

# Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group

Phil Lieberman, MD\*; Carlos A. Camargo, Jr, MD, DrPH†; Kari Bohlke, ScD‡; Hershel Jick, MD§; Rachel L. Miller, MD¶; Aziz Sheikh, MD||; and F. Estelle R. Simons, MD\*\*

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**Objective:** To improve understanding of the epidemiology of anaphylaxis.

**Data Sources:** We performed a qualitative review by hand of the major epidemiology studies of anaphylaxis. This review was restricted to articles in the English language.

**Study Selection:** Articles chosen were selected by the committee and dated back to 1968. There was no specific criterion used for selection except the determination of the members of the committee.

**Results:** Data on anaphylaxis incidence and prevalence are sparse and often imprecise. Findings are based on diverse study designs and are not entirely comparable. These factors have contributed to widely varying estimates of the frequency of this important condition. The roundtable discussion led to an improved estimation of the frequency of anaphylaxis: approximately 50 to 2,000 episodes per 100,000 persons or a lifetime prevalence of 0.05% to 2.0%. The largest number of incident cases is among children and adolescents. In addition to underdiagnosis, we noted undertreatment, especially for those at highest risk (ie, those without immediate access to treatment with epinephrine).

**Conclusions:** Anaphylaxis is a relatively common problem, affecting up to 2% of the population. Further data on epinephrine dispensing could improve current estimates. Another way to improve current understanding would be through better population-based study designs in different geographic regions. A recurring theme was the importance of broader access to self-injectable epinephrine for high-risk populations. An improved epidemiologic understanding of this disorder would aid ongoing efforts to reduce morbidity and mortality from anaphylaxis and could provide important clues for primary prevention.

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## INTRODUCTION

The American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group, composed of

experts in epidemiology, allergy, and immunology, convened in Boston, MA, in November 2004 to improve understanding of the epidemiology of anaphylaxis. After a qualitative review of the literature, the Working Group sought to establish better estimates of the incidence and lifetime prevalence of anaphylaxis. The roundtable discussion was followed by a few smaller meetings and e-mail correspondence to update the manuscript and obtain consensus.

One of the obvious weaknesses of any such review is the lack of a consensus definition of anaphylaxis. At the time of this review, no such consensus existed; therefore, we simply accepted the criterion of each author(s) of every article reviewed. Not all articles offered a specific criterion for the diagnosis of anaphylaxis. Thus, we relied on the perceptions of the original author(s) and the fact that each article reviewed was in a peer-reviewed journal to accept the validity of the diagnoses themselves. No other course was available to us.

Anaphylaxis is an acute systemic reaction caused by IgE-mediated immunological release of mediators from mast cells

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\* Division of Allergy/Immunology, Departments of Medicine and Pediatrics, University of Tennessee College of Medicine, Germantown, Tennessee.

† Department of Epidemiology, Harvard Medical School, and Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts.

‡ University of Washington Medical School and Group Health Cooperative, Center for Health Studies, Seattle, Washington.

§ Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

¶ Department of Medicine, Columbia University, New York, New York.

|| Primary Care Research and Development, University of Edinburgh, Edinburgh, Scotland.

\*\* Department of Pediatrics and Child Health, The University of Manitoba, Manitoba, Canada.

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and basophils to allergenic triggers, such as food, insect venoms, latex, and medications.<sup>1,2</sup> An alternative definition was recently proposed as follows: anaphylaxis is a “condition caused by an IgE mediated reaction” that is “often life threatening and almost always unanticipated.”<sup>3,4</sup> The reaction can be severe enough to lead to the rapid onset of symptoms, including dizziness, upper airway occlusion, bronchial constriction, hypotension, urticaria, cardiovascular arrhythmias, and possible cardiac arrest.<sup>3,4</sup> Severity, onset, and appearance of symptoms can vary, resulting in discrepancies in diagnosis among clinicians.<sup>5-7</sup> Clinically indistinguishable symptoms also are seen in non-IgE-mediated anaphylactoid reaction, and the Working Group considered the 2 conditions together under a single term, *anaphylaxis*.

