

Primary and Secondary Allergies to Laboratory Animals

Leslie E. Goodno, MPH

Gregg M. Stave, MD, JD, MPH

Although laboratory animal allergy (LAA) is a significant occupational hazard among workers exposed to laboratory animals, few studies have evaluated long-term risks to workers who remain in the workplace. This short-term focus has obscured the evaluation of subsequent animal allergies (secondary LAA). We analyzed surveillance data from a 10-year LAA prevention program to estimate incidence rates of primary and secondary LAA and to evaluate the effectiveness of the prevention program in reducing the development of primary LAA. The 10-year incidence rates of primary and secondary LAA were 1.34 (95% CI, 0.78–1.90) and 11 (95% CI, 7.4–14.6) cases per 100 person-years, respectively. The annual incidence of primary LAA was reduced from 3.6% to 0 in the first 5 years and did not rise above 1.2% over the remaining years, whereas the incidence of secondary LAA was greater than 8% in most years. These findings suggest that programs effective at preventing primary LAA may need to be evaluated for their effectiveness at protecting against further risk. (J Occup Environ Med. 2002;44:1143–1152)

Workers who are exposed to laboratory animals are at risk for developing allergic reactions to animals and animal housing. The resultant condition has been termed laboratory animal allergy (LAA) and is characterized by one or more symptoms of allergy involving the skin, eyes, nose, and respiratory tract. LAA has been recognized as a serious occupational hazard in the United States and the United Kingdom for more than 20 years^{1,2} and is receiving increasing attention in other countries.^{3–8} It has been estimated that 40,000 to 125,000 workers in the United States⁹ and 15,000 workers in the United Kingdom² regularly work with laboratory animals and that up to one third of these workers may develop symptoms of allergy.^{10,11}

Cross-sectional studies have estimated the prevalence of LAA to be as high as 44% in some groups¹¹; however, only a few studies have estimated measures of incidence. Because the risk of developing LAA is thought to be highest in the first few years of exposure to laboratory animals, studies have generally limited their focus to estimates of first-year incidence, which have ranged from 10% to 37%.^{12,13}

This limited focus may have obscured information about additional risk to workers who remain in the workplace after development of LAA. Laboratory animal workers comprise a heterogeneous group of animal handlers, including scientists, veterinarians, physicians, and other specialists whose work may not afford easy removal from exposure even if they develop allergies to an-

From the Department of Epidemiology, UNC School of Public Health, University of North Carolina, Chapel Hill (Ms. Goodno) and GlaxoSmithKline, Inc., Research Triangle Park, North Carolina (Dr Stave).

Address correspondence to: Leslie Goodno, Department of Epidemiology, CB #7435 McGavran-Greenberg Hall, UNC School of Public Health, University of North Carolina, Chapel Hill, NC 27599-7435; e-mail: goodno@email.unc.edu.

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imals. The observation that workers do not necessarily leave the workplace after developing allergy was supported by Botham et al,¹³ who reported that symptomatic workers are just as likely as asymptomatic workers to remain in their jobs. This observation was a departure from the more familiar hypothesis that symptomatic workers often leave the workforce.¹⁴⁻¹⁷

Additional risks to workers with LAA may include development of allergy to multiple animal species. It has been reported that some workers have allergies to more than one species,^{3,12,14,17,18} but the natural history of multiple allergies has not been described. In particular, previous studies have not been designed to evaluate whether allergies develop sequentially over time. Such temporality is best established through prospective observation and requires an observation period of sufficient length to include new and subsequent allergies.

This study reports the ongoing success of a broad multi-faceted LAA prevention program implemented by GlaxoSmithKline (Research Triangle Park, NC) in 1991 to comprehensively address and reduce the risks to workers exposed to laboratory animals. An earlier report described the program and its effectiveness at reducing the annual incidence of primary LAA from 10.3% to 0 over the first 5 years of the program.¹⁹

The main objectives of this study were as follows: (1) to evaluate the effectiveness of a 10-year prevention program in reducing the incidence of primary LAA; (2) to estimate the incidence rates of primary and secondary LAA; and (3) to describe risk factors associated with the development of primary and secondary LAA.

Methods

Beginning January 1991, all employees with work-related exposure to laboratory animals were enrolled in the LAA surveillance programs at

Glaxo, Inc. (Research Triangle Park, NC), and Burroughs Wellcome Co (Research Triangle Park, NC). Both programs included a baseline questionnaire and medical screening with annual follow-up. Baseline examinations were completed at time of employment for employees hired after the commencement of the surveillance program.

