 expansion. If translated to humans, exposure to both grass pollen and Alternaria may be a potential cause of thunderstorm-related asthma. © 2013 S. Karger AG, Basel.

109. Kim, S. H. and H. J. Yoon (2011). "Climate change and respiratory allergic diseases." Journal of the Korean Medical Association **54**(2): 161-168.
110. Knox, R. B. (1993). "Grass pollen, thunderstorms and asthma." Clinical and Experimental Allergy **23**(5): 354-359.
111. Knox, R. B., et al. (1997). "Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution." Clin Exp Allergy **27**(3): 246-251.
- a. BACKGROUND: Grass pollen allergens are known to be present in the atmosphere in a range of particle sizes from whole pollen grains (approx. 20 to 55 microns in diameter) to smaller size fractions < 2.5 microns (fine particles, PM<sub>2.5</sub>). These latter particles are within the respirable range and include allergen-containing starch granules released from within the grains into the atmosphere when grass pollen ruptures in rainfall and are associated with epidemics of thunderstorm asthma during the grass pollen season. The question arises whether grass pollen allergens can interact with other sources of fine particles, particularly those present during episodes of air pollution. OBJECTIVE: We propose the hypothesis that free grass pollen allergen molecules, derived from dead or burst grains and dispersed in microdroplets of water in aerosols, can bind to fine particles in polluted air. METHODS: We used diesel exhaust carbon particles (DECP) derived from the exhaust of a stationary diesel engine, natural highly purified Lol p 1, immunogold labelling with specific monoclonal antibodies and a high voltage transmission electron-microscopic imaging technique. Results: DECP are visualized as small carbon spheres, each 30-60 nm in diameter, forming fractal aggregates about 1-2 microns in diameter. Here we test our hypothesis and show by in vitro experiments that the major grass pollen allergen, Lol p 1, binds to one defined class of fine particles, DECP. CONCLUSION: DECP are in the respirable size range, can bind to the major grass pollen allergen Lol p 1 under in vitro conditions and represent a possible mechanism by which allergens can become concentrated in polluted air and thus trigger attacks of asthma.
112. Laaidi, K. (2001). "Predicting days of high allergenic risk during *Betula* pollination using weather types." International Journal of Biometeorology **45**(3): 124-132.
- a. The aim of this study was to build up a picture of the influence of meteorological conditions on pollen and pollinosis, taking account of weather types., pollen concentrations in the air and pollinosis symptoms. with the aim of preventing allergic responses. The study took place in Burgundy from 1996 to 1998, during the pollination of the birch (*Betula*), which is the most important arboreal allergen in this region. We used daily pollen data from four Hirst volumetric traps, identified weather types by Benichou's classification, and obtained data on the occurrence of rhinitis, conjunctivitis, asthma and coughing from a sample of 100 patients. These data were analysed by multiple-component analysis. The results show that pollen dispersal is favoured by windy conditions, low relative humidity, precipitation below 2 mm and temperatures above 6 degrees C. Such weather also favours pollinosis. but other particular meteorological situations. even if they do not assist pollen dispersal, can act directly on the development of symptoms: a decrease of temperature (3 degrees C) led to the development of rhinitis and conjunctivitis, while strong winds were associated with many cases of conjunctivitis and asthma, owing to the irritant effect of cold or wind: asthma was favoured by temperature inversions with fog, probably because such weather corresponds to high levels of pollution, which act on bronchial hyperreactivity. Because the weather types favouring pollination and pollinosis are predicted by the meteorological office, this can constitute a tool for reducing the effect of high-risk allergenic days.
113. Laurence, A. R., et al. (2011). "AIRBORNE STARCH GRANULES AS A POTENTIAL CONTAMINATION SOURCE AT ARCHAEOLOGICAL SITES." Journal of Ethnobiology **31**(2): 213-232.
- a. Well-known allergy literature attests to a presence of airborne starch granules from human and natural activities and illustrates that starch granules within pollen grains from starch-rich plants are released when pollen grains rupture in mid-air during thunderstorms. This study reports on starch granules extracted from Texas air samples and ruptured pollen grains from seven ethnographically important geophyte species, as well as maize (*Zea mays* L.). Starch granules from pollen grains are compared to those in storage organs of these plants. Results confirm that storage-like starch granules are airborne and that starch granules inside pollen can be indistinguishable from starch granules in the respective storage organs.
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116. Lewis, S. A., et al. (2000). "Combined effects of aerobiological pollutants, chemical pollutants and meteorological conditions on asthma admissions and A & E attendances in Derbyshire UK, 1993-96." Clinical and Experimental Allergy **30**(12): 1724-1732.
117. Lewis, S. A., et al. (1999). "Aeroallergens, air pollutants, thunderstorms, & asthma morbidity in Derby." American Journal of Respiratory and Critical Care Medicine **159**(3): A127-A127.
118. Lombardi, C., et al. (2017). "Is allergic sensitisation relevant in severe asthma? Which allergens may be culprit?" World Allergy Organisation Journal **10**(1).
- a. Severe asthma is a major health concern. The allergic (IgE-mediated) form of asthma is well known from a pathogenic viewpoint. We searched the available literature to identify which allergens are most frequently associated with severe, refractory or life threatening asthma. According to the results, molds, pet dander, cockroach and ragweed were more frequently responsible for severe asthma. Thunderstorm asthma, in addition, represents a special association between allergic sensitisation and an external climatic factor. A detailed knowledge of the most harmful allergens is mandatory for an appropriate diagnostic and preventive approach.
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121. Marks, G. B., et al. (2001). "Thunderstorm outflows preceding epidemics of asthma during spring and summer." Thorax **56**(6): 468-471.
- a. Background-A study was undertaken to assess the importance of thunderstorms as a cause of epidemics of asthma exacerbations and to investigate the underlying mechanism. Methods-A case control study was performed in six towns in south eastern Australia. Epidemic case days (n = 48) and a random sample of control days (n = 191) were identified by reference to the difference between the observed and expected number of emergency department attendances for asthma. The occurrence of thunderstorms, their associated outflows and cold fronts were ascertained, blind to case status, for each of these days. In addition, the relation of hourly pollen counts to automatic weather station data was examined in detail for the period around one severe epidemic of asthma exacerbations. The main outcome measure was the number of epidemics of asthma exacerbations. Results-Thunderstorm outflows were detected on 33% of epidemic days and only 3% of control days (odds ratio 15.0, 95% confidence interval 6.0 to 37.6). The association was strongest in late spring and summer. Detailed examination of one severe epidemic showed that its onset coincided with the arrival of the thunderstorm outflow and a 4-12 fold increase in the ambient concentration of grass pollen grains. Conclusions-These findings are consistent with the hypothesis that some epidemics of exacerbations of asthma are caused by high concentrations of allergenic particles produced by an outflow of colder air, associated with the downdraught from a thunderstorm, sweeping up pollen grains and particles and then concentrating them in a shallow band of air at ground level. This is a common cause of exacerbations of asthma during the pollen season.
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123. Mireku, N., et al. (2009). "Changes in weather and the effects on pediatric asthma exacerbations." Annals of Allergy Asthma & Immunology **103**(3): 220-224.
- a. Background: Pediatric asthma exacerbations may correlate with changes in weather, yet this relationship is not well defined. Objective: To determine the effects of fluctuations in climatic factors (temperature, humidity, and barometric pressure) on pediatric asthma exacerbations. Methods: A retrospective study was performed at 1 large urban hospital during a 2-year period (January 1, 2004, to December 31, 2005). Children presenting to the emergency department (ED) for an asthma exacerbation were included. Data on climatic factors, pollutants, and aeroallergens were collected daily. The relationship of daily (intraday) or between-day (interday) changes in climatic factors and asthma ED visit was evaluated using time series analysis, controlling for seasonality, air pollution, and aeroallergen exposure. The effects of climatic factors were evaluated on the day of admission (T = 0) and up to 5 days before admission (T - 5 through T - 1). Results: There were 25,401 asthma ED visit. A 10% intraday increase in humidity on day T - 1 or day T - 2 was associated with approximately 1 additional ED visit for asthma (P < .001 and P = .01, respectively). Interday changes in humidity from day T - 3 to T - 2 were also associated with more ED visit (P < .001). Interday changes in temperature from T - 1 to T = 0 increased ED visit, with a 10 degrees F increase being associated with 1.8 additional visit (P = .006). No association was found with changes in barometric pressure. Conclusion: Fluctuations in humidity and temperature, but not barometric pressure, appear to influence ED visit for pediatric asthma. The additional ED visit occur 1 to 2 days after the fluctuation. Anti Allergy Asthma Immunol. 2009; 103:220-224.
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125. Motta, A., et al. (2004). "Phleum pratense pollen starch granules induce humoral and cell-mediated immune responses in a rat model of allergy." Clinical and Experimental Allergy **34**(2): 310-314.
- a. Background: Timothy grass (*Phleum pratense*) pollen allergens are an important cause of allergic symptoms. However, pollen grains are too large to penetrate the deeper airways. Grass pollen is known to release allergen-bearing starch granules (SG) upon contact with water. These granules can create an inhalable allergenic aerosol capable of triggering an early asthmatic response and are implicated in thunderstorm-associated asthma. Objective: We studied the humoral (IgE) and bronchial lymph node cells reactivities to SG from timothy grass pollen in pollen-sensitized rats. Methods: Brown-Norway rats were sensitized (day 0) and challenged (day 21) intratracheally with intact pollen and kept immunized by pollen intranasal instillation by 4 weeks intervals during 3 months. Blood and bronchial lymph nodes were collected 7 days after the last intranasal challenge. SG were purified from fresh timothy grass pollen using 5 µm mesh filters. To determine the humoral response (IgE) to SG, we developed an original ELISA inhibition test, based on competition between pollen allergens and purified SG. The cell-mediated response to SG in the bronchial lymph node cells was determined by measuring the uptake of [<sup>3</sup>H]thymidine in a proliferation assay. Results: An antibody response to SG was induced, and purified SG were able to inhibit the IgE ELISA absorbance by 45%. Pollen extract and intact pollen gave inhibitions of 55% and 52%, respectively. A cell-mediated response was also found, as pollen extract, intact pollen and SG triggered proliferation of bronchial lymph node cells. Conclusions: It was confirmed that timothy grass pollen contains allergen-loaded SG, which are released upon contact with water. These granules were shown to be recognized by pollen-sensitized rats sera and to trigger lymph node cell proliferation in these rats. These data provide new arguments supporting the implication of grass pollen SG in allergic asthma.
126. Motta, A. C., et al. (2006). "Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen." International Archives of Allergy and Immunology **139**(4): 294-298.
- a. Background/Aim: Pollen cytoplasmic granules (PCG) are loaded with allergens. They are released from grass pollen grains following contact with water and can form a respirable allergenic aerosol. On the other hand, the traffic-related air pollutants NO<sub>2</sub> and O<sub>3</sub> are known to be involved in the current increase in the prevalence of allergic diseases via their adjuvant effects. Our objective was to determine the effects of air pollutants on the release of PCG from *Phleum pratense* (timothy grass) pollen. Methods: *P. pratense* pollen was exposed to several concentrations of NO<sub>2</sub> and O<sub>3</sub>. The induced morphological damages were observed by environmental scanning electron microscopy, and the amount of PCG released from the pollen upon contact with water was measured. Results: The percentages of damaged grain were 6.4% in air-treated controls, 15% after treatment with the highest NO<sub>2</sub> dose (50 ppm) and 13.5% after exposure to 0.5 ppm O<sub>3</sub>. In treated samples, a fraction of the grains spontaneously released their PCG. Upon subsequent contact with water, the remaining intact grains released more PCG than pollen exposed to air only. Conclusions: Traffic-related pollutants can trigger the release of allergen-containing granules from grass pollen, and