The Working Group agreed that definitive statements about the incidence or prevalence of anaphylaxis are difficult and estimates vary widely.<sup>6</sup> The most useful measure of occurrence to quantify anaphylaxis remains unclear. The common use of *incidence* to describe the frequency of anaphylaxis (without referring to specific intervals) is problematic and needs to be addressed. Often *incidence* is used when the more accurate term would be *prevalence*, which is defined as the proportion of the population with a condition at a specific point in time. Since prevalence depends on both incidence and duration, prevalence itself may vary, depending on the period specified and even how one defines the duration of anaphylaxis status. For example, for determination of lifetime prevalence (ie, the proportion of people who have experienced anaphylaxis during their lifetime), the anaphylaxis status would continue with the patient long after the actual allergic reaction had subsided. Typically, data for anaphylaxis have relied on simple proportions (eg, percentage of individuals with a lifetime history of anaphylaxis, percentage of all hospitalizations due to anaphylaxis), but with age-related prevalence data now emerging, it may be possible to determine a more accurate lifetime prevalence. Arriving at an accurate estimate of the distribution and determinants of anaphylaxis is the ultimate goal of epidemiologic research on anaphylaxis.

This review was undertaken to improve understanding of the epidemiology of anaphylaxis. We performed a qualitative review by hand of the major epidemiology studies of anaphylaxis. This review was restricted to articles in the English language. Articles chosen were selected by the committee and dated back to 1968. There was no specific criterion used for selection except the determination of the members of the committee.

## INCIDENCE AND PREVALENCE

The Working Group focused on seminal articles in the medical literature that addressed the issue of frequency of anaphylaxis. In the late 1980s, Sorenson et al<sup>8</sup> reported results from their retrospective review of all anaphylaxis hospitalizations at a Danish hospital and found an incidence of 3.2 cases per 100,000 inhabitants per year. Amornmarn and colleagues<sup>9</sup> looked at the number of patients with anaphylaxis

admitted to a German university hospital in 1990 and found 9 cases (0.04%) of 20,064 admissions. Stewart and Ewan<sup>10</sup> reviewed admissions to the emergency department of a major teaching hospital and regional referral center in Cambridge, England, and found 24 anaphylaxis cases (0.04%) in 55,000 patients seen. In 1995, Klein and Yocum<sup>11</sup> reported a retrospective analysis of all emergency department visits to a single US emergency department and found an anaphylaxis frequency of 0.09%. Pastorello and associates<sup>12</sup> more recently conducted a similar retrospective analysis of emergency department visits to a general hospital in Milan, Italy, and found an anaphylaxis frequency of 0.4%; 13 of the 140 identified cases were considered severe, which yields a frequency of 0.03%.

In a 9-center study of the epidemiology of anaphylaxis in hospital patients, Kaufman<sup>13</sup> found the interpolated risk for definite and probable cases of anaphylaxis was 154 per 1 million hospital admissions (or approximately 0.02% of all hospitalizations). Similar monitoring efforts have been conducted in Denmark<sup>14</sup> and the Netherlands.<sup>15</sup> In the Danish study by Lenler-Petersen and colleagues,<sup>14</sup> only 30 cases of fatal, drug-induced anaphylactic reactions were identified between 1968 and 1990. In the Netherlands study by Van der Klauw et al,<sup>15</sup> 936 cases with adverse drug reactions were registered as anaphylaxis between the years 1974 and 1994. Most of these patients, as in many other studies, were female (65%). The Dutch authors calculated that there are approximately 50 drug-associated anaphylaxis deaths per year in the Netherlands, which has a population of 13 million to 15 million.

Until recently, studies have been limited by small sample size or samples that may not represent the general population. Neugut et al<sup>6</sup> suggested that the better approach to estimating risk would be to “use estimates specifically calculated from epidemiologic studies measuring anaphylaxis in the general population.” Despite the obvious difficulties in estimating the overall incidence of anaphylaxis, the authors addressed this issue via a review of the literature of what they termed were the “four major subtypes of anaphylaxis (food, drugs, latex, and insect stings).”<sup>6</sup> They calculated an overall estimate of the risk of anaphylaxis using data derived from the incidence of episodes to these specific agents. Then, based on a 1999 US population of 272 million, they attempted to estimate the population at risk; their calculations yielded between 3.3 million and 43 million Americans. They also estimated that a total of 1,443 to 1,503 were at risk for a fatal event attributable to food, medications, latex, and insect stings. Thus, they concluded that the reported frequency of anaphylaxis was not as rare as previously believed and estimated that 1.2% to 15% of the total US population may experience an anaphylactic reaction and that 0.002% of these might experience a fatal event.<sup>6</sup>

