Epidemiologic Studies of Asthma Epidemics in Barcelona*

Josep M. Antó, M.D.; and J. Sunyer, M.D.

IgE = Immunoglobulin E; RAST = Radioallergosorben test

Epidemiology investigates the distribution of diseases, their causes, and determining factors. For an epidemiologic investigation to be possible, a measurable definition of diseases based on a satisfactory understanding of their biologic or psychological nature is required.

Several characteristics of asthma complicate the application of an epidemiologic approach. The true biologic nature of bronchial asthma is not well known; the distinction between bronchial asthma and chronic bronchitis is a subject of discussion,[1,2] and short-lasting symptomatic crises can occur irregularly in many asthmatics, making it difficult to diagnose the disease in periods between crises. In addition, some asthma-related symptoms (*eg*, dyspnea or wheezing) are found in other diseases. Finally, there are 2 asthma-related conditions, atopy and bronchial hyperreactivity, which are relevant in any epidemiologic study of asthma but whose importance as a basis for establishing the definition of the disease is not well established. For these reasons, most descriptive asthma epidemiology based on questionnaire definitions is not considered of value unless it incorporates tests of bronchial reactivity.[3] These limitations also affect the application of classic epidemiologic designs to research on asthma. Recently, the findings in a case–control study of asthma deaths were challenged on the basis of inadequate control for severity.[4,5]

Another approach of interest is epidemiologic surveillance, which aims to identify temporal and geographic variations in disease patterns. Although initially concerned with epidemics, particularly of infectious diseases, epidemiologic surveillance can also be used to monitor prevalence, incidence, or other disease-related indicators without the goal of specific and immediate intervention. Again, a good definition of the disease is desirable, but in some circumstances mortality or morbidity indicators can be adequate for tracing the evolution of a disease in the community, providing useful information for policy-making as well as clues to the etiology. Of special importance is the application of epidemiologic surveillance methods to the study of epidemics.

Epidemics represent a special situation for epidemiology. Often an epidemic is due to an abrupt change in the temporospatial distribution of normal, nonnecessary or nonsufficient causes. At other times a necessary cause can be identified, thus providing opportunities for intervention. When the causes of a disease are largely unknown, the study of epidemics can result in a better understanding of the disease. Although epidemics can appear as massive or abrupt phenomena, and thus may be easily identifiable, they may also be occult. In both cases epidemiologic surveillance provides an appropriate framework for timely identification, giving opportunities for more specific studies or interventions. Epidemiologic surveillance data bases can also allow retrospective identification of epidemics, which may be of practical importance.

In this article we review the epidemiologic surveillance framework that has provided the basis for most of the studies of asthma epidemics in Barcelona. The various steps from the identification of the epidemics to the establishment of their cause are considered. Finally, the limitations and possibilities of the use of asthma emergency admissions data for research are discussed.

Identification of Asthma Outbreaks: Choice of Monitoring System

Asthma outbreaks in Barcelona were first identified in 1981 in the emergency room of the Hospital Clinic of Barcelona following an abrupt and massive influx of patients in severe asthma crisis. A retrospective study of 6 outbreaks was carried out in 1983, comparing admissions during outbreaks with admissions on 12 randomly selected days.[6] All outbreaks showed similar features: most of the patients arrived at the hospital within a period of 4 h and reported a short interval between the onset of symptoms and their admission to the emergency room. The asthma attacks were unusually severe, with many patients needing mechanical ventilation. During the epidemics, the air had been still and atmospheric pressure high. No etiologic hypothesis was advanced on the basis of this study, although atmospheric pollution was considered a possible cause. Average 24-h levels of sulfur dioxide and black smoke were not unusually high, but short-term peaks in air pollution could not be excluded. During a new outbreak (the seventh), high levels of nitric oxide were recorded during the hours at which most of the patients arrived at the emergency room. This hourly-time coincidence led clinicians to suspect the etiologic role of this contaminant.[7]

In 1984, a Collaborative Asthma Group made up of epidemiologists and clinicians from the main hospitals of the city was established by the city's Department of Public Health. All available evidence on previously identified outbreaks was reviewed, and the principal objectives and guidelines for future research were discussed.