increase the bioavailability of airborne pollen allergens. This is a new mechanism by which air pollution concurs with the current increase in the prevalence of allergic diseases. Copyright (C) 2006 S. Karger AG, Basel.

127. Murray, V., et al. (1994). "Epidemic of asthma possibly related to thunderstorms." *Bmj* **309**(6947): 131.

128. Nasser, S. M. and T. B. Pulimood (2009). "Allergens and thunderstorm asthma." *Current Allergy and Asthma Reports* **9**(5): 384-390.

a. Thunderstorm-related asthma is increasingly recognized in many parts of the world. This review focuses on important advances in the understanding of the mechanism of the role of allergens, in particular fungal spores such as *Alternaria*, in asthma epidemics associated with thunderstorms. From our observations, we have proposed that the prerequisites for this phenomenon are as follows: 1) a sensitized, atopic, asthmatic individual; 2) prior airway hyperresponsiveness before a sudden, large allergen exposure; 3) a large-scale thunderstorm with cold outflow occurring at a time and location during an allergen season in which large numbers of asthmatics are outdoors; and 4) sudden release of large amounts of respirable allergenic fragments, particularly fungal spores such as *Alternaria*. © Current Medicine Group, LLC 2009.

129. Nastos, P. T., et al. (2006). "The effect of weather types on the frequency of childhood asthma admissions in Athens, Greece." *Fresenius Environmental Bulletin* **15**(8): 936-942.

a. The aim of this study was to investigate the influence of weather conditions on the number of admissions for childhood asthma in Athens, Greece. Daily counts of childhood asthma admissions (2764) of the three main Children's Hospitals in Athens, from hospital registries during a 3-year period (2001-2003), were obtained. The meteorological data reviewed consists of daily values of 20 parameters recorded at the National Observatory of Athens during the study period: maximum temperature (T-max); minimum temperature (T-min); mean temperature (T-mean); diurnal temperature range (T-range = T-max - T-min); day-to-day change in maximum temperature (Delta T-max); day-to-day change in minimum temperature (Delta T-min); day-to-day change in mean temperature (Delta T-mean); day-to-day change in diurnal temperature range (Delta T-range); mean relative humidity (RH); day-to-day change in mean relative humidity (Delta RH); mean water vapor pressure (e); day-to-day change in mean water vapor pressure (Delta e); mean atmospheric pressure at sea level (P); day-to-day change in mean atmospheric pressure (Delta P); mean irradiance (I); day-to-day change in mean irradiance (Delta I); mean sunshine (S); day-to-day change in mean sunshine (Delta S); mean wind speed (v) and day-to-day change in mean wind speed (Delta v). The performed statistical methods were: (i) Pearson's chi(2) test, using contingency tables and (ii) Factor and Cluster analysis. The application of this 2-part analysis revealed the relationship between the extracted weather types and the frequency of childhood asthma admissions in Athens. The results showed that weather conditions with low temperature, low water vapor pressure and cold anticyclonic presence were significantly correlated with an increase in the number of asthma admissions among children in Athens. The impact of these specific weather conditions on asthma exacerbation should be interpreted either by the asthmogenic effect of humid weather per se or the association with respiratory viral infection, mold's and mites' allergy.