The baseline questionnaire included items related to occupational and nonoccupational exposures, such as job title and work location, exposure to laboratory animals, frequency and duration of specific tasks in the animal facility, use of personal protective equipment, personal and family history of allergy, smoking status, and pet ownership. Questions about worker symptoms, such as type, onset, and cause, were also included on the questionnaire. The annual follow-up questionnaire was similar to the baseline questionnaire except that it excluded some demographic information and personal/family history.

The same questionnaire was used by the occupational health departments of both Glaxo and Burroughs Wellcome in a collaborative effort to evaluate overall risks to laboratory animal workers. When the two companies merged in 1995, information from the two programs was combined, and Glaxo Wellcome continued the comprehensive program. (GlaxoSmithKline was established in December 2000 after the merger of Glaxo Wellcome and SmithKline Beecham.)

The company's computer-based medical record system was used to identify workers enrolled in the LAA prevention program at any time from January 1991 through December 2000. Medical records of the workers were examined, and questionnaires were photocopied and entered into the LAA database. Some workers had completed baseline questionnaires upon initial employment but had subsequently been placed in positions that did not require exposure to animals or the animal room. These

workers, and students hired for short-term employment as summer interns, were excluded from the study. All other workers who completed at least two questionnaires were included in the analyses; workers who completed at least one questionnaire were included in estimation of annual prevalence.

LAA was defined as the self-reported presence of one or more symptoms of sneezing spells, runny or stuffy nose, watery or itchy eyes, coughing, wheezing, or shortness of breath while working with laboratory animals or their cages, corroborated by GlaxoSmithKline medical review. Allergy to a specific animal species was defined as the presence of these symptoms when exposed to that species.

Analysis

Statistical analyses were performed using PC SAS software v.8.1 (SAS, Cary, NC). For workers who completed more than one questionnaire, the follow-up period was calculated from the date of the baseline questionnaire to the date of the last questionnaire. Workers with missing questionnaires were assumed to have continued in the surveillance program during the period of missing data, with unchanged allergy status until the next completed questionnaire. Forty-five percent of the workers were missing at least one questionnaire; however, only 23% of the total expected questionnaires were missing.

The lifetable method was used for survival analysis of primary and secondary allergies. A stratified Cox proportional hazards model was used to examine the effects of both time-independent and time-dependent covariates on the development of a new allergy. In this analysis, the main exposure was defined as existence of primary LAA so that development of a new allergy among this group represented secondary LAA and development of a new allergy among the "unexposed" group represented primary LAA. Time-independent infor-

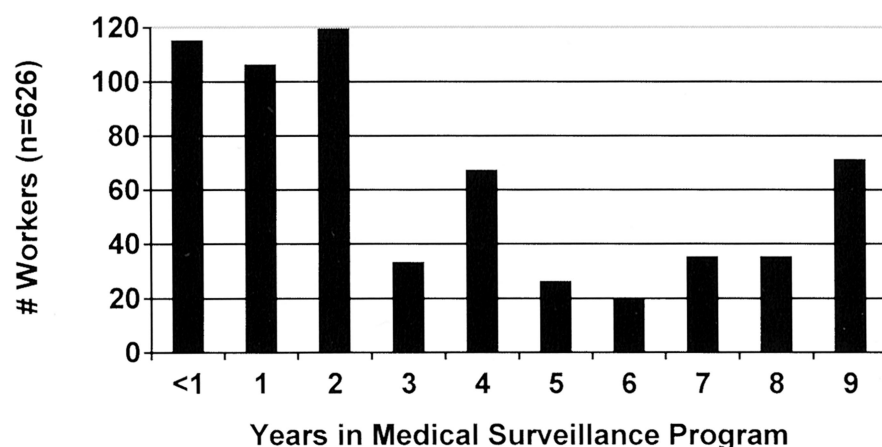


Fig. 1. Workers enrolled in the LAA medical surveillance program at any time from January 1, 1991 through December 31, 2000 by the number of years in surveillance program.

mation (eg, race, gender, family history, prior exposure to laboratory animals) was derived from the baseline questionnaire, whereas time-dependent information (eg, age, personal atopic status, number of species with which an employee worked, pet ownership, and use of personal protective equipment) was derived from both baseline and follow-up questionnaires. Time interaction terms were included for variables that did not meet the proportional hazards assumption. A backward elimination strategy was used in the modeling procedure, with all variables and interaction terms entered into the initial model. Likelihood ratio tests (P value cutoff of 0.05) and comparison of stratum-specific hazard ratios were used to determine inclusion of interaction terms. In assessment of predictors, variables were retained in the model if their exclusion resulted in $>10\%$ change in the beta coefficient of the main exposure. Results were reported as hazard ratios, and precision was reported as 95% confidence intervals.