Among several limitations, the following were considered by the Collaborative Group to be of particular importance: (1) identification of outbreaks had been based on the subjective experience of clinicians,[6] (2) emergency room admissions on epidemic and control days were not available

*From the Department d'Epidemiologia i Salut Pública, IMIM, Barcelona, Spain.
Reprint requests: Dr. Anto, Institut Municipal d'Investigacio Medica, Passeig Maritim 25-29, Barcelona, Spain 08003

for other respiratory diseases, although the clinicians' perceptions suggested that similar increases in chronic bronchitis emergencies had not occurred, and (3) statistical evaluation of epidemics had been restricted to only one hospital in the city, so that a population-based description of the outbreaks was not available.

For these reasons the Collaborative Asthma Group decided to set up a prospective monitoring system for respiratory emergency room admissions. The most important objectives were (1) to estimate baseline data on asthma emergency room (ER) admissions; (2) to identify significant increases in the daily number of asthma admissions and to assess them independently of subjective criteria; (3) to compare the latter estimates between different districts within the city; (4) subsequently, to generate or test hypotheses regarding the etiology of the outbreaks, and particularly (5) to assess the relationship between variations in asthma emergencies and variations in air pollution levels and meteorologic parameters.

Methods

Monitoring System of Respiratory ER Admissions

The emergency rooms of the four largest hospitals in the city were recruited. They provided a reasonable geographic coverage and accounted for more than 90% of total hospital emergency admissions in Barcelona. For each hospital, the total number of emergency admissions was registered and a distinction was made between medical and surgical causes for admission. Among medical emergencies, the total number of admissions for respiratory causes was also registered.

Patients admitted for emergency treatment of asthma or chronic bronchitis and living in Barcelona were identified and their age, sex, address, day and hour of arrival, and details of referral were recorded. Specific operational definitions of asthma and chronic bronchitis emergencies were established by identifying lists of equivalent terms used by clinicians at other emergency rooms in the diagnosis of both diseases. A panel of respiratory physicians from all the participant hospitals was convened, and the terms to be included in the final list were selected by consensus. Special difficulties were observed in separating asthma from other respiratory disorders with wheezing in children. The following terms were included under the category of asthma: asthmatic bronchitis, spastic bronchitis, bronchial hyperreactivity, asthmatic status, and bronchospasm. Another list was made for chronic bronchitis. Data were collected from the clinical records at the emergency rooms by physicians specially trained to identify asthma and chronic bronchitis admissions using the list of accepted terms. Air pollution and meteorologic variables were recorded in parallel with emergency admissions.

A standardized questionnaire was prepared for on-the-spot administration to asthmatic patients affected by outbreaks in order to interview them about the specific epidemiologic circumstances. The variables included in the questionnaire were time and place of onset of symptoms, activities and itineraries on the day of the outbreak, presence of asthma-related symptoms during the day before the outbreak, medication patients were receiving, and opinions about possible triggers of the asthma attacks.

Identification of Point-Source Epidemics

On Nov 26, 1984, a marked influx of patients suffering from asthma attacks was detected at the emergency room of the Hospital Clinic. The monitoring system together with the questionnaire provided a complete descriptive study of this, the eighth outbreak.[8] Forty-three adult emergency admissions for asthma and 22 admissions of children (<14 years old) were registered. Based on the Poisson distribution, the probability that this outbreak had been a random event was very low for adults ($p = 1.5 \times 10^{-17}$) but not statistically significant for children ($p = 0.087$). The number of emergency admissions for chronic bronchitis and other respiratory diseases was normal. Hourly cluster was assessed by means of a Knox approximation to the scanning method. The greatest density of patients (70%) arrived at the hospital between noon and 4 PM. The 4-h cluster was highly significant ($p = 1.4 \times 10^{-27}$).

The geographic distribution of cases was studied. Considered were the places where the symptoms started, as reported on the questionnaire, and the patients' addresses. The results showed a striking cluster of cases in the harbor areas of the city. The 24-h average level of sulfur dioxide was 54 $\mu g/m^3$ and that of black smoke was 98 $\mu g/m^3$. The highest hourly mean for nitrogen dioxide was 10 ppb. Meteorologic data showed high atmospheric pressure and stagnancy of the air with a very low wind speed.