130. Newson, R., et al. (1997). "Effect of thunderstorms and airborne grass pollen on the incidence of acute asthma in England, 1990-94." *Thorax* **52**(8): 680-685.

a. Background - Thunderstorms and prior grass pollen counts were investigated as predictors of daily hospital admissions for asthma in England. This study was motivated by reports in the literature of spectacular asthma epidemics associated with thunderstorms, particularly in the grass pollen season. Methods - Asthma admissions for two age groups (0-14 years and 15 and over) were measured using the Hospital Episodes System (HES) in the 14 regional health authorities (RHAs) in England. Thunderstorms were measured daily in each RHA using densities of sferics (lightning flashes). Relative asthma excesses for moderate positive and exceptionally high sferic densities, with or without previous high grass pollen counts, were measured using log linear autoregression - allowing for weekly, seasonal, and longer term background variation - and pooled over RHAs by calculating geometric means. Results - Relative risks from all RHAs were pooled to form geometric means. Exceptional sferic densities were associated with a relative excess risk of around 25% in both age groups. Moderate sferic densities were associated with a smaller excess, statistically significant in the two age groups taken together. In five RHAs in which grass pollen counts were available, high pollen counts for the previous five days were associated with an amplification of the excess associated with thunderstorms. Conclusion - Very large sferic densities are associated with moderate rises in hospital admissions for acute asthma. However, typical thunderstorm days are not associated with spectacular asthma epidemics of the scale previously reported in the literature. Thunderstorm-associated excesses are amplified after a run of high pollen counts.

131. Newson, R., et al. (1998). "Acute asthma epidemics, weather and pollen in England, 1987-1994." *European Respiratory Journal* **11**(3): 694-701.

a. Recent epidemics of acute asthma have caused speculation that, if their causes were known, early warnings might be feasible. In particular, some epidemics seemed to be associated with thunderstorms. We wondered what risk factors predicting epidemics could be identified. Daily asthma admissions counts during 1987-1994, for two age groups (0-14 yrs and ≤15 yrs), were measured using the Hospital Episodes System (HES). Epidemics were defined as combinations of date, age group and English Regional Health Authority (RHA) with exceptionally high asthma admission counts compared to the predictions of a log-linear autoregression model. They were compared with control days 1 week before and afterwards, regarding seven meteorological variables and 5 day average pollen counts for four species. Fifty six asthma epidemics were identified. The mean density of sferics (lightning flashes), temperature and rainfall on epidemic days were greater than those on control days. High sferics densities were overrepresented in epidemics. Simultaneously high sferics and grass pollen further increased the probability of an epidemic, but only to 15% (95% confidence interval 2-45%). Two thirds of epidemics were not preceded by thunderstorms. Thunderstorms and high grass pollen levels precede asthma epidemics more often than expected by chance. However, most epidemics are not associated with thunderstorms or unusual weather conditions, and most thunderstorms, even following high grass pollen levels, do not precede epidemics. An early warning system based on the indicators examined here would, therefore, detect few epidemics and generate an unacceptably high rate of false alarms.

132. O'Connor, D. J., et al. (2014). "Atmospheric concentrations of *Alternaria*, *Cladosporium*, *Ganoderma* and *Didymella* spores monitored in Cork (Ireland) and Worcester (England) during the summer of 2010." *Aerobiologia* **30**(4): 397-411.

a. This study represents the first international intercomparison of fungal spore observations since 1990, focusing on atmospheric concentrations of *Alternaria*, *Cladosporium*, *Ganoderma* and *Didymella* spores. The campaigns were performed at sites located in Cork (Ireland) and Worcester (England) during summer

2010. Observations were made using Hirst-type volumetric spore traps and corresponding optical identification at the genus level by microscope. The measurements at both sites (including meteorological parameters) were compared and contrasted. The relationships between the fungal spore concentrations with selected meteorological parameters were investigated using statistical methods and multivariate regression trees (MRT). The results showed high correlations between the two sites with respect to daily variations. Statistically significant higher spore concentrations for *Alternaria*, *Cladosporium* and *Ganoderma* were monitored at the Worcester site. This result was most likely due to the differences in precipitation and local fungal spore sources at the two sites. *Alternaria* and *Cladosporium* reached their maxima a month earlier in Cork than in Worcester, and *Didymella* with *Ganoderma* peaked simultaneously with similar diurnal trends found for all the investigated spore types. MRT analysis helped to determine threshold values of the meteorological parameters that exerted most influence on the presence of spores: they were found to vary at the two sites. Our results suggest that the aeromycological profile is quite uniform over the British Isles, but a description of bioaerosols with respect to overall load and daily concentration can be quite diverse although the geographical difference between sites is relatively small. These variations in the concentrations therefore need to be explored at the national level.

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134. Pab, W. and J. L. Simpson (2001). "Airway inflammation in acute asthma following a thunderstorm is associated with increased sputum eosinophilia and eosinophil degranulation." Respirology **6**(SUPPL. 1).
135. Packe, G. E. and J. G. Ayres (1985). "Asthma outbreak during a thunderstorm." Lancet **2**(8448): 199-203.
- a. An outbreak of acute asthma occurred in Birmingham and the surrounding area on July 6 and 7, 1983. In most patients symptoms began at the time of sudden climatic changes associated with a thunderstorm. Air pollution was not a factor. The large and sudden increase in numbers of airborne fungal spores, especially *Didymella exitialis* and *Sporobolomyces*, around the time of the outbreak suggests that they may have been partly contributory, although a direct causal effect has not yet been established.
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137. Paulley, J. W. (2002). "Asthma attacks and thunderstorms." Qim-an International Journal of Medicine **95**(7): 485-486.
138. Premaratne, U. N., et al. (1997). "A reliable method to retrieve Accident & Emergency data stored on a free-text basis." Respiratory Medicine **91**(2): 61-66.
- a. Accident & Emergency (A & E) data on asthma-related attendances are useful for studies on the effectiveness of asthma interventions, and to determine the relationship of environmental factors to asthma and asthma epidemics. The final diagnoses made in the A & E departments are not usually coded when entered into hospital databases in the U.K., although the 'presenting complaint' can be retrieved from the computerized Hospital Information & Support Systems (HISS), from a free-text attendance diagnosis field entered by the reception clerk when the patient arrives at the A & E department. The validity of this as an indication of the final diagnosis is unevaluated. The aim of this study was to measure the validity of the string 'asth' in the A & E attendance diagnosis field for identifying patients attending the A & E departments of two hospitals for asthma-related conditions. A list of patients who attended the A & E department of two hospitals was retrieved from the HISS along with the attendance diagnosis field. If the attendance diagnosis field contained the text string 'asth', mentioned wheeze or breathing problems, or the patients were referred by their GP without any diagnostic information entered on HISS, the records were selected for evaluation. The remaining attendances, which were not evaluated further, were attributed to another diagnosis based on the evidence of the recorded attendance diagnosis. The results indicated that the string 'asth' in the attendance diagnosis field had a sensitivity of 80.3% (95% CI 75.1-85.5%) and a specificity of 96.70% (95% CI 95.6-97.8%) for a final diagnosis of asthma. It is concluded that free-text attendance diagnosis fields in hospital databases can be searched with suitable strings to obtain reliable data on attendance with asthma. As part of another investigation, the present authors attempted to retrieve a list of the attendances with asthma at the same two A & E departments at a time that was reportedly associated with an epidemic of asthma following a thunderstorm. On this occasion, the string 'asth' proved to be significantly less sensitive. The possible reasons for this and the implications for using this method for identifying cases are discussed.
139. Pulimood, T. B., et al. (2007). "Epidemic asthma and the role of the fungal mold *Alternaria alternata*." Journal of Allergy and Clinical Immunology **120**(3): 610-617.
- a. Background: After July 29, 2002, an epidemic of asthma admissions was associated with a thunderstorm in the United Kingdom. Objective: We sought to study the cause of epidemics of asthma associated with thunderstorms. Methods: We performed a case-control study of 26 patients presenting to Cambridge University Hospital with asthma after the thunderstorm. Control subjects were 31 patients with summer seasonal asthma. Subjects underwent skin tests and specific IgE serology to inhaled aeroallergens. Meteorologic and aerobiologic data correlated with asthma admissions were analyzed. Results: Twenty-three of 26 cases had IgE sensitisation to *Alternaria* species. Eleven of 31 control subjects gave a history of asthma exacerbation during thunderstorms. Ten of these 11 control subjects were sensitive to *Alternaria* species on skin testing, but *Alternaria* species sensitivity was only identified in 4 of the 20 remaining control subjects who did not report thunderstorm-related asthma symptoms. The odds ratio of having epidemic thunderstorm-related asthma if sensitive to *Alternaria* species was 9.31 (95% CI, 2.305-37.601; P = .0008) and 63.966 (95% CI, 3.577-1143.9; P < .0001) if sensitive to *Alternaria* species, *Cladosporium* species, or both. Poisson regression analysis showed that counts of broken *Alternaria* species and *Didymella* and *Cladosporium* species were significantly correlated with each other and with asthma admissions. The thunderstorm was associated with increased levels of *Alternaria*, *Cladosporium*, and *Didymella* species. Conclusions: *Alternaria alternata* sensitivity is a compelling predictor of epidemic asthma in patients with seasonal asthma and grass pollen allergy and is likely to be the important factor in thunderstorm-related asthma. Clinical implications: *Alternaria* species sensitisation in asthmatic subjects with grass pollen sensitivity predicts susceptibility to thunderstorm-associated asthma.

