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Anaphylaxis in Spain: where are the bees and other observations

This editorial discusses the findings of the paper in this issue by M. A. Tejedor-Alonso et al. [1], pp. 578–589.

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Dr. Tejedor-Alonso and his co-workers have made a valuable contribution to the understanding of the epidemiology of anaphylaxis with the publication of their article *Incidence of Anaphylaxis in the City of Alcorcon (Spain): A Population-Based Study* [1] in this issue of *Clinical and Experimental Allergy*. These authors have two companion publications in other journals: *Incidence of Anaphylaxis and Subtypes of Anaphylaxis in a General Hospital Emergency Department* [2] and *Incidence of Anaphylaxis in Hospitalized Patients* [3].

Alcorcon is an urban area with a population of about 150 000 [1] within the Madrid metropolitan area. Its latitude (40.3°N) and population are not that different from that of Rochester, Minnesota, USA (44°N).

The authors' case finding methods identified patients seen in primary care centres, in the hospital allergy unit, the hospital emergency department, as well as hospitalized patients. They were careful to not count any individuals twice. Although the authors do not explicitly state in their methods [1] that only residents of Alcorcon were included in their analyses, they do indicate that this was so in a later direct communication with the journal editorial office. The authors report their results in person-years treating 'incidence proportion' as 'incidence rate.' 'Person-time' such as

'person-years' is impossible to calculate unless one knows how long each individual in the population of interest was under observation. Incidence proportion (also known as 'cumulative incidence') is calculated as *New Cases/Total Population at Risk*. Incidence rate (also known as incidence density) is *New Cases/Total Person-Time of Observation*. Some of the residents may have recently moved into the population of interest and only contributed a few months of person-time. One needs to track each person and determine how long they were in residence and at risk (i.e. alive) during the study period. Incidence rate should be the measure of disease frequency, rather than incidence proportion, when there are unequal lengths of follow-up. Incidence proportion is bounded by 0 and 1 (that is, 0% risk and 100% risk). Incidence rate is not a proportion and hence can be greater than 1, e.g. 300 cases per 10 person-years.

The authors found 103 episodes of anaphylaxis per 100 000 people. This is greater than the incidence that was reported in Rochester, Minnesota, USA [4] (58.9 per 100 000 persons in 2000) where essentially all patient visits were also available for analysis. Both studies probably captured essentially all cases of anaphylaxis by using computer searchable strings or codes. The codes used in the Rochester study and the strings used in the Alcorcon study are almost identical. These similar rates for the total incidence of anaphylaxis probably approximate the true incidence of this syndrome.

There are interesting differences in the findings in Alcorcon and in Minnesota. For example, there was only one Hymenoptera-induced episode of anaphylaxis

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in Alcorcon (0.3%) [1]. This compares with 18.5% of anaphylaxis cases in Minnesota being due to *Hymenoptera* stings [4]. In subsequent communications with the editorial office the Alcorcon authors attributed the low incidence of *Hymenoptera* anaphylaxis to their urban setting. Although the published studies of urban vs. rural *Hymenoptera* sting anaphylaxis are inconclusive, the Spanish study that addressed this question found the increased rural incidence to not be statistically significant [5]. The authors' companion article [2] reported seven cases of anaphylaxis in their Emergency Department during the same time period (2004–2005). However, only one of these patients was from Alcorcon. This, and other reports [6], document that *Hymenoptera* are active in their geographical region. However, this latter study in 2006 found that *Hymenoptera* anaphylaxis was uncommon in Spanish children (14 cases among a population of 44 million in 2006) [7]. This contrasts with the incidence of *Hymenoptera* anaphylaxis in children in Florida, USA (population 18 million) over a 2 year period (2005–2006) in which 28 cases were severe enough to require Emergency Department treatment [8]. Although proportional morbidity ratios have their limitations, comparisons of the proportions of *Hymenoptera* sting anaphylaxis in the Alcorcon population as a whole, and in emergency department and hospitalized patients with similar groups in the United States suggest that there are significantly fewer *Hymenoptera* sting anaphylaxis episodes in Spain than in the United States (Table 1). A partial explanation for the lower incidence of *Hymenoptera* sting reactions might be related to fewer bees in the environment due to bee colony collapse disorder in Spain [9]. As the authors point out

there are differences in anaphylaxis triggers in Spain, e.g. allergy to *Anisakis*.