All these data helped to demonstrate that the abrupt increase in asthma emergencies was a true epidemic, revealing a simultaneous time and space clustering suggestive of a point-source epidemic. Routinely measured air pollutants and pollen or fungal spores were considered unlikely to be etiologically related to the epidemic. The most affected neighborhood was next to the harbor and near an industrial area, which, it was considered, could contain the point source of the causative factor.[8]

During the period 1985–1986, six outbreaks were identified by clinicians; all were confirmed by epidemiologic assessment. Retrospective data were also collected for 5 of the 7 outbreaks that occurred between 1981 and November 1984. This made it possible to carry out a homogeneous study of 12 of the 14 outbreaks that had occurred since 1981, using the same methodology as was used for the 8th epidemic.[9] All outbreaks showed a simultaneous time and space cluster. District I, nearest the harbor, had the highest attack rate (age-adjusted) in all the outbreaks. All the outbreaks were also characterized by the presence of a statistically significant cluster of admissions during a 4-h or shorter period. The consistency of this feature was interpreted as strongly supporting the point-source hypothesis as well as confirming the potential location of the point source in the harbor or in the industrial area near it.

It was also noted that in all outbreaks, a proportion of patients had been admitted to an emergency room during a previous outbreak. This proportion ranged from 22.6% (19 second or later admissions among 83 patients affected) to 56.2% (18 second or later admissions among 32 patients affected).

In the outbreaks that occurred after the monitoring system had begun to operate, patients were interviewed about possible triggers of the epidemic attacks, but no plausible hypothesis was forthcoming. Unusual environmental events were not identified during outbreaks.[10]

Development of an Epidemiologic Definition of Asthma Outbreaks

The 12 outbreaks described had been identified by clinicians because of an extraordinary and hourly clustered influx of asthma patients to the emergency room of one of the two hospitals located nearest to the epidemic area. All outbreaks were retrospectively assessed by means of epidemiologic and statistical criteria, based on the data provided by the monitoring system. During the evaluation, the possibility was considered that other epidemics might have occurred but were not recognized by clinicians because a smaller number of people were affected and the cases were more widely spread among the hospitals. To determine whether unrecognized small outbreaks existed, an epidemiologic definition of asthma outbreak was developed based

on the empirical features already known.[11]

Following previous studies by Goldstein et al[12,13] on asthma epidemics in New York and in New Orleans, an unusual asthma day was defined as the day on which the number of emergency room visits was so high that the probability that such a number or higher could arise by chance was 0.025 or less. This probability was calculated by assuming a Poisson distribution, with the 15-day moving average representing the number of cases expected. Instead of using a more restrictive probabilistic cutoff point (*ie*, $p \leq 0.001$) for defining epidemic days, as had been done by Goldstein and associates, hourly and geographic cluster phenomena were considered criteria of epidemicity.

An asthma epidemic day was defined as an unusual asthma day on which the asthma emergencies were clustered on an hourly and geographic basis. An hourly cluster was defined as the occurrence in one 4-h period of so many emergency room visits for asthma that the probability that such a high number of visits could occur by chance was 0.05 or less. This probability was calculated by the Knox and Lancashire approximation[14] to the scan method.[15] Geographic clusters were assessed by crude inspection of the distribution of addresses on the map of the city. Maps for all unusual asthma days were constructed and evaluated independently by 2 observers.

During the period 1985–1986, 23 unusual asthma days were identified (13 in 1985 and 10 in 1986). Among them, 13 showed an hourly cluster. A geographic cluster was considered present in all unusual asthma days with an hourly cluster, except in 2 cases in which it was considered present by 1 observer but doubtful by the other. By contrast, on the 10 unusual asthma days without hourly cluster, a geographic cluster was considered present on 2 days and absent on 5 days. The addresses were missing on 3 days.

Among the 13 unusual asthma days with both hourly and geographic clusters (thus fulfilling the criteria of an epidemic day), only 6 had been previously identified by clinicians. These 6 days had an average of 40.6 asthma emergencies (range, 18–83) and the highest p value was 0.005. On the other hand, the seven unusual days with both hourly and geographic clusters that had not been identified by clinicians had an average of 16.2 asthma emergencies (range, 12–23), with the highest p value being 0.017. The other 2 groups (unusual days with geographic cluster but without hourly cluster, and unusual days with neither hourly cluster nor geographic cluster) were similar, with 11.5 and 11.6 asthma emergencies on average (ranges, 8–15 and 10–14) and highest p values of 0.019 and 0.020, respectively.