As noted by Neugut and colleagues,<sup>6</sup> most past epidemiologic studies focused on special populations and could not be applied to the wider general population. Yocum and colleagues<sup>5</sup> addressed this issue with an extensive, population-

based epidemiologic study of incident anaphylaxis in Olmstead County, Minnesota. The investigators reviewed the medical records of county residents to identify individuals who had experienced anaphylaxis; cases were identified by a computer-linked, medical diagnostic indices program. The investigators reported an occurrence rate of anaphylaxis of 30 per 100,000 person-years and an annual incidence rate of 21 per 100,000 person-years based on data from the Rochester Epidemiology Study. The investigators concluded that "the incidence of anaphylaxis is less than 1% and death rarely occurs." These data, however, likely underestimate the true incidence and lifetime prevalence of anaphylaxis, both in the United States and elsewhere.<sup>16</sup> In his accompanying analysis of the study by Yocum et al, Weiler<sup>17</sup> projected these data over the US population in 1999 (272,500,000) to arrive at an occurrence rate of 81,750 (from 30 per 100,000 person-years) and an annual incidence rate of 57,225 (from 21 per 100,000 person-years). He calculates, based on 1% of cases resulting in fatality, that there would be between 600 and 800 annual deaths in the United States from anaphylaxis.<sup>17</sup>

Reviewing data from another population-based study, Peng and Jick<sup>7</sup> sought to estimate the incidence, cause-specific frequency, and severity of anaphylaxis in the United Kingdom by using the extensive General Practice Research Database (GPRD), which has more than 4 million registrants. The approach of this study was to identify hospital admissions, since anaphylaxis in the United Kingdom frequently results in a hospital visit. The authors estimated the incidence to be 8.4 per 100,000 person-years. Despite the apparent completeness of the database, the authors note that the GPRD computer record may not include cases of anaphylaxis that occur within a hospital setting; therefore, the GPRD record may represent an underreporting of the actual incidence.

In a complementary approach to the epidemiology of anaphylaxis, Sheikh and Alves<sup>18</sup> used data from hospital admissions to the English National Health Service between 1991 and 1995. Of 13.5 million emergency inpatient admissions, 2,323 had a primary diagnosis of anaphylaxis for an overall rate of anaphylaxis of 17 emergency admissions per 100,000 total emergency admissions (or 0.02% of hospitalizations). In a subsequent study, as part of an analysis of national hospital admissions data on systemic allergic disorders, including anaphylaxis, Gupta and colleagues<sup>19</sup> reported that although the rate for all allergies has been rising in the United Kingdom since 1991, the rate for anaphylaxis (and food allergy) has risen the most. The authors concluded that, although there have been changes in health care, their data "almost certainly reflect an increase in incidence." Anaphylaxis hospital admissions peaked in infants younger than 1 year at 2.9 per 100,000 person-years, with a second smaller peak in the 20- to 60-year age group. Although the age-related pattern of hospital discharge was similar in both sexes, significantly more females than males were discharged with an anaphylaxis diagnosis (relative risk, 1.23;  $P < .0001$ ). Confirming reports that the incidence of anaphylaxis is rising, the study noted a greater than doubling of discharges after primary

diagnosis of anaphylaxis between 1991 to 1992 and 1994 to 1995. According to Sheikh, these numbers are underestimates of the overall anaphylaxis frequency, since, for example, only 1 in 5 patients who are seen in Cambridge emergency departments for management of anaphylaxis are admitted to the hospital. US emergency department data suggest even lower admission rates (<10%) for patients with food-related or insect sting-related anaphylaxis.<sup>20,21</sup>

In the United States, Bohlke and colleagues<sup>22</sup> recently used data from a health maintenance organization from western Washington state to identify potential anaphylaxis episodes among children and adolescents enrolled between 1991 and 1997. In this article, the automated hospital, emergency department, and outpatient clinical records were reviewed for all occurrences of *International Classification of Diseases, Ninth Revision (ICD-9)* codes indicative of anaphylaxis (995.0, anaphylactic shock; 995.6, anaphylactic shock caused by adverse food reaction; 999.4, anaphylactic shock caused by serum; and 995.4, shock caused by anesthesia). The ICD-9 code 995.6 was introduced during the study (effective October 1993). Confirmed cases (those classified as probable or possible anaphylaxis) with these diagnoses formed the basis of the incidence calculations. Since previous studies have indicated that anaphylaxis may be found among those with other diagnoses, the following ICD-9 codes were also reviewed: 708.0 (allergic urticaria), 708.9 (urticaria, unspecified), 995.1 (angioneurotic edema), 995.3 (allergy, unspecified), and 695.1 (erythema multiforme). Using the diagnosis codes specific for anaphylaxis, the incidence rate was 10.5 episodes per 100,000 person-years. Incorporating the other allergy diagnoses to identify additional cases with extrapolation from this sample suggested a higher incidence of 68.4 cases per 100,000 person-years. Incidence rates were stable over time, which differs from the UK hospitalization findings of Gupta et al<sup>19</sup> and studies on specific subpopulations, such as allergy clinics.<sup>23</sup> In a second study, Bohlke and colleagues<sup>24</sup> reported that vaccine-associated anaphylaxis is extremely rare, with only 5 cases identified after administration of 7,644,049 vaccine doses (a risk of 0.65 cases per million doses).