Results

A total of 626 workers were identified as eligible participants in the program during the period January 1, 1991 through December 31, 2000. These employees provided 2113

questionnaires for the analysis and 2231 person-years of follow-up. Fifty-four percent (340/626) of the participants were enrolled in the program for 2 years or less, and among the workers who remained in the program for more than 2 years, 24.9% were in the program for the entire follow-up period (Fig. 1). These distributions were derived from completed questionnaires and not from employment records, so it is possible that some workers remained in the program for longer periods if they failed to report for an annual examination.

The typical laboratory animal worker in this population was white, nonsmoking, with at least a college education (Table 1). At baseline evaluation, which occurred for each employee either in the first year of the study or upon entry into the surveillance program (eg, change in job or new employment), 103 (16.4%) employees reported allergy to at least one species of animal. The age distributions of workers with and without LAA at baseline were similar; however, workers over the age of 49 years were more likely to be LAA-free at the beginning of follow-up.

Workers with LAA were more likely to report general indicators of atopy, including history of asthma, other allergy, shortness of breath,

skin tests, skin rashes, use of allergy medications, and family history of allergy or asthma. Although symptomatic workers were less likely than other workers to be smokers, the prevalence of smoking for the entire population of animal workers was relatively low (9.1%).

The annual prevalence of LAA remained fairly constant over the 10-year period, ranging from 19.1% to 24.0% (Fig. 2). The annual incidence of primary LAA was reduced to 0 after the first 3 years of the LAA prevention program and did not rise above 1.2% over the remaining years of follow-up. The average number of workers each year was 275.2 (range 229–387), depending on employee turnover and business needs.

The 10-year incidence rate for primary LAA was 1.34 per 100 person-years, with 1641 person-years at risk. During the period from 1991 to 2000, only 22 (4.2%) of the at-risk workers developed primary LAA. Of these workers, 59.2% had worked with laboratory animals for 0 to 5 years before baseline examination, 9.1% had worked with animals between 5 and 10 years, and 27.4% had worked with animals for over 10 years. Although most studies suggest that LAA occurs within the first 3 years of exposure, at least 36.5% of the incident cases did not develop until after 5 years of exposure, and 9.2% occurred after at least 20 years of exposure.

Over the 10-year period, rats and mice were used more frequently than other laboratory animals, and the numbers of workers reporting symptoms of allergy to these animals were similar (Fig. 3). Among the remaining species to which workers were exposed, rabbits were associated with the highest proportion of symptomatic workers, even though 28% more workers were exposed to dogs than to rabbits. Figure 3 summarizes the number of workers exposed to each species over the 10-year period and the number of exposed workers reporting allergy to each species.

TABLE 1

Baseline Demographic Characteristics of Workers Enrolled in the LAA Surveillance Program During the Period January 1, 1991 through December 31, 2000

	Workers Without LAA at baseline (%) (<i>n</i> = 523)*	Workers with LAA at Baseline (Prevalent Cases) (%) (<i>n</i> = 103)	<i>P</i> value†
Gender‡			
Female	41.7	49.5	0.1465
Male	58.1	50.5	
Race			
Asian	7.0	5.8	0.7385
Black	13.8	7.8	0.0928
White	76.1	83.5	0.1096
Other/unspecified	3.1	2.9	
Age at entry into surveillance program (years)			
19–29	21.0	19.4	0.7119
30–39	45.9	47.6	0.7541
40–49	21.4	30.1	0.0551
>49	7.3	0	0.0048
Mean (Std. Dev.)	35.9 (8.3)	35.8 (6.6)	
Education			
Grade school	0.4	0	0.5296
High school	14.9	6.8	0.0279
College	36.1	39.8	0.4803
Graduate school	33.4	45.7	0.0183
Prior work with laboratory animals (years)			
0	40.7	25.4	0.0039
0.1–5	23.7	29.1	0.2433
5.1–10	14.9	21.4	0.1027
10.1–20	14.2	17.5	0.3835
> 20	2.8	2.9	0.9803
Mean (SD)	5.0 (6.7)	6.2 (6.4)	
Current Smokers	10.1	3.9	0.0483
History of:			
Asthma	6.4	13.6	0.0104
Shortness of breath	7.2	20.4	<0.0001
Parent/sibling with allergy/asthma	31.9	44.0	0.0164
MD-diagnosed allergy	23.9	42.7	<0.0001
Skin tests	14.4	24.3	0.0101
Allergy shots	8.0	16.5	0.0071
Medications for allergy	23.5	52.4	<0.0001
Skin rash	21.0	52.4	<0.0001
Pet ownership	54.3	59.4	0.3485

* LAA, Laboratory Animal Allergy.