Taking into account these results, we decided to consider the presence of an unusual asthma day together with hourly and geographic cluster as an acceptable definition of an asthma epidemic day. However, as geographic clusters were present whenever a 4-h cluster existed, and because it is difficult to measure geographic clusters objectively, only time-cluster measures were included in the definition of asthma epidemic day.

All epidemic asthma days that had not been identified by clinicians showed a proportion of repeaters ranging from 35.3% (3 repeaters among 17 patients affected) to 60.8% (14 repeaters among 23 patients affected) that was similar to or higher than the number found on the other epidemic days. On the other hand, 2 unusual days with geographic cluster but without hourly cluster both had only one repeater. Finally, of the 5 days with neither hourly nor geographic cluster, 3 days showed 0 or 1 repeater and 2 days had 4 repeaters out of 10 patients affected (40%) and 6 out of 13 (46%), respectively. Consequently, if the proportion of repeaters could be taken as a reference criterion of an asthma epidemic in Barcelona, our definition of an asthma epidemic day would be considered satisfactory except for these last 2 days, which may be considered false negatives.

A Change in Research Strategy: Establishment of the Soybean Hypothesis

In 1987, the Collaborative Asthma Group reviewed all the available evidence on Barcelona asthma outbreaks in Barcelona. Even though an important number of asthma epidemics had been identified (directly by clinicians or by epidemiologic surveillance) and a useful definition of asthma epidemic had been established, no etiologic hypotheses had been ventured. Efforts to identify point sources in the harbor or in the industrial area close to the harbor were repeatedly negative. Therefore, as far as etiology was concerned, no progress had been made since 1985 when the eighth outbreak was described; however, it was considered most likely that the asthma epidemics were caused by a biologic or chemical agent spread from a point source, probably located in the harbor or in an important industrial area near the harbor.

It was considered advisable to keep the respiratory emergency monitoring system working and to intensify environmental investigation whenever an asthma outbreak occurred. In addition, two other strategies were designed. The first was aimed at investigating the population affected during outbreaks with 2 principal objectives in mind: (1) the identification of clinical or physiologic characteristics associated with susceptibility to being affected by the agent causing the asthma outbreaks, and (2) identification of the biologic agent causing the epidemics of asthma. The second strategy was aimed at investigating the air in an attempt to identify a substance able to produce asthma and specifically present in the air on epidemic days compared with nonepidemic days.

Coincident with the development of these new strategies, it was observed that at least 3 asthma epidemics (2 of them in 1987) had occurred on days on which soybeans were unloaded in the harbor. However, data on ship unloadings were not available to screen completely for the presence of soybean unloadings for all the outbreaks. Since asthma as an apparent result of exposure to airborne soybean particulates had been reported only rarely, and given the lack of previous reports of epidemic asthma due to soybean dust, we considered soybean unloadings an unlikely cause of asthma outbreaks. Conversely, the only vegetable agent repeatedly reported as a cause of asthma epidemics was ricin, a powerful agent in producing immediate allergy.[16,17] The possibility that a contamination of soybean cargoes by ricin dusts was considered.

The presence of specific IgE antibodies against 22 different commercial antigens, including both Barcelona's airborne common antigens and the soybean and ricin antigens,

was surveyed in a panel of 18 serum samples of patients affected in at least two asthma epidemics. (Serum samples of patients affected by the epidemics had been stored since 1985.) IgE reactivity was assessed blindly by RAST techniques by the same technician. Results showed that 8 of 13 patients had levels of total IgE higher than 150 IU/ml. Moreover, 13 of 18 patients had specific IgE antibodies to soybean antigen, whereas only 4 positive responses were observed to the rest of the antigens. These results were considered strongly suggestive of a possible relationship between the unloading of soybeans in the Barcelona harbor and asthma outbreaks.