The Working Group also reviewed results from an Australian survey by Boros et al.<sup>25</sup> Based on questionnaires completed by parents with children known to have allergies, the authors reported a history of allergy in 7.3% and a history of anaphylaxis in 0.59% in the underlying school population. The latter figure yields an estimate of 590 cases of anaphylaxis per 100,000 Australian children in the 3- to 17-year age group. Similar surveys from other countries would be helpful, particularly if the surveys were conducted in more representative samples of the general population.

Finally, the Working Group discussed a series of important studies from the University of Manitoba.<sup>26-28</sup> Rather than focusing on allergen-specific anaphylaxis, Simons and colleagues<sup>26</sup> hypothesized that an important perspective on the prevalence of at-risk individuals would emerge from studying epinephrine-dispensing patterns for outpatients in a defined

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general population. They used an administrative claims pharmaceutical database to analyze dispensing data for all injectable epinephrine formulations dispensed for out-of-hospital treatment more than 5 consecutive fiscal years in a population of 1.15 million persons. Patient level data were provided by real-time computer links with all retail pharmacies in Manitoba. In this population, all but the poorest individuals or their caregivers had to pay for the epinephrine at the time the prescription was dispensed. The investigators identified the number and percentage of individuals in the general population for whom epinephrine was dispensed on one or more occasions, their age, and their sex. During the 5-year period, 0.95% of this defined general population had injectable epinephrine dispensed for out-of-hospital treatment.

This number might be an underestimate of the overall anaphylaxis frequency for a variety of reasons. Patients would be excluded from this database if they had anaphylaxis in a health care setting triggered by a diagnostic agent, medication, vaccine, or other biologic agent; if they died of anaphylaxis; or if their anaphylaxis was not recognized, not diagnosed, or not deemed to be serious enough to warrant an epinephrine prescription. Furthermore, patients would be excluded if they received an epinephrine prescription from a physician but failed to pick up the medication from a pharmacy (ie, the epinephrine was not actually dispensed and recorded electronically as such). Although the figure of 0.95% might also be an overestimate if epinephrine was prescribed for patients with a positive skin test or in vitro test result and no history of anaphylaxis, this was not the usual physician practice in this community.<sup>26</sup>

## MAJOR CAUSES

The cause of any given episode of anaphylaxis may not be apparent, especially in adults; however, when the cause is determined, antibiotics and nonsteroidal anti-inflammatory drugs appear to be the most common culprits in most adult series. For adults, antibiotics, especially penicillin, have been found to be the most common offender.<sup>1,2,29-32,34</sup> Penicillin reactions occur with a frequency of approximately 1 to 5 per 10,000 patient courses of treatment, and fatalities can occur at a rate of 1 per 50,000 to 100,000 courses.<sup>33</sup> Data regarding the incidence of anaphylaxis to penicillin, however, date back to 1968, and the prevalence may no longer be consistent with these previous observations. However, penicillin may account for approximately 75% of fatal anaphylactic cases in the United States each year.<sup>33</sup> It has also been estimated that nonfatal drug-induced anaphylaxis to penicillin may affect as many as 1.9 million to 27.2 million Americans.<sup>6</sup> In a Swedish study,<sup>33</sup> the incidence of anaphylaxis to phenoxymethylpenicillin was 7 cases per million treatment weeks, and the incidence for benzylpenicillin was 26 times higher.  $\beta$ -Lactam antibiotics were also one of the most common offenders in a recent series of patients from Milan, Italy, accounting for 22% of all drug-related episodes.<sup>12</sup>

Insect stings are another common cause of anaphylaxis. Valentine<sup>35</sup> estimated, on the basis of population studies, that

the frequency of Hymenoptera sting reactions is 0.5% to 5% in the general population or 1.36 million to 13.6 million Americans.