141. Pulimood, T. B., et al. (2005). "Sensitivity to *Alternaria alternata* in grass pollen sensitive asthmatics is an important factor in thunderstorm outbreaks of asthma." *Thorax* **60**: 1132-1132.
141. Qasem, J. A., et al. (2008). "Meteorological factors, aeroallergens and asthma-related visit in Kuwait: a 12-month retrospective study." *Annals of Saudi Medicine* **28**(6): 435-441.
- a. **BACKGROUND:** The increasing prevalence of asthma in many countries has been related to weather factors and aeroallergen concentrations, but this has not been studied in Kuwait. We evaluated the effect of meteorological factors and the occurrence of aerobiologicals on the number of asthma cases in Kuwait. **METHODS:** The number of daily asthma visits to the allergy center and emergency department at Al-Sabha Hospital for 1 year were examined on a monthly basis for correlation with major meteorological factors (temperature, relative humidity, rain, wind speed and direction). Spore and pollen counts were collected hourly. **Results:** A total of 4353 patients received asthma treatment during the year. The highest pollen count was in the month of September with a maximum relative humidity of 471% and no precipitation, but with a high mean temperature of 39.7 degrees C. Pollen counts were higher in the late summer (September) and occurred with a high patient visit to the allergy center. Fungal spore counts were significantly higher in early winter (December). The high fungal spore count seemed related to high relative humidity and high precipitation with a low mean average temperature of 19.7 degrees C. The increase in number of patients with bronchial asthma visiting an emergency clinic during December was significantly associated with high aerial counts for fungal spores ( $P < .03$ ), and the months of September and October were more significant for pollen. **CONCLUSION:** This study indicates that meteorological factors, aeroallergen concentrations and asthma-related visits are interrelated. The results may prove useful in the generation of hypotheses and development of designs for more comprehensive, individual-based epidemiological studies.
142. Rabe, U. (2011). "Are fungal spores relevant outdoor allergens?" *Atemwegs- und Lungenkrankheiten* **37**(8): 334-343.
143. Rael, E. L. (2014). "Are environmental factors more important than genetic factors in incident asthma?" *Journal of Allergy and Clinical Immunology* **133**(2): AB241.
- a. **RATIONALE:** Asthma is a reversible disease marked by mucus hypersecretion, bronchial hyperreactivity, and airway obstruction. Gene and environment components are linked to this condition. Here we report amongst a cohort of asthmatics at a university-based allergy, asthma, and immunology specialty clinic, increasing incident asthma development across age ranges and ethnic groups suggesting that environmental change may be a more important component to present-day asthma than genetic components. **METHODS:** After informed consent and IRB approval, 287 asthmatics, recruited to the study between 2011 and 2013 were asked when their asthma symptoms began. Subjects ranged in age from 4 through 81 with an average age of 36. Ethnic ancestry was represented from all continents on the globe. **Results:** 25 percent of subjects developed asthma within a 6-year period from 2007-2013; 25 percent of subjects developed asthma over a 9-year period 1998-2007; 25 percent of subjects developed asthma over a 12-year period 1986-1998; and 25 percent of subjects developed asthma over a 42-year period 1944-1986. **CONCLUSIONS:** Genetic heritability changes slowly over generations. However, environmental changes can occur rapidly. Environmental triggers have been linked to asthma flares including thunderstorm-induced asthma, diesel exhaust particles, and obesity. Here we report an increase in new, incident asthma across age ranges and amongst ethnic backgrounds, at an academic medical center. Further work is necessary to characterize the magnitude of the effect of environmental factors on asthma severity to give guidance on how to focus international asthma priorities and resources to advance asthma research and patient care.
144. Richardson, D. (2012). "Altitude of residence and thunderstorm-associated asthma." *EMA - Emergency Medicine Australasia* **24**: 31.
- a. **Objective:** To determine the relationship between hospital presentation due to an outbreak of thunderstorm-associated asthma and altitude of normal residence. **Methods:** Case-control study of all self-referred respiratory presentations aged 5-54 years to The Canberra Hospital ED over the 51 hours of this epidemic. Controls were the first self-referred non-respiratory presentation of the same age and sex presenting beginning 30-Oct-2010. The altitude of the stated home address was obtained using a geographic information system. The null hypothesis was that there was no difference between the altitude of residence of cases and controls. Secondary analysis considered the relationship with presentation time. **Results:** 45 cases were matched with 45 controls. The mean altitude for cases was 610 m (95% CI 603-618) and for controls 621 (607-636) ( $P = 0.21$ , paired t-test). For the 17 presenting in the first 10 hours it was 597 m (95% CI 587-606), the 19 in the next 10 hours 622 m (610-635) ( $P = 0.003$ , t-test), and the 9 in the last 22 hours 611 m (601-622). Subgroup analysis showed a trend to lower altitude between cases and controls only in that first 10 hours (597 m vs 634 m,  $P = 0.06$  paired t-test). **Conclusions:** Early presenters in this epidemic of thunderstorm-associated asthma lived at lower altitudes than late presenters ( $P = 0.003$ ) and matched controls ( $P = 0.06$ ). There was no difference found between cases and controls later in the epidemic although numbers are small and factors such as socioeconomic status cannot be excluded. This is a new finding which is consistent with current knowledge of the pathogenesis of these unusual outbreaks.
145. Rivera-Mariani, F. E. and B. Bolanos-Rosero (2012). "Allergenicity of airborne basidiospores and ascospores: need for further studies." *Aerobiologia* **28**(2): 83-97.
- a. Many known fungal species are grouped among basidiomycetes and ascomycetes. Active mechanisms of spore release into air currents are among the main features of these fungi. Aerobiological studies have described their presence in many regions worldwide. In some areas, fungi have been described as the predominant outdoor airborne biological particulate with much higher concentrations than pollen. Other studies have determined that among the fungal aerospora, the highest concentrations belong to basidiospores and ascospores. Nevertheless, the allergenic potential of spores from basidiomycetes and meiotic forms of ascomycetes has not been studied to the extent of mitospore fungi and allergens from other sources. The need to further evaluate the role of basidiomycetes and meiotic ascomycetes in allergies is evidenced by the few genera with characterized allergens and limited studies that had demonstrated levels of sensitization similar or higher to that of mitospore fungi and other allergens. In this review, based on the existing aerobiological, epidemiological, immunological, and molecular biology studies, we provide evidence that the role of basidiomycetes and ascomycetes deserves more attention with respect to their roles as potential aeroallergens.