Tejedor-Alonso et al. have also published a study of the hospital admission-based incidence of anaphylaxis in hospitalized patients based on primary or secondary discharge diagnoses [3]. They report that 53% of patients experienced anaphylaxis on the first day of hospitalization. This suggests that most of these patients had experienced anaphylaxis prior to their admission to the hospital and were admitted because of the severity of their episode. We performed a population-based study of hospitalizations in Florida for anaphylaxis [10]. Our results differed from those of Tejedor-Alonso et al. [3] in that we found that older rather than younger patients were more likely to be hospitalized for anaphylaxis. This might be due to the more frequent admission of children 4 years of age or younger in Alcorcon (2.2/1000 people) [3] as compared to in the United States (6.2–8.2/100 000) [10]. We found a prevalence for hospitalization for anaphylaxis of 19.8 cases/100 000 patients hospitalized for all causes [10]. Tejedor-Alonso et al. report 1.5 cases/5000 admissions = 30 cases/100 000 admissions. This group's study of emergency department visits for anaphylaxis [2] found an estimate (non-Alcorcon residents were not excluded) of 0.8 emergency cases/1000 people = 80/100 000. This compares with 90/100 000 in Rochester, Minnesota [11] and 7.6/100 000 in Florida [8]. These differences may relate to case finding methods and accessibility to care in these different locations. The Alcorcon study reported that 3.3% of emergency department cases were due to *Hymenoptera* venom. We found that 3% of emergency department cases were due to *Hymenoptera* venom if ICD-9CM

Table 1. Comparison of *Hymenoptera* anaphylaxis in Spain and the United States. *Hymenoptera* anaphylaxis is less likely to occur in Alcorcon than in Minnesota or Florida USA. $P < 0.0001$ for all comparisons

	Anaphylaxis all sources prevalence*		Hospitalization only†		Emergency department only‡	
	Only hymenoptera (% of total anaphylaxis)	Total anaphylaxis patients	Only hymenoptera (% of total anaphylaxis)	Total anaphylaxis	Only hymenoptera (% of total anaphylaxis)	Total anaphylaxis
Spain [1–3]	1 (0.3)	336	0 (0)	34	7 (3.3)	213
United States [4, 8, 10, 11]	11 (17.7)	62§	159 (34.2)	465¶	192 (16.5)	1166¶

The Minnesota, USA study [4] and the Alcorcon report [1] assessed similar sized populations (~100 000). Both probably captured essentially all individuals who sought medical attention. The Alcorcon paper collected data over 24 months (1 Jan 2004–31 Dec 2005). The Minnesota paper [4] collected data over 10 years. Data for the most recent 2 year period (1998–2000) are presented in Table 1.

*Alcorcon vs. Olmsted County Minnesota $P < 0.0001$ Fisher's exact test.

†Alcorcon vs. Florida $P < 0.0001$ Fisher's exact test.

‡Alcorcon vs. Florida $P < 0.0001$ Fisher's exact test.

§Minnesota, USA [4, 11].

¶Florida, USA [8, 10].

codes were used for case identification [8]. However, 16% of cases were venom-induced when our diagnostic algorithm was used [12]. This may account in part for the relatively small number of venom-induced anaphylaxis identified in the Alcorcon emergency department.

Multiple sources of data

A strength of the study by Tejedor-Alonso and colleagues [1] is their use of four databases. Clinical material was gathered from primary care practitioners, an allergy outpatient clinic, the emergency department of their regional hospital, and its inpatient records. Future investigators interested in the epidemiology of anaphylaxis should also consider using multiple sources of information. The linkage of multiple registries or databases may increase the probability of identifying cases [13]. Combining information from multiple registries has been used to ensure the complete ascertainment of a variety of conditions including paediatric tumours, trauma, and fatal episodes of preeclampsia [14].

The availability of multiple sources of health data can allow researchers to use a technique known as capture-recapture sampling to determine how many cases were missed by each database [13]. This simple technique assumes that the probability of being captured by one dataset is independent of the probability of being captured by the other dataset. It is possible that this assumption can be relaxed if three or more overlapping databases are available [13]. A unique patient identifier, for example, a social security number, will be needed to identify an individual patient in the multiple databases. However, for rare conditions, the use of multiple demographic variables may allow the identification of a subject found in various public-use health datasets that are lacking unique identifiers such as a social security or national identification number [14].

Assuming that only two sources of anaphylaxis incidence data with patient identifiers are available for a region, then the number of incident cases can be arranged as shown:

	Captured	Not captured
Captured	a	b
Not captured	c	d

The number of cases missed by both sources (the 'd' cell) is calculated using the formula bc/a [13]. Adding the number of cases captured (recorded) by Database 1 ($a+b$) to the number of cases captured by Database 2 ($a+c$) and then subtracting the number of cases common to both databases (represented by the 'a' cell) will yield the number of cases captured by both databases. Adding this total to the 'd' cell will give the estimated number of cases of anaphylaxis in a particular region during a particular period.

In conclusion, the study by Tejedor-Alonso *et al.* in this issue [1] reports what is likely to be the true incidence of anaphylaxis in Spain that is severe enough to result in a physician's evaluation. The small number of *Hymenoptera*-induced cases identified may be due to the documented deficiency in identification of such cases when a recently published diagnostic algorithm is not used [12]. Alternatively, there may have been fewer stings due to the decrease of the bee population because of colony collapse disorder or fewer reactions to the stings themselves. Anaphylaxis epidemiology is probably specific for particular locations as shown by the comparison of anaphylaxis epidemiology in Spain with that in the United States. Tejedor-Alonso *et al.* have an unusual opportunity to determine the likelihood that cases were missed in each of their four databases using capture-recapture analysis.

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