Etiologic Studies of Asthma Epidemics

Two epidemiologic studies were designed to test the soybean hypothesis. The relationship between soybean unloadings in the harbor and the occurrence of asthma outbreaks was investigated in a time–ecological study. The relationship between epidemic asthma and serum IgE antibodies reactive with soybean antigen was tested in a case–control study. Both epidemic asthma day and epidemic patient definitions used for subject selection were based on the respiratory emergency room monitoring system.

Time–Ecological Study of Asthma Epidemics[18]

During the period 1985–86, 13 asthma epidemic days had been identified by means of epidemiologic analysis. All products identified as having been loaded or unloaded during at least one asthma outbreak were also studied. The days on which each product was loaded or unloaded were recorded during the same 2-year period. In the case of soybeans, the use of 2 harbor silos (A and B) for soybean unloading was also examined.

For each product unloaded, a risk ratio was calculated between the probability of an asthma epidemic on the days when the product was being unloaded and the probability of an asthma epidemic on days when it was not being unloaded. Thus, the unit of observation and analysis was the 24-h day.

All 13 asthma epidemic days in these two years coincided with soybean unloadings (lower 95% confidence interval of the risk ratio = 7.2). Of the remaining 25 products studied, only wheat was related to the epidemics of asthma, although when adjusted for the unloading of soybeans, the relationship was not statistically significant (risk ratio, 5.03; 95% confidence interval: 0.95 to 26.46). Soybean unloadings also occurred on May 27, 1985, and Oct 21, 1985, the days that could be considered potential epidemic days but had not been identified by our method (false negative epidemics). When the site of soybean unloading (silo A or B) was taken into account, the association was too high to be determined in silo A ($p<0.001$), but not statistically significant for silo B ($p=0.22$). This latter observation was consistent with the characteristics of the silos: silo A did not have bag filters installed in the cyclone dust collection system, thereby allowing the release of soybean dust into the air.

Case–Control Study of Reactivity to Soybean Antigens in Epidemic Asthma[19]

On Sept 4 and 7, 1987, two large asthma epidemics occurred, causing 157 emergency room admissions for asthma. Serum samples were taken from 86 of these patients at the emergency room; these patients were considered as cases in this study. Controls were selected from emergency room admissions for asthma during the period October 1987 to January 1988, when no epidemic days occurred and when soybean was unloaded under controlled conditions. Potential controls previously seen for asthma on an epidemic day were excluded. Eighty-six controls were individually matched to cases by age, sex, and area of residence. Total serum IgE was measured by paper radioimmunosorbent test. Specific IgE levels to soybean and other common antigen levels were measured by RAST. In addition to a commercial soybean antigen, a soybean dust extract was prepared from dust collected from a ship involved in an epidemic. In 64 of 86 cases (74.4%), there was a reaction with commercial soybean antigen extracts, compared with only four of 86 (4.6%) controls (odds ratio = 61; lower 95% confidence limit = 8.1). For the antigen prepared with a soybean dust extract collected from the ship whose unloading coincided with one epidemic, the association was stronger (odds ratio unquantifiably high; lower 95% confidence limit = 11.7). No other serologic covariates included in the study confounded the association between serum antisoybean IgE antibodies and epidemic asthma. These results strongly supported a causal relationship between the releases of dust during the unloading of soybean and the occurrence of asthma outbreaks. Also, the results suggested that the asthma outbreaks had an underlying allergic mechanism.

Immunologic Evidence of Antigen in Air on Epidemic Days[20]

Soybean allergens on urban aerosols collected with glass-fiber filters were studied in a sample of 24-h average filters corresponding to epidemic and nonepidemic days. The antigens were assayed by a RAST inhibition technique that used antiserum from epidemic asthma patients. The reference antigen preparation was an extract of soybean hull from beans collected in the harbor. The results showed highly statistically significant differences between soybean antigen concentrations on epidemic days in comparison to those on nonepidemic days (the average soybean antigen concentrations were 7,131.4 and 428.4 units/m^3, respectively). These findings provide evidence that an airborne soybean particulate antigen, reactive with serum from epidemic asthma patients, reached the city on epidemic days.