Most cases of anaphylaxis are in children, where food allergies are the most common cause.<sup>36</sup> As much as 2% of the US population has food allergies.<sup>36</sup> Sampson<sup>37</sup> has estimated that there are as many as 100 deaths due to anaphylactic reactions to foods each year in the United States. Bock,<sup>38</sup> evaluating the incidence of anaphylactic reactions to food in Colorado and extrapolating these data to the United States as a whole, surmised that approximately 0.0004% of the US population or 1,080 Americans have an anaphylactic reaction to food each year. Peanuts appear to be the primary cause of anaphylaxis in children,<sup>39</sup> whereas shellfish appear to be the most common food to cause anaphylaxis in adults.<sup>19,34</sup> Other implicated foods include tree nuts, fish, eggs, milk, soy, and wheat.<sup>40,41</sup> Sicherer et al<sup>36</sup> found that 1.1% of the US population (approximately 3 million Americans) may have an allergy to tree nuts or peanuts. European data confirm the importance of foods as a cause of anaphylaxis. In a recent Italian study, foods were the most common cause of anaphylactic events seen in an emergency department, accounting for 39% of cases.<sup>12</sup>

## FACTORS THAT AFFECT INCIDENCE AND PREVALENCE

Geographic location, socioeconomic status, age, and sex have all been evaluated for their effects on the frequency of anaphylaxis. Few studies have examined race/ethnicity, but one study from the United Kingdom suggests that race exerts no effect.<sup>18</sup> Data are also sparse on geographic location, which until recently was only rarely discussed. The study by Sheikh and Alves<sup>18</sup> found that geographical location was related to the incidence of anaphylaxis. Rural residency, living in the southern or western parts of England, had an increased incidence of anaphylaxis, although no definitive reason was given for the observed geographical variation.

Socioeconomic status may play a role in the incidence of anaphylaxis, based on epidemiologic data obtained by Simons and colleagues in the Manitoba model.<sup>27</sup> These investigators found that, in an urban population, epinephrine was dispensed more frequently for those in the higher income quintiles (1.3%) than those in the lower income quintiles (0.6%). This difference could not be accounted for by better access to specialist care in the higher income quintiles. The dispensing patterns for epinephrine contrasted with the dispensing patterns found for other classes of medication in this population, which were more commonly dispensed for individuals in the lower income quintiles.

From the Manitoba studies, it appears that both sex and age play a significant role in the epidemiology of anaphylaxis. In infancy, childhood, and early adolescence, boys were more likely to have epinephrine dispensed than girls. Beginning at the age of 15 years and continuing into adulthood, girls and women were much more likely to have epinephrine dispensed

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than boys and men. In elderly patients, there were no differences in dispensing patterns between the sexes. The highest epinephrine-dispensing rate was found in young boys. The authors concluded that in the out-of-hospital setting, anaphylaxis from all triggers appears to peak in early childhood, remains relatively common through the teenage years and young adulthood, and then declines gradually into old age.<sup>26</sup> In an earlier study in the same population, using similar methods but a shorter time frame, the investigators found that epinephrine formulations were dispensed to 1.2% of children from birth up to, but not including, the 17th birthday.<sup>28</sup>

## DISCUSSION

Using the actual results of the most current and extensive population studies, the frequency of anaphylaxis is between 0.03% and 0.06% (or 30 to 60 cases per 100,000 population) at the lower end and 0.95% (950 cases per 100,000 population) at the higher end.<sup>5-26</sup> Even the higher end, however, may be an underestimate because of underdiagnosing of anaphylaxis and underprescribing of self-injectable epinephrine to individuals with known anaphylaxis. Of note, this high-end estimate is considerably lower than the upper estimate of 15% described in 2001 by Neugut et al.<sup>6</sup>

There are several reasons to support the Working Group's opinion that most (if not all) of the reviewed studies probably underestimate the true incidence and prevalence of anaphylaxis. Underreporting of anaphylactic events has been documented on a number of occasions. For example, only 4% to 8% of anaphylactic reactions were reported to the Dutch Inspectorate for Health Care in the Netherlands.<sup>15,42</sup> Pumphrey and Davis reviewed the issue of underreporting in an editorial that appeared in *The Lancet*.<sup>16</sup> The authors cited a study of fatal anaphylaxis in the United Kingdom, conducted between the years of 1992 and 1997, where only 33 of 67 fatal reactions to drugs were reported. This pattern of underreporting has been consistent throughout the years and was noted as early as 1979.<sup>43</sup>