† Chi square for proportions.

‡ Percentages that do not add to 100% reflect missing data.

Initial and final questionnaires were compared to assess changes in the types and frequencies of symptoms reported by workers with LAA. Over 60% of all workers with LAA reported initial symptoms of runny or stuffy nose, watery or itchy eyes, and sneezing. Frequencies of all symptoms increased during the period of observation, with the greatest increases occurring for shortness of breath (171% change) and coughing (100% change). The increased reports of shortness of breath occurred only among prevalent cases, while

increased reports of wheezing and coughing occurred among both prevalent and incident cases.

Secondary LAA

Of the 103 workers reporting LAA at entrance into the surveillance program, 39.8% reported allergies to two or more species (Table 2A). During the period of follow-up, 33% of the workers with primary LAA reported the development of secondary allergy to at least one additional species. Of the 22 workers who developed primary LAA during follow-

up, three workers developed secondary allergy in subsequent years of follow-up (Table 2B). Although these workers developed primary LAA in their first year of follow-up, they developed secondary allergy 3, 7, and 8 years after the onset of primary LAA (not shown).

Annual incidence of secondary allergy ranged from 1.6% to 19.1% over the period 1991 through 2000 (Fig. 4). All workers who had at least one animal allergy, including those who developed primary allergy during follow-up, were considered to be

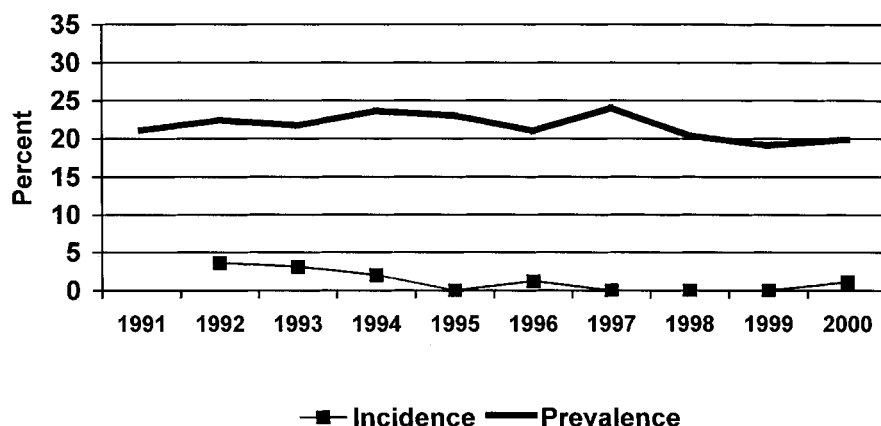


Fig. 2. Annual incidence and prevalence of primary LAA among laboratory animal workers enrolled in the LAA medical surveillance program during the period January 1, 1991 through December 31, 2000.

at risk for developing secondary allergy. The development of additional allergy was considered a repeatable event in the analysis of annual incidence, so the annual estimates of incidence include workers who developed additional allergies more than once. Figure 4 compares the annual incidence of primary and secondary LAA. The small numbers of workers at risk for secondary LAA (less than 50 for most years) contributed to the wide fluctuations of annual incidence; however, the incidence was greater than 8% in most years.

Workers who developed secondary LAA during follow-up were more likely to have a family history of atopy ($P = 0.0003$) and a history of skin rash ($P < 0.0001$). This group also reported more physician-diagnosed allergies ($P = 0.0004$), which may be attributable in part to the previous diagnosis of LAA.

Over the period 1991 to 2000, the estimated incidence rate of secondary LAA was 11 per 100 person-years, with 319 person-years at risk. Survival curves for the development of primary and secondary allergy are shown in Fig. 5. These curves illustrate the differences between development of primary and secondary allergy over the study period and not actual survival of the population. The separation between the two curves

begins in the second year of follow-up, and the curves continue to diverge through the end of follow-up. The log rank test of equality gave a chi-square statistic of 82.81 ($P < 0.0001$).