Remarks on Methodology

Validity of Asthma ER Diagnoses

An important problem for our monitoring system lies in the potential biases that can affect the classification of asthma in emergency room settings. A patient in asthma crisis could be incorrectly classified as having chronic bronchitis, or vice versa. Also, the same patient might be classified as suffering from asthma at one time and from chronic bronchitis during another emergency room admission. Although this misclassification error would usually be nondifferential, thus biasing estimation toward the null hypothesis, it could possibly occur systematically in the same direction (chronic bronchitis patients being classified as having asthma) when an asthma outbreak is identified by

clinicians at the emergency room.

The validity and reliability of asthma diagnosis can also vary from one hospital to another, being determined in part by the local characteristics of emergency rooms. The four hospitals included in our study had similar emergency room organization. Clinical records were compiled by staff physicians or residents with a similar degree of training. Finally, our monitoring system was specifically designed to promote accurate data collection through the use of standardized definitions of asthma and chronic bronchitis emergency room admissions, which distinguished it from routine data collection serving primarily administrative purposes. Although more research is needed to evaluate quantitatively the impact of these potential biases, inclusion of the number of emergency room admissions by asthma, chronic bronchitis, and by all other respiratory causes in the same monitoring system has proved to be a satisfactory approach for epidemiologic surveillance.

Representativeness of Asthma ER Admissions

A measure of asthma emergency room admissions may be considered an indirect indicator of asthma occurrence in the population. We may assume that when an asthma crisis fails to improve despite adequate ambulatory treatment, a proportion of patients go to emergency rooms for more intensive care. However, a number of factors make this assumption unrealistic. The decision of an asthmatic patient to attend an emergency room could be strongly influenced by a number of factors other than the severity of the asthma crisis. These factors include the quality of the ambulatory care the patients receive, the organization of the services and the accessibility of the emergency rooms, and previous experiences of asthma crisis treated at the emergency room. Even more important may be the patient's perception of the severity of the asthma crisis. All these factors can affect the representativeness of the rate of emergency room admissions, when used in long-term trend analysis as well as in the study of suspected outbreaks.

The need for caution when interpreting the representativeness of the rate of asthma emergency room admissions can be illustrated by a small ad hoc survey carried out during an asthma outbreak. Two different samples were selected. The first included a panel of 39 epidemic asthma patients admitted during previous outbreaks but who did not seek emergency room care during the outbreak in question. The second included 29 people admitted to an emergency room for asthma on nonepidemic days. Both groups were interviewed by telephone in the 2 days following the asthma outbreaks. Among the epidemic patients, 79% reported an abrupt attack of shortness of breath during the same hours that an epidemic occurred. Among the nonepidemic patients, only 1 reported respiratory symptoms on the day of the epidemic.

These results suggest several considerations. First, asthma outbreaks in Barcelona affected an undetermined proportion of people who did not seek emergency room care during most of the outbreaks. Thus, the attack rate estimated by the number of asthma emergency room admissions was likely to be an underestimation of the true attack rate. Second, some possible biases could have occurred if such underestimation had been differentially distributed among geographic areas or hospitals. Third, the analysis of long-term trends of asthma emergency room admissions frequently assumes that the combination of factors influencing a patient in asthma crisis to seek treatment at an emergency room remains constant. In other words, an unexpected increase in the number of asthma emergency room admissions could be explained by several factors other than a real increase in the number of severe asthma crises.

Autocorrelation Bias in the Analysis of Asthma Outbreaks

Another limitation that deserves comment is the temporal dependence of data in the form of a time series. This lack of temporal independence could have produced an analytical bias in the identification of unusual asthma days, in the assessment of hourly clusters, and in the testing for statistical significance of the risk ratios in the time-ecological study. This problem can be overcome by means of several modeling techniques usually grouped under the label of time series analysis.

In a current study, we are comparing the results obtained in the time–ecological study[18] with those obtained using Box-Jenkins modeling techniques. The preliminary results have confirmed the association between the occurrence of asthma epidemics and soybean unloadings. Furthermore, this methodology could be of general application to the study of asthma epidemics, being of special value in cases where an operational definition of an asthma epidemic day is not available. In such situations, time series analysis can provide appropriate analytic tools for the identification of unusual events as well as for etiologic hypothesis testing.