Additional support may be found in the 1995 results of Klein and Yocum,<sup>11</sup> who reported that 13 (76%) of 17 anaphylaxis cases were undocumented by emergency physicians at one location, often by diagnosing allergic reaction instead of anaphylaxis (9/17 or 53%). Further work by this group identified a failure to diagnose anaphylaxis in the absence of fully developed shock, with an accompanying failure to prescribe epinephrine.<sup>5</sup> Since initial presentations may not include fully developed shock, they may be treated as a mild allergic reaction, even though it has recently been documented that between 44% and 59% of such patients may exhibit life-threatening anaphylaxis after a second exposure to the same allergic trigger.<sup>44</sup> Also, anaphylaxis attributed to medications or biologic agents within a health care setting may have led to other treatments and not necessarily prescription of self-injectable epinephrine for patient use in the community.<sup>1,2</sup> Patients or caregivers may fail to recognize anaphylaxis and, especially for initial episodes, may recover without seeking medical care. There is no clear way to

identify this pool, which may be large and contribute to a significant underestimation of anaphylaxis incidence. There may be underreporting for anaphylaxis in adulthood that reflects an age bias in prescribing and dispensing of epinephrine.<sup>26,27</sup> The Manitoba study identified the last potential source as also likely, since at the time of the Manitoba study epinephrine autoinjectors were expensive (US \$60) and most of the population had to pay for their medications at the time of dispensing.

Our review of the study from Australia by Boros and colleagues<sup>25</sup> underscored the importance of emergency medication available on site at schools or daycare centers, since this is the population at highest risk for incident anaphylaxis. This study was important for its different approach to the epidemiology question (ie, via population survey) and for producing an estimate (0.5%) intermediate to the values described herein (ie, 0.05% to 2.0%). The Australian investigators emphasized that school and preschool staff should be able to recognize anaphylaxis and begin first-aid management in children, the age group with the highest frequency of occurrence, while at school. Their specific recommendation was to maintain a trained school staff who can administer injectable epinephrine using an autoinjector. Since school staff in half the cases in their study was unable to administer epinephrine, the investigators concluded that the remainder of students were at added risk of morbidity and even mortality as a result of possible subsequent anaphylactic reactions at school.

Although the exact magnitude of underreporting and misdiagnosis of anaphylaxis remains unclear, the Working Group reached a consensus that all measures used are still likely to underestimate the true burden of anaphylaxis. With ambiguity about the precise characteristics of anaphylaxis among lay people and medical professionals alike,<sup>3,4</sup> underreporting is likely to continue. The higher end of the range suggested by the Working Group (0.05% to 2.0%) suggests that the maximum number of Americans with a lifetime history of anaphylaxis is significantly higher than estimated by most prior epidemiological studies.

## SUMMARY AND FUTURE DIRECTIONS

Anaphylaxis remains largely underreported, and challenges remain in gathering precise data on its incidence and prevalence. Our review of the most extensive recent studies in North America, Europe, and Australia allows for the best estimate possible: approximately 0.05% to 2% lifetime prevalence of anaphylaxis. Taking into account the likelihood of underreporting for adults and even among high-risk populations, we estimate the number of individuals with a lifetime history of anaphylaxis to be higher than reported in most individual research studies.

The Working Group would like to see an expansion of the key studies discussed herein, especially the Manitoba study<sup>26</sup> and the Australian survey,<sup>25</sup> as well as a more concentrated effort to initiate studies from established and complete databases such as health maintenance organizations.<sup>22</sup> Refinement

of these diverse study designs and their consistent application to different geographic regions should allow for accurate determination of the local anaphylaxis burden and more region-specific screening procedures. Special attention will need to be paid to groups now seen as having a higher incidence of anaphylaxis than previously reported and to groups that may have poor access to epinephrine during an initial or life-threatening anaphylactic reaction. The challenge of increasing our understanding of anaphylaxis epidemiology will be met by identifying the types of studies that provide the best estimate of anaphylaxis frequency (incidence or prevalence), as well as moving toward the use of more consistent terms across all studies.

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- Requests for reprints should be addressed to:*  
*Phil Lieberman, MD*  
*Allergy & Asthma Care*  
*7205 Wolf River Blvd*  
*Suite 200*  
*Germantown, TN 38138*  
*E-mail: aac@allergymemphis.com*
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