The crude hazard ratio (HR) comparing development of secondary allergy with primary allergy was 8.21 (95% CI, 7.33–8.83, $P < 0.001$), which suggests that secondary allergy occurred at a rate 8.21 times that of primary allergy over the 10-year period. The adjusted HR was 6.12, controlling for age, race, atopic status, family atopic history, use of respirator, and prior exposure to laboratory animals. Family atopic history (HR 1.72, 95% CI, 1.01–2.95) and personal atopy (HR 3.45, 95% CI, 1.29–9.19) were found to be significant predictors of both primary and secondary LAA. In the proportional hazards model, the effects of race (white versus other) and years of prior exposure (0, 1 to 4, 5+) changed over time, and modifications were made for violation of the proportional hazards assumption. A time interaction term was used to model the changing effects of prior exposure to laboratory animals; hazard ratios were increased during the first 2 years of follow-up for workers with prior exposure, but the risk decreased after 2 years. During the first 2 years of follow-up, the HR for

workers with 1 to 4 years prior exposure (referent = 0 years) was 6.00 (95% CI, 2.33–15.47, $P = 0.0002$), and the HR for workers with 5+ years prior exposure was 3.54 (95% CI, 1.5–8.34, $P = 0.0038$). Workers who entered the surveillance program between the ages of 18 to 25 years or 47 to 63 years were more likely than other workers to develop allergy to animals, with hazard ratios of 8.53 (95% CI, 2.57–28.34, $P = 0.0005$) and 2.23 (95% CI, 1.02–4.89, $p = 0.0456$), respectively. The hazard ratios were higher for whites than for other races in the first few years of exposure, but the difference was not proportional over time. The final model was stratified on race to relax the proportional hazards assumption and to capture the effects of race over time.

Discussion

We evaluated 10 years of medical surveillance data on workers in the pharmaceutical industry to estimate incidence rates and risk factors for development of initial laboratory animal allergy (primary LAA) and subsequent allergies to additional species (secondary LAA). During the period of follow-up, 4.2% of the workers without LAA developed primary allergy, and 33% of the workers with primary LAA developed secondary allergy. The 10-year incidence rates for primary and secondary LAA were 1.34 and 11 cases per 100 person-years. The crude relative rate was 8.21 (95% CI, 7.33–8.83, $P < 0.001$), suggesting that secondary allergy occurred at a rate 8.21 times that of primary allergy. After adjusting for age, race, atopic status, family atopic history, use of respirator, and prior exposure to laboratory animals, the relative rate was 6.12 (95% CI, 3.35–11.13, $P < 0.0001$).

This study suggests that the incidence of primary LAA can be reduced and possibly eliminated with effective preventive practices. After introduction of a comprehensive LAA prevention program at Glaxo-SmithKline, the annual incidence of

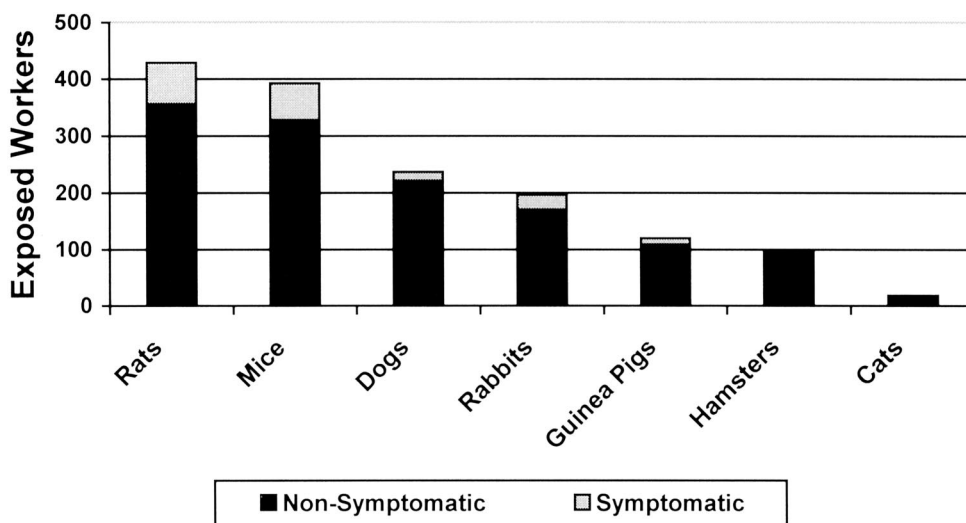


Fig. 3. Species-specific exposures and symptoms among workers enrolled in the LAA medical surveillance program during the period January 1, 1991 through December 31, 2000. Categories are not mutually exclusive because many workers were exposed to more than one species.