146. Schuh, A. (2003). "[Asthma after summer thunderstorm, stroke in cold weather, death in heat. When weather causes illness]." *MMW Fortschr Med* **145**(35-36): 25.
147. Shoushtari, M. H., et al. (2016). "Bronchial hyperresponsiveness among patients presented to the university emergency departments in Ahvaz, Iran: Impact of ecosystem on human life?" *Chest* **150**(4): 935A.
- a. PURPOSE: Previous studies demonstrated more severe bronchospasm during seasonal thunderstorms (thunderstorm asthma). Ahvaz, a metropolitan city located in Southwest of Iran, was named the World's worst air polluted city by the World Health Organisation (WHO) in 2011. Drastic changes in the ecosystem resulted in more thunder- and sand-storms. This is believed to be due to substantial ecologic changes in the Southern part of Iraq & Iran after decades of wars and industrialisation. Evidence is lacking on spirometric changes after thunderstorms. In the current study, we aimed to examine the difference of spirometric indices among patients presented to the Ahvaz Jundishapur Medical University (AJMU) emergency departments (ED) with symptoms of thunderstorm-asthma during seasonal thunderstorms compared to those presented during other times. METHODS: In a cross-sectional case control study, we reviewed all patients presented to the AJMU's nine hospital emergency departments in November 2013 (peak incidence of regional thunderstorms) with patients presented during seasons other than Fall. Overall, 585 patients were randomly selected, all of which underwent spirometry. If spirometry did not show evidence of obstruction, then patient underwent methacholine challenge test (MCT). All studies were conducted 3 weeks after resolution of acute symptoms. Primary outcome was spirometric indices and MCT results. Patients with history of COPD, pregnant women, those with hemoptysis or nonacceptable spirometry and chest pain were excluded. Using Chi-square and student's t-test, we compared the characteristics and spirometric indices between two groups. Results: Overall, 284 patients were enrolled during the thunderstorm period (cases) and 267 from other time-periods (controls). Cases and controlled were age and sex matched. Higher rate of history of asthma and smoking were noted among control (35.2% vs. 26.1%, p-value <0.001) and (20% vs. 13.7%, p-value 0.02), respectively. Despite insignificant difference between two groups in rate of obstructive pattern (30.6% vs. 33.3% among cases and controls, respectively), the severity of obstructive pattern and positive MCT were substantially higher among cases. CONCLUSIONS: The results of the current study showed more severe bronchial hyperresponsiveness during seasonal thunderstorms.
148. Singh, B. and D. W. Denning (2012). "Allergic bronchopulmonary mycosis due to *Alternaria*: Case report and review." *Medical Mycology Case Reports* **1**(1): 20-23.
- a. While allergic bronchopulmonary aspergillosis and mycosis are well recognised, no cases have been described related to *Alternaria* spp. *Alternaria* is a common sensitising fungus in asthmatics and related to thunderstorm asthma. We report a case of an asthmatic who presented with worsening asthma control, mild eosinophilia on high dose inhaled corticosteroids (800. µg/day), a total IgE of 3800. KIU/L, an *Alternaria*-specific IgE of 21.3. KUa/L and positive skin prick test, negative specific IgE and skin prick test to *Aspergillus fumigatus*, *Penicillium* spp., *Cladosporium* spp., *Trichophyton* spp. and a normal CT scan of the thorax. He responded well to a short course of oral prednisolone and then oral itraconazole, given over 17 months but relapsed 1 month after stopping it. © 2012 International Society for Human and Animal Mycology.
149. Singh, M. and A. Hays (2016). "Indoor and Outdoor Allergies." *Primary Care - Clinics in Office Practice* **43**(3): 451-463.
- a. In last 30 to 40 years there has been a significant increase in the incidence of allergy. This increase cannot be explained by genetic factors alone. Increasing air pollution and its interaction with biological allergens along with changing lifestyles are contributing factors. Dust mites, molds, and animal allergens contribute to most of the sensitisation in the indoor setting. Tree and grass pollens are the leading allergens in the outdoor setting. Worsening air pollution and increasing particulate matter worsen allergy symptoms and associated morbidity. Cross-sensitisation of allergens is common. Treatment involves avoidance of allergens, modifying lifestyle, medical treatment, and immunotherapy.
150. Smit, H. J. M., et al. (1999). "Atmospheric pressure changes and outdoor temperature changes in relation to spontaneous pneumothorax." *Chest* **116**(3): 676-681.
- a. Study aims: To examine the influence of atmospheric pressure (AP) and temperature changes on the incidence of idiopathic spontaneous pneumothorax (SP), Methods: From December 1991 through November 1993, 115 consecutive SP cases were selected. Patients were included after being in Amsterdam at least 1 full day, before contracting the SP, Differences in air temperature and AP (provided hourly by the national weather bureau) for the days of the SP occurrence and the days previous to it were recorded to measure influences of air temperature and AP, The correlation between days with lightning and SP and clustering of SP was evaluated. Results: SP occurred on 14.7% of the days in the 2-year period. There was no relationship between SP and a rise or fall in AP (Poisson regression). There was an average temperature rise of 0.57 degrees C from the day prior to the day of the SP, compared with a 0.08 degrees C fall on the days without SP, This difference is statistically significant and was consistent over the four seasons and both years, Seventy-three percent of the SP cases were clustered. A relationship between SP and thunderstorms was found. Conclusions: AP differences do not seem to influence the chance of developing SP. SP occurs in clusters, and more often 1 to 2 days after thunderstorms, Whether the identified temperature rise prior to the SP is a causative factor is unlikely; coexisting weather phenomena might explain this unexpected finding and should be studied in the future.
151. Soneja, S., et al. (2016). "Exposure to extreme heat and precipitation events associated with increased risk of hospitalisation for asthma in Maryland, USA." *Environmental Health* **15**.
- a. Background: Several studies have investigated the association between asthma exacerbations and exposures to ambient temperature and precipitation. However, limited data exists regarding how extreme events, projected to grow in frequency, intensity, and duration in the future in response to our changing climate, will impact the risk of hospitalisation for asthma. The objective of our study was to quantify the association between frequency of extreme heat and precipitation events and increased risk of hospitalisation for asthma in Maryland between 2000 and 2012. Methods: We used a time-stratified case-crossover design to examine the association between exposure to extreme heat and precipitation events and risk of hospitalisation for asthma (ICD-9 code 493, n = 115,923). Results: Occurrence of extreme heat events in Maryland increased the risk of same day hospitalisation for asthma (lag 0) by 3 % (Odds Ratio (OR): 1.03, 95 % Confidence Interval (CI): 1.00, 1.07), with a considerably higher risk observed for extreme heat events that occur during summer months (OR: 1.23, 95 % CI:

- 1.15, 1.33). Likewise, summertime extreme precipitation events increased the risk of hospitalisation for asthma by 11 % in Maryland (OR: 1.11, 95 % CI: 1.06, 1.17). Across age groups, increase in risk for asthma hospitalisation from exposure to extreme heat event during the summer months was most pronounced among youth and adults, while those related to extreme precipitation event was highest among <= 4 year olds. Conclusion: Exposure to extreme heat and extreme precipitation events, particularly during summertime, is associated with increased risk of hospitalisation for asthma in Maryland. Our results suggest that projected increases in frequency of extreme heat and precipitation event will have significant impact on public health.
152. Suphioglu, C. (1998). "Thunderstorm asthma due to grass pollen." *International Archives of Allergy and Immunology* **116**(4): 253-260.
- a. It is widely known and accepted that grass pollen is a major outdoor cause of hayfever. Moreover, grass pollen is also responsible for triggering allergic asthma, gaining impetus as a result of the 1987/1989 Melbourne and 1994 London thunderstorm-associated asthma epidemics. However, grass pollen is too large to gain access into the lower airways to trigger the asthmatic response and micronic particles < 5 µm are required to trigger the response. We have successfully shown that ryegrass pollen ruptures upon contact with water, releasing about 700 starch granules which not only contain the major allergen Lol p 5, but have been shown to trigger both in vitro and in vivo IgE-mediated responses. Furthermore, starch granules have been isolated from the Melbourne atmosphere with 50-fold increase following rainfall. Free grass pollen allergen molecules have been recently shown to interact with other particles including diesel exhaust carbon particles, providing a further transport mechanism for allergens to gain access into lower airways. In this review, implication and evidence for grass pollen as a trigger of thunderstorm-associated asthma is presented. Such information is critical and mandatory for patient education and training in their allergen avoidance programs. More importantly, patients with serum IgE to group 5 allergens are at high risk of allergic asthma, especially those not protected by medication. Therefore, a system to determine the total atmospheric allergen load and devising of an effective asthma risk forecast is urgently needed and is subject to current investigation.
153. Sutherland, A. and I. Hall (1994). "Thunderstorms and asthma admissions." *The Lancet* **344**(8935): 1503-1504.
154. Taylor, P. E., et al. (2002). "Release of allergens as respirable aerosols: A link between grass pollen and asthma." *Journal of Allergy and Clinical Immunology* **109**(1): 51-56.
155. Taylor, P. E., et al. (2007). "Links between pollen, atopy and the asthma epidemic." *International Archives of Allergy and Immunology* **144**(2): 162-170.
- a. Pollen allergy has been found in 80-90% of childhood asthmatics and 40-50% of adult-onset asthmatics. Despite the high prevalence of atopy in asthmatics, a causal relationship between the allergic response and asthma has not been clearly established. Pollen grains are too large to penetrate the small airways where asthma occurs. Yet pollen cytoplasmic fragments are respirable and are likely correlated with the asthmatic response in allergic asthmatics. In this review, we outline the mechanism of pollen fragmentation and possible pathophysiology of pollen fragment-induced asthma. Pollen grains rupture within the male flowers and emit cytoplasmic debris when winds or other disturbances disperse the pollen. Peak levels of grass and birch pollen allergens in the atmosphere correlated with the occurrence of moist weather conditions during the flowering period. Thunderstorm asthma epidemics may be triggered by grass pollen rupture in the atmosphere and the entrainment of respirable-sized particles in the outflows of air masses at ground level. Pollen contains nicotinamide adenine dinucleotide phosphate (reduced) oxidases and bioactive lipid mediators which likely contribute to the inflammatory response. Several studies have examined synergistic effects and enhanced immune response from interaction in the atmosphere, or from co-deposition in the airways, of pollen allergens, endogenous pro-inflammatory agents, and the particulate and gaseous fraction of combustion products. Pollen and fungal fragments also contain compounds that can suppress reactive oxidants and quench free radicals. It is important to know more about how these substances interact to potentially enhance, or even ameliorate, allergic asthma. Copyright © 2007 S. Karger AG.
156. Taylor, P. E. and H. Jonsson (2004). "Thunderstorm asthma." *Current Allergy and Asthma Reports* **4**(5): 409-413.
- a. Thunderstorms have often been linked to epidemics of asthma, especially during the grass flowering season, however, the precise mechanisms explaining this phenomenon are unknown. Evidence of high respirable allergen loadings in the air associated with specific meteorologic events combined with an analysis of pollen physiology suggests that rupture of airborne pollen can occur. Strong downdrafts and dry, cold outflows distinguish thunderstorm rain from frontal rain. The weather system of a mature thunderstorm likely entrains grass pollen into the cloud base, where pollen rupture would be enhanced, then transports the respirable-sized fragments of pollen debris to ground level where outflows distribute them ahead of the rain. The conditions occurring at the onset of a thunderstorm might expose susceptible people to a rapid increase in concentrations of pollen allergens in the air that can readily deposit in the lower airways and initiate asthmatic reactions. Copyright © 2004 by Current Science Inc.
157. Thibaudon, M., et al. (2011). "Moulds, thunderstorm and asthma." *Revue Francaise d'Allergologie* **51**(6): 560-563.
- a. The scientific literature for over 25. years shows that relationships exist between exacerbation of asthma during thunderstorms and presence in the air of biological microparticles. Among these particles are primarily mould spores and pollen fractions and pauciparticles. Atmospheric moulds are not often measured and above, there is little measured health impact associated with these moulds. Allergists only care about moulds for which they have allergenic extracts, in particular *Alternaria* and *Cladosporium*, *Aspergillus* and *Penicillium* even. Analyses of the slides from the RNSA pollen traps confirm previous publications on the presence of spores of *Didymella* peaks during some days. The aim of this project is to work on relationships that may exist between the particles in the air and some weather conditions (thunderstorms), aggravation of asthma attacks being only a goal in the longer term. This work should allow further diagnostic aid for doctors, information predictive for asthma and an additional parameter for the health authorities in setting health alert bulletins. © 2011 Elsevier Masson SAS.
158. Thibaudon, M., et al. (2012). "Moulds and thunderstorms." *Allergy: European Journal of Allergy and Clinical Immunology* **67**: 82.
- a. Background: Identify molds which would be preferentially in the air during some weather conditions such as thunderstorms. Method: The technicians of the Strasbourg hospital allergy laboratory make every week, from May to September, the analysis of the molds' contents of *Alternaria*, *Cladosporium* and *Didymella* with optical microscopy method. Our study concerns the countings from 2008 till 2010. The data of relative humidity, precipitation and temperature are

transmitted by the ASPA (Association pour Surveillance et l'étude de la Pollution Atmosphérique en Alsace). During a stormy peak, the relative humidity increases then decreases within hours which follow. The results of the countings are put in parallel with these data to observe the evolution of molds according to stormy periods. Result: From 2008 till 2010, we observed in July an increase of the concentrations of *Didymella* >2000 spores/m<sup>3</sup> during thunderstorms while the concentrations were lower than 250 spores/m<sup>3</sup> outside these periods. The peaks of *Didymella* arose within hours following the thunderstorm during the diminution of the relative humidity. During the same period, *Alternaria* and *Cladosporium* decreased, even were absent, while they were present during periods without thunderstorms. Conclusion: The results of Strasbourg suit to the data of the literature. However, it would be advisable to confirm this work by a forward-looking study of longer term. Secondarily, if these data are confirmed, it will be necessary to estimate the links between the increase of asthma and *Didymella* peaks.