Conclusions

The respiratory emergency monitoring system developed in Barcelona to study asthma epidemics has proved to be a useful epidemiologic tool. It has mainly contributed to (1) case finding of asthma outbreaks; (2) the development of a useful definition of asthma epidemic days; (3) the setting up of a time–ecological design; (4) the provision of a framework for subject selection in a case–control study; and (5) the design of an intervention study for the evaluation of control measures in the harbor. However, these contributions, although clearly positive, should be considered in light of the conceptual and methodologic limitations enumerated earlier.

Finally, research into Barcelona asthma epidemics, employing principles of epidemiologic surveillance, has led to the identification of a specific etiologic hypothesis that has been tested using analytic designs. The validity of this hypothesis has been demonstrated and has enabled the causative point source to be removed. After this intervention, no other asthma outbreaks were observed.

References

1 Burrows B, Bloom JW, Traver B, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. N Engl J Med 1987; 317:1309-14

2 Dodge R, Cline MG, Burrows B. Comparison of asthma, emphysema and chronic bronchitis diagnoses in a general population sample. Am Rev. Respir Dis 1986; 133:981-86

3 Woolcook A. Epidemiologic methods for measuring prevalence of asthma. Chest 1987; 6:895-925

4 Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981–83: case-control study. Lancet 1989; 1:917-22
5 Feinstein A, Horwitz R, Lanne S, Rebuck A, Spizer W. Fenoterol and fatal asthma (letter). Lancet 1989; 1:1071
6 Ussetti P, Roca J, Agusti AGN, Montserrat JM, Rodriguez-Roisin R, Agusti-Vidal A. Asthma outbreaks in Barcelona. Lancet 1983; 2:280-81
7 Ussetti P, Roca J, Agusti AGN, Montserrat JM, Rodriguez-Roisin R, Agusti-Vidal A. Another asthma outbreak in Barcelona. Lancet 1984; 1:156
8 Antó JM, Sunyer J, Barcelona Asthma Collaborative Group. A point-source asthma outbreak. Lancet 1986; 1:900-3
9 Plasencia A, Antó JM, Sunyer J, Galbe A. Epidemiology of Barcelona asthma outbreaks: a retrospective analysis of 12 epidemics (abstr). In: Proceedings and Abstracts of the 11th Scientific Meeting of the International Epidemiological Association, Helsinki, August 8–13, 1987. Helsinki: International Epidemiological Association, 1987:291
10 Antó JM, Sunyer J, Plasencia A. Nitrogen dioxide and asthma outbreaks. Lancet 1986; 2:1096-97
11 Antó JM, Sunyer J, Plasencia A, Galbe A, Roca J. Time and space clusters on unusual asthma days in Barcelona (abstr). In: Proceedings and Abstracts of the 11th Scientific Meeting of the International Epidemiological Association, Helsinki, August 8–13, 1987. Helsinki: International Epidemiological Association, 1987:28
12 Goldstein IF, Raush LE. Time series analysis of morbidity data for assessment of acute environmental health effects. Environ Res 1978; 17:266-75
13 Goldstein IF, Cuzick J. Daily patterns of asthma in New York City and in New Orleans: an epidemiological investigation. Environ Res 1983; 30:211-23
14 Knox EG, Lancashire R. Detection of minimal epidemics. Stat Med 1982; 1:183-89
15 Wallenstein S. A test for detecting of clustering over time. Am J Epidemiol 1980; 111:367-72
16 Figley KD, Elrod RH. Endemic asthma due to castor bean dust. JAMA 1928; 90:79-82
17 Ordman D. An outbreak of bronchial asthma in South Africa, affecting more than 200 persons, caused by castor bean dust from an oil-processing factory. Int Arch Allergy 1955; 7:10-24
18 Antó JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M. Vazquez L, Toxicoepidemiological Committee. Community outbreaks of asthma associated with inhalation of soybean dust. N Engl J Med 1989; 320:1097-102
19 Sunyer J, Antó JM, Rodrigo MJ, Morell F, Clinical and Toxicoepidemiological Committee. Case-control study of serum immunoglobulin-E antibodies reactive with soybean in epidemic asthma. Lancet 1989; 1:179-82
20 Antó JM, Sunyer J, Grimalt J, Aceves M, Reed CE. Outbreak of asthma associated with soybean dust. N Engl J Med 1989; 321(16):1128