TABLE 2

A. Workers with LAA at Entrance into Surveillance Program (Prevalent Cases), Grouped by the Number of Species Causing Allergy Symptoms at Baseline Examination

Number of Animal Allergies at Baseline	Workers (%)	Workers Developing an Additional Allergy (%)
1	62 (60.2)	22 (35.5)
2	27 (26.2)	8 (29.6)
3	9 (8.7)	3 (33.3)
4	3 (2.9)	1 (33.3)
5–6	2 (1.9)	0
Total	103 (16.5%)	34 (33%)

B. Workers Developing LAA During Follow-up (Incident Cases), Grouped by the Number of Species Causing Symptoms at Initial Presentation of Allergy

Number of Animal Allergies at Presentation	Workers (%) Primary LAA	Workers Developing an Additional Allergy (%) Secondary LAA
1	12 (54.5)	2 (16.7)
2	7 (31.8)	1 (14.3)
3	2 (9.0)	0
4	1 (4.5)	0
5–6	0	0
Total	22 (4.2%)	3 (13.6%)

primary LAA was reduced to 0 over the first 5 years and did not rise above 1.2% over the remaining period of follow-up.

Comparison of LAA incidence across studies is not straightforward because studies have calculated and reported incidence in different ways. For example, 1-year and 2-year cumulative incidence estimates of

2.25% and 4.35% have been reported, with LAA defined as two or more work-related allergy symptoms attributed to animals.²⁰ Other studies have reported 1-year incidence from 0 to 37%,^{12,19,21} 2-year incidence from 13% to 43%,^{7,12,20,22} and 5-year cumulative incidence of 9.5%,⁸ with LAA defined as one or more symptoms of allergy.

Incidence rates (also called incidence density), on the other hand, are readily compared between studies, because they include time contributed by every worker who was at risk during the period of follow-up and do not require closed populations for specified periods of time. Kruize et al⁶ estimated a 16-year incidence rate of 1.97 cases per 100 person-years among 99 employees who had completed prescreening questionnaires upon employment and returned mailed questionnaires after termination of employment. Our study calculated the 10-year incidence rate of 1.34 cases per 100 person-years among all employees exposed to laboratory animals during the period January 1, 1991 through December 31, 2000 and followed prospectively until the end of the study or termination of employment. The prospective observation of workers in our study reduced recall bias and allowed corroboration of allergy status by medical personnel.

It is likely that the lower incidence rate estimated in our study is a result of the comprehensive LAA prevention program and not merely an indication of the Healthy Worker Effect, where symptomatic workers leave the workplace before being diagnosed with LAA. Exposed work-

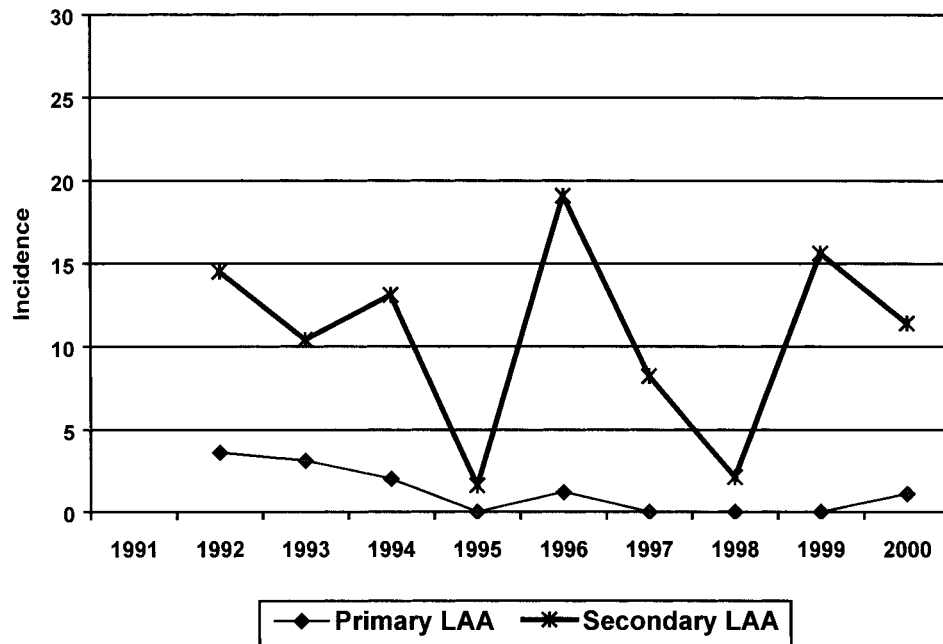


Fig. 4. Annual incidence of primary and secondary LAA among workers enrolled in the LAA prevention program during the period January 1, 1991 through December 31, 2000.