- 159.Thibaudon, M., et al. (2014). "Moulds - Thunderstorms - Asthma." *Revue Francaise d'Allergologie* **54**(3): 124-126.
- a. An increase in respiratory diseases during stormy summer periods has been noted for many years. The purpose of this study, besides a literature search, was to relate different aerobiological parameters (concentrations of molds and pollens), weather (temperature, relative humidity, rainfall and storms), and air pollution (PM<sub>10</sub>, PM<sub>2.5</sub>, O<sub>3</sub>, NO<sub>2</sub>...) to hospitalisations based on emergency department data or "SOS médecins" calls for serious respiratory problems. The current study was carried out in the summer seasons from 2008 to 2013 with the help of the personal of the Pulmonary and Allergy department, the Division of Public Health and the Emergency Department of the Strasbourg University Hospital, "SOS médecins" in Strasbourg, as well as the RNSA (Réseau national de surveillance aérobiologique), the ASPA Alsace, Météo-France and Météorage. Among aerobiological parameters, a sharp increase in concentrations of *Didymella* sp. was observed during stormy periods. These periods also favor occasional increase in respiratory diseases. © 2014 Elsevier Masson SAS.
- 160.Todea, D. A., et al. (2013). "The effect of climate change and air pollution on allergenic potential of pollens." *Notulae Botanicae Horti Agrobotanici Cluj-Napoca* **41**(2): 646-650.
- 161.Turbyville, J. C. (2012). "Adverse reactions to subcutaneous allergen immunotherapy following thunderstorms." *Journal of Allergy and Clinical Immunology* **129**(2): AB194.
- a. RATIONALE: Thunderstorm asthma is a well described phenomenon and the risk factors proposed to account for the association may be similar to those for adverse reactions to immunotherapy. METHODS: Patient data were collected retrospectively over a 3 year time period and compared to weather data over the same time period. Patient data included the total number of injections received and the number of local and systemic reactions recorded. Weather data were analyzed both in terms of rainfall alone ("wet" vs. "dry") and also in terms of "thunderstorm" vs. "non-thunderstorm" based on whether at least 1 inch of rainfall was recorded in 24 hours or if lightning was recorded in the presence of rain. Results: The total number of injections recorded over the study period was 24,684 administered to 271 patients. Adverse reactions were not more likely to occur on wet days compared to dry days (p=1.00 for systemic reactions and p=0.69 for local reactions). Systemic reactions were not more likely to occur on thunderstorm days than on non-thunderstorm days (p=0.64) but local reactions were significantly more likely to occur on thunderstorm days than on non-thunderstorm days (p=0.008). A subset of 27 patients was identified who either only had adverse reactions or had the majority of their adverse reactions in association with thunderstorms. CONCLUSIONS: Rainfall alone does not appear to increase the risk of adverse reactions to subcutaneous immunotherapy. A subset of allergic patients likely exists for whom thunderstorms increase the risk of adverse reactions to immunotherapy.
- 162.Venables, K. M., et al. (1997). "Thunderstorm-related asthma - The epidemic of 24/25 June 1994." *Clinical and Experimental Allergy* **27**(7): 725-736.
- a. Background A large epidemic of asthma occurred following a thunderstorm in southern and central England on 24/25 June 1994. A collaborative study group was formed. Objectives To describe the epidemic and the meteorological, aerobiological and other environmental characteristics associated with it. Methods Collation of data from the Meteorological Office, the Pollen Research Unit, the Department of the Environment's Automatic Urban Network, from health surveillance by the Department of Health and the National Poisons Unit, from clinical experience in general practice and hospitals, and from an immunological study of some of the affected cases from north east London. Results The thunderstorm was a Mesoscale Convective System, an unusual and large form of storm with several centres and severe wind gusts. It occurred shortly after the peak grass pollen concentration in the London area. A sudden and extensive epidemic occurred within about an hour affecting possibly several thousand patients. Emergency services were stretched but the epidemic did not last long. Cases had high serum levels of IgE antibody to mixed grass pollen. Conclusion This study supports the view that patients with specific IgE to grass pollen are at risk of thunderstorm-related asthma. The details of the causal pathway from storm to asthma attack are not clear. Case-control and time series studies are being carried out.
- 163.Venables, K. M., et al. (1996). "Causes of thunderstorm-related asthma." *Thorax* **51**(SUPPL. 3).
- 164.Villeneuve, P. J., et al. (2005). "Frequency of emergency room visit for childhood asthma in Ottawa, Canada: The role of weather." *International Journal of Biometeorology* **50**(1): 48-56.
- a. The aim of this study was to evaluate associations between meteorological conditions and the number of emergency department visit for asthma in a children's hospital in Ottawa, Canada. A case-crossover study design was used. Hospital emergency department visit for asthma between 1992 and 2000 were identified based on patients' presenting complaints. We obtained hourly measures for the following meteorological variables: wind speed, temperature, atmospheric pressure, relative humidity, and visibility. Particular emphasis was placed on exploring the association between asthma visit and fog, thunderstorms, snow, and liquid and freezing forms of precipitation. In total, there were 18,970 asthma visit among children between 2 and 15 years of age. The number of visit and weather characteristics were grouped into 6 h case and control intervals. The occurrence of fog or liquid precipitation was associated with an increased number of asthma visit, while snow was associated with a reduced number (P<0.05). Stratified analyses by season found no association in any of the four calendar intervals between the number of asthma visit and visibility, change in relative humidity and change in temperature. In contrast, summertime thunderstorm activity was associated with an odds ratio of 1.35 (95% CI=1.02-1.77) relative to summer periods with no activity. Models that incorporate calendar and

- meteorological data may help emergency departments to more efficiently allocate resources needed to treat children presenting with respiratory distress. © ISB 2005.
165. Visez, N., et al. (2015). "Wind-induced mechanical rupture of birch pollen: Potential implications for allergen dispersal." *Journal of Aerosol Science* **89**: 77-84.
- a. Mechanical rupture of pollen grains after a mechanical shock against a solid surface was tested as a new approach to one of the mechanisms related to the release of allergen loaded particles from pollen. Birch pollen was aerosolized and sent into an impactor to mimic a shock against a surface (trees, soil, walls, etc.) at wind speeds of atmospheric-relevance. Small particles in the range of 1-2.5. µm were released subsequently to pollen impaction. The number of particles released increased with the velocity of impaction and with the water content of pollen. Damaged grains were observed by transmission electron microscopy and released particles are most likely cytoplasmic granules. This mechanism of pollen rupture and/or discharge may be of great importance in urban environment and may significantly contribute to thunderstorm-related allergic asthma and other associated pollen subparticles IgE mediated diseases.
166. Wanka, E. R., et al. (2014). "Weather and air pollutants have an impact on patients with respiratory diseases and breathing difficulties in Munich, Germany." *International Journal of Biometeorology* **58**(2): 249-262.
- a. This study determined the influence of various meteorological variables and air pollutants on airway disorders in general, and asthma and/or chronic obstructive pulmonary disease in particular, in Munich, Bavaria, during 2006 and 2007. This was achieved through an evaluation of the daily frequency of calls to medical and emergency call centres, ambulatory medical care visit at general practitioners, and prescriptions of antibiotics for respiratory diseases. Meteorological parameters were extracted from data supplied by the European Centre for Medium Range Weather Forecast. Data on air pollutant levels were extracted from the air quality database of the European Environmental Agency for different measurement sites. In addition to descriptive analyses, a backward elimination procedure was performed to identify variables associated with medical outcome variables. Afterwards, generalised additive models (GAM) were used to verify whether the selected variables had a linear or nonlinear impact on the medical outcomes. The analyses demonstrated associations between environmental parameters and daily frequencies of different medical outcomes, such as visit at GPs and air pressure (-27 % per 10 hPa change) or ozone (-24 % per 10 µg/m<sup>3</sup> change). The results of the GAM indicated that the effects of some covariates, such as carbon monoxide on consultations at GPs, or humidity on medical calls in general, were nonlinear, while the type of association varied between medical outcomes. These data suggest that the multiple, complex effect of environmental factors on medical outcomes should not be assumed homogeneous or linear a priori and that different settings might be associated with different types of associations.
167. Wardman, A. E. D., et al. (2002). "Thunderstorm-associated asthma or shortness of breath epidemic: A Canadian case report." *Canadian Respiratory Journal* **9**(4): 267-270.
- a. Thunderstorm-associated asthma epidemics have been documented in the literature, but no Canadian experience has been reported. On July 31, 2000, a thunderstorm-associated epidemic of asthma or shortness of breath occurred in Calgary, Alberta. The Calgary Health Region investigated the event using diagnostic data from emergency departments, an urgent care medical clinic and patient interviews, in addition to bioaerosol counts, pollutant data and weather data reflecting atmospheric conditions at that time. On July 31, 2000 and August 1, 2000, 157 people sought care for asthma symptoms. The expected number of people to seek care for such symptoms in a 48 h period in Calgary is 17. Individuals with a personal or family history of asthma, allergies or hayfever who were not taking regular medication for these conditions and who were outdoors before the storm appeared to have been preferentially affected. A stagnant air mass the day before the thunderstorm may have resulted in declining bioaerosol concentrations, and the possible accumulation of spore and pollen reservoirs within mould and plant structure. The elevated bioaerosol concentrations observed on the day of the thunderstorm may be attributed to the sudden onset of high winds during the thunderstorm, which triggered a sudden release of spores and pollens into the atmosphere, which was probably responsible for the epidemic. Several pollutant levels slightly increased on the day of the storm and possibly also played a role in symptom development. It is unclear whether an atmospheric pressure drop contributed to the release of spores and pollens.
168. Wark, P. A. B., et al. (2002). "Airway inflammation in thunderstorm asthma." *Clinical and Experimental Allergy* **32**(12): 1750-1756.
- a. Background: Epidemics of acute asthma associated with thunderstorms occur intermittently worldwide, though airway inflammation during these acute episodes has not been characterized. The aim of this study was to characterize airway inflammation in thunderstorm asthma. Methods: Cases were recruited after presentation to the emergency room with acute asthma immediately following a thunderstorm (n = 6). They were compared to two control groups: a group of atopic asthmatics that had presented with acute asthma to the emergency room prior to the thunderstorm (n = 12), and a second group of corticosteroid naive asthmatics who presented to the emergency room in the prior 12 months (n = 6). Subjects had spirometry, sputum induction and allergy skin tests acutely and at review 4 weeks later. Results: Thunderstorm (thunderstorm) cases were more likely to have a history of hayfever and grass pollen allergy, and less likely to be on inhaled corticosteroids (ICS) prior to presentation. Cases and control groups had a similar degree of moderate to severe acute airway obstruction (P = 1.0). thunderstorm cases had elevated sputum eosinophils (14.8% of total cell count) compared to controls (1%, 2.6%, P < 0.01). thunderstorm cases had higher sputum eosinophil cationic protein (ECP; 11 686 ng/mL) compared to controls (1883, 3300, P = 0.02) acutely. thunderstorm cases had more cells positive for IL-5 (30%) compared to controls (1, 1.5%, P = 0.02). When adjusted for ICS use, thunderstorm cases had a risk ratio for elevated sputum eosinophils of 2.4 (1.23-4.69). Conclusion: Thunderstorm asthma is characterized by airway inflammation with IL-5-mediated sputum eosinophilia and eosinophil degranulation. These results are consistent with allergen exposure as the cause of the exacerbation, and are consistent with the thunderstorm-induced grass pollen deluge as the cause of epidemic asthma after thunderstorms.
169. Wasilievich, E., et al. (2010). "Short-term outdoor temperature change and emergency department visit for asthma among children-a case-crossover study." *American Journal of Respiratory and Critical Care Medicine* **181**(1).
- a. Rationale: The impact of weather changes on the frequency of emergency department (ED) visit for asthma is not well understood. Previous studies that have considered weather have focused on climatic status over days and weeks and not short-term changes in weather conditions. The objective of this study was to determine the association between short-term (≤24 hours) outdoor temperature change and hospital ED visit for asthma among children. Methods: A

retrospective study was performed at a large urban pediatric hospital during the two year period, January 1, 2000 through December 31, 2001. The study population included children (3 to 18 years) with an asthma ED visit during the study period that did not result in an inpatient admission. Analyses of ED visit were conducted to assess the distribution of age at visit, race, sex, closest weather station, and temporal characteristics of the visit: meteorological season, month, day of the week, time of day. A case-crossover study was conducted to determine the independent effect of maximum temperature change and maximum temperature change rate measured during 4, 8, 12, and 24 hour exposure periods. Multivariable conditional logistic regression analyses, stratified by exposure period, were done to demonstrate the relationship between the individual exposures of interest and other weather conditions during the exposure period (relative humidity, wind speed, barometric pressure, thunderstorm, and liquid precipitation) and daily outdoor air pollutant measures (SO<sub>2</sub>, NO<sub>2</sub>, O<sub>3</sub>, and PM<sub>2.5</sub>). Results: There were 4,804 asthma ED visit during the study period. They occurred most frequently in the fall and between 9:00 am and 12:00 pm. (Table 1) Results from the case-crossover study show that neither short-term temperature change nor temperature change rate is predictive of an asthma ED event, regardless of the exposure period. (Table 2) The addition of other climatic and pollutant factors adjusted models did not alter the findings. Conclusions: ED visit for asthma are not likely to be associated with temperature change during the 24 hours prior to the event. (Table Presented) .

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a. Climate and weather have a huge impact on the presence of pollen and mold spores in the atmosphere. Although prevalent weather helps define climate, individual weather conditions, such as rain, humidity; wind speed and direction, temperature, or amount of sunshine, may have direct and indirect effects on bioaerosols. Weather is an inherently unpredictable chaotic system of numerous variables that interact in an additive or synergistic fashion. It seems likely that from year to year, different variables may have a more central role in determining pollen counts. How specific meteorologic parameters affect aeroallergen burden is addressed. Spore-release mechanisms and the primary effects of humidity and precipitation also are discussed. Special circumstances, such as the release of submicronic particles and the clinical impact of thunderstorms and mechanisms, are addressed.

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172. Wilson, J. and B. Pyatt (1996). "Thunderstorms and asthma - A review of current research progress." *Journal of Meteorology* **21**(208): 121-125.

173. Woodhead, M. (2016). "Hospitals overwhelmed with patients after "thunderstorm asthma" hits Melbourne." *Bmj* **355**: i6391.

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