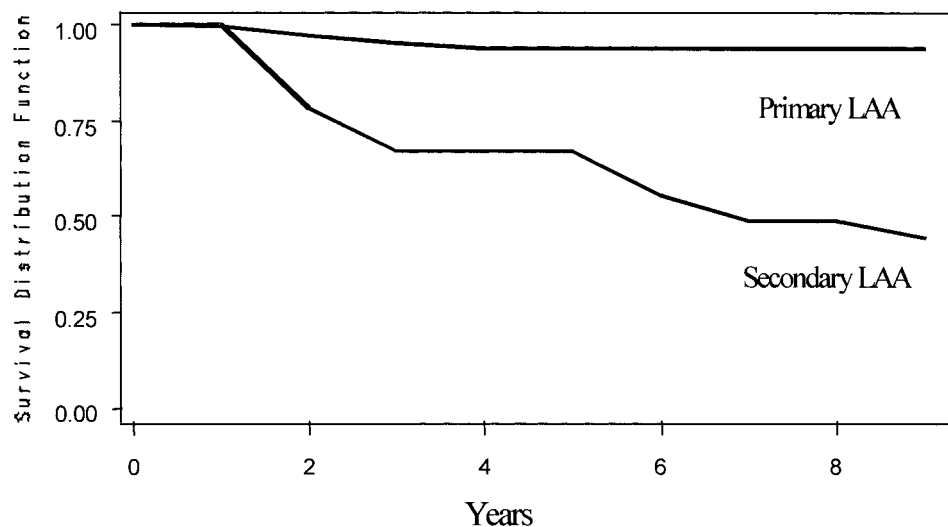


Fig. 5. Survival curves illustrating the development of primary and secondary LAA among laboratory animal workers in the LAA Prevention program during the period January 1, 1991 through December 31, 2000. At year 2, approximately 97% of LAA-free workers had not developed LAA (ie, had "survived") and approximately 75% of workers with primary LAA had not developed secondary LAA.

ers receive intensive education about the risks, prevention, and early reporting of symptoms as part of the overall LAA prevention program. The ongoing educational effort, combined with active medical surveillance, makes it unlikely that workers will leave their jobs without reporting symptoms. The prevention program has utilized a multidisciplinary approach, involving the Occupa-

tional Health Department, Department of Animal Technology and Compliance, and Occupational Safety Department, to implement a variety of controls that have reduced exposure. These controls, described in a previous report,¹⁹ include (1) administrative controls, such as control of animal-stock density and the use of wet shaving techniques; (2) environmental controls, such as fil-

ter-topped cages, high-efficiency particulate air-filtered room ventilation, increased room air exchanges, and dust-free bedding; (3) personal protective equipment, including disposable gloves, bonnets, gowns, and shoe covers, and the mandatory use of respirators (generally dust-mist respirators); and (4) regular house-keeping routines, such as wet mopping and water-hosing.

This study found that workers with LAA had increased risk of developing additional allergies to multiple species of laboratory animals, which we have termed “secondary allergy.” Some workers developed additional allergy more than once during follow-up, but the survival analysis included only the first occurrence of secondary allergy. Although we included multiple events in estimates of annual incidence, our exclusion of multiple events in incidence rate actually yielded an underestimate of the continued risk to workers with primary LAA.

The phenomenon of multiple allergies has been described in previous studies in a way that suggests that the onset of allergies to multiple species occurs as a single event. Agrup et al³ suggested that some cases of multiple allergies were actually a result of cross sensitivity between some animal species. They described cross sensitivity between guinea pigs and hamsters when nine workers with positive radioallergosorbent tests (RAST) to guinea pigs also exhibited positive RAST to hamsters, though only two of the people had been exposed to hamsters. They also found cross sensitivity between rat and mouse allergens. Cross sensitivity does not necessarily imply multiple allergies, however, because cross-reacting antibodies do not necessarily confer symptoms.

In our study, the diagnosis of LAA was based on one or more symptoms. This appears to be a more reliable method of diagnosing LAA than positive RAST because some workers with positive RAST do not have symptoms. Furthermore, both sensitivity and specificity are limited with the use of positive RAST as a diagnosis for LAA. Sensitivity is limited by the lack of standardized antigens used for the test and by RAST measurement of circulating antibodies rather than antibodies bound to mast cells, which are the actual antibodies responsible for the allergic reaction. Both shortcomings in RAST may result in false negatives. Low speci-

ficity resulting in false positives may be related to cross reactivity that has been observed when allergens have similar properties.

Similar homology of animal allergens may be a key to understanding the mechanism of secondary LAA. Immunochemical techniques have facilitated the identification and characterization of specific antigens implicated in LAA, many of which belong to the same family of proteins called lipocalins.²³ Lipocalins, largely produced in the liver or secretory glands of animals, share biological and structural properties that elicit similar responses from the human immune system.²⁴ One hypothesis to explain the phenomenon of secondary LAA is that once the immune system is “primed” with immunoglobulin E in response to one antigen, there is an increased likelihood that a structurally similar antigen would be recognized. This could lead to a subsequent proliferation of a clone of cells producing a more specific IgE antibody to a new, but related, protein. This could explain the body’s response to multiple animal allergens and the cross reactivity seen in RAST results.

If lipocalin proteins are similar in structure, this raises the question as to why there are different rates of allergy to different laboratory animals, such as the higher rate of allergy to rabbits than to dogs. The difference in response could be the result of factors such as different allergic potential, different secretions of allergens, or different handling or care of the animals. This subject needs further study.

An important finding in this study was the increased report of respiratory symptoms from the first presentation of symptoms (or the baseline questionnaire for prevalent cases) to the last date of follow-up. The increased reports of shortness of breath occurred entirely among workers who began follow-up with existing animal allergy, which suggests a possible additional risk of severe respiratory disease to long-term workers.

Most information about the natural history of LAA comes from cross-sectional studies, in which the development of symptoms over time is difficult to ascertain. Results from some epidemiologic studies describe a possible progression of symptoms,^{3,4} but this hypothesis has relied on retrospective information from symptomatic workers, which is subject to recall bias. It seems likely, however, that the course of the disease is variable; one investigator has even suggested that there are two syndromes associated with LAA, a “regional” form characterized by the presence of rhinitis alone, and a “progressive” form characterized by the progression to asthma.²⁵ The progression of symptoms may be dependent on exposure type (eg, specific animals), intensity (eg, specific task), or patterns, which will need to be assessed in further work.

The risk factors for developing primary and secondary LAA in this population were similar to those found in other studies. Personal atopy was more strongly associated with development of LAA than a family history of allergy or asthma. Although not all studies have found a relationship between personal atopy and LAA,^{8,26} most studies have found a clear relationship.

Smoking has been considered as a risk factor for the development of LAA by increasing mucosal transport of antigen,²⁷ but study results have been equivocal.^{3,5,26–28} Only current smoking information was available for this population, and the prevalence of smoking was less than 10%. We were unable to demonstrate a relationship between smoking and LAA.

In this study, 55% of the workers reported that they had domestic pets and 65% of those developing secondary allergy had pets. The lack of historical information about pet ownership made it difficult to identify a clear relationship between pet ownership and development of LAA.

The exposure-response relationship between animal allergens and the de-

velopment of LAA remains elusive, with questions about the importance of specific allergens versus that of intensity and duration of exposure. Most studies evaluating exposure-response relationships have focused on rat or mouse urinary aeroallergens.^{29,30} These studies have identified important determinants of exposure, such as job task, ambient levels of allergen, and room characteristics, but their cross-sectional design has limited the ability to adequately assess an exposure-response relationship. The examination of specific exposure patterns was beyond the scope of this study; however, further work will focus on the intensity, frequency and duration of exposure to specific animals and tasks.

Until the questions about the exposure-response relationship between animal allergens and development of LAA are resolved, there is a need to respond to the heightened risk for symptomatic workers who remain in their jobs. Regardless of the mechanisms involved, it is clear that workers with at least one animal allergy are at risk of becoming allergic to additional species.

To reduce exposure, we believe that it is prudent to require all workers to don personal protective equipment, especially respirators, when working with animals, and to maintain existing engineering and administrative controls until suitable engineering controls can be developed. Our experience suggests that it is possible to prevent primary LAA. However, once allergy develops, the same controls that are effective against primary LAA are not sufficiently protective against secondary LAA. Information on secondary LAA should be incorporated into the ongoing education and training of clinicians and workers. Clinicians can use this information to more thoroughly evaluate a worker's risk of developing more serious respiratory symptoms related to exposure, and workers can make more informed decisions about exposures to animals at work and in their homes.

As a result of evaluation of the LAA prevention program, the surveillance questionnaire has recently been revised to obtain more refined information about exposure frequency and duration, smoking history, pet ownership history, and use of personal protective equipment. There is still a need to understand the exposure-response relationships that contribute to the development of primary and secondary LAA. Ongoing medical surveillance and evaluation, environmental monitoring, and cooperation among laboratory animal workers, occupational, engineering, and safety departments are necessary for elucidating these relationships and developing programs and policies that will be protective for all workers who are at risk for developing LAA.

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