

Allergen immunotherapy: exploring areas for further inquiry

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Background: Allergy-related illness impacts millions of individuals worldwide. Our objectives were to characterize current trends of clinical trials research relating to allergen immunotherapy and to describe the landscape of allergen immunotherapy in National Institutes of Health (NIH)-supported research inquiry.

Methods: On ClinicalTrials.gov, the following terms were searched: allergen immunotherapy OR allergy immunotherapy. Variables, including completion status, dates, design, study population, funder, location, and allergen were recorded. The NIH Research Portfolio Online Reporting Tools (RePORTER) system was also used to gather relevant variables.

Results: A total of 372 clinical trials met inclusion criteria. The proportion of industry-funded clinical trials has declined over 15 years. There has been a slow decline in pollen allergy immunotherapy research, with an increase in both food and animal allergy immunotherapy research. Otolaryngologists comprised only 6.4% of clinical trials

principal investigators (PIs). There was a total adjusted NIH funding of \$74,986,125 for the 118 total funding years.

Conclusion: Despite an immense interest in allergen immunotherapy, this analysis demonstrates that otolaryngologists represented a small proportion of PIs leading associated clinical trials and basic science inquiry. The proportion of trials with industry sponsorship has declined considerably in recent decades. These trends could help direct future resource allocation for allergen immunotherapy. © 2017 ARS-AAOA, LLC.

Key Words:

allergen immunotherapy; allergy immunotherapy; NIH funding; asthma; anaphylaxis; allergic rhinosinusitis

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Allergic disease, including, asthma, allergic rhinosinusitis, and food allergy, is a key public health concern.¹⁻⁴ The prevalence of allergic diseases has continued to rise in the industrialized world for more than 50 years, and sensitization among school-aged children is at an all-time

high, approaching 50%.⁵ Contemporary management includes allergen avoidance, pharmacotherapy, patient education, and allergen immunotherapy. While allergen avoidance is considered the first-line treatment of allergic disease, it is often insufficient for pollen allergies. Additionally, allergen avoidance may not be enough to prevent allergic reaction, as even trace quantities can induce a systemic reaction.⁶ Furthermore, the symptomatic treatment of allergic disease using antihistamines, topical and systemic corticosteroids, and leukotriene receptor antagonists is purely symptomatic; they do not offer a definitive cure. These treatments are also not without significant side effects, including sedation.^{7,8} When allergic disease is refractory to conventional medication, allergen immunotherapy can be an important modality to allow patients to become as symptom free as possible. While allergen immunotherapy has some side effects, such as severe anaphylactic reaction, it is still the only therapy that can change the natural history of allergic disease by reorienting inappropriate immune responses in allergic patients.⁹⁻¹² The efficacy of allergen immunotherapy has been shown

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to be superior to that of placebo^{13–15} and it may offer economic advantages over symptomatic drug treatment by the second year.¹⁶

With this highly effective treatment, there is clearly a vested interest in advancing allergen immunotherapy research. In spite of that, allergen immunotherapy research is still relatively new, and questions remain regarding the current state of allergen immunotherapy research. Our main objectives were to characterize current trends of clinical trials research in allergen immunotherapy and to describe the overall landscape of allergen immunotherapy research funding by the National Institutes of Health (NIH). These trends in current clinical trials and NIH funding may offer certain recommendations for improvement or additional research.

Materials and methods

Clinical trials

ClinicalTrials.gov (<https://clinicaltrials.gov/>) is a web-based resource that houses information on past and current clinical trials on human volunteers. We searched the following terms on the site: allergen immunotherapy OR allergy immunotherapy; and excluded trials that were withdrawn or not yet recruiting. Additionally, the trials' details were reviewed to ensure that only relevant trials were included. In 372 trials meeting the selection criteria, we recorded the following variables: title, completion status, start date, study design, delivery method, study population, funder, location, and allergen being studied. We further classified allergens into 3 groups: animal (house dust mite, cockroach, cat, dog, mouse), pollen (grass pollen, birch pollen, and others), and food allergens (nuts, seafood, egg, milk, wheat). Stings from wasps were not considered in any of the above groups as they have a different exposure mechanism. These groups, as well as their components, were trended over the period between 2001 and 2015. To investigate the average amount of time needed to complete each phase, the number of days between the start date and the completion date of complete trials were recorded and divided into the following time intervals: less than 3 months, 3 months to 6 months, 6 months to 1 year, 1 year to 2 years, 2 years to 5 years, 5 years to 10 years, and more than 10 years. The number of trials in each interval were counted to obtain the time length needed for most trials to complete a phase. Trials with pharmaceutical or biotechnology companies acting as either sole sponsors or collaborators were marked as industry involvement. Similarly, trials with NIH acting as either sole sponsors or collaborators were marked as NIH-funded trials. Locations of the trials were not always available on this site. If the location was not provided, we inferred the location from the principal investigator's (PI's) affiliated institute. If neither the location from the location heading nor the PI's affiliation was provided, we marked them as "unknown." The PI's specialty was searched online using their name and their affiliated institute.

ClinicalTrials.gov did not open for registration until 2000, which means that the number of trials before 2001 were scarce; therefore, graphs that involve timeline and volume of cases per year do not include years prior to 2001.

NIH Research Portfolio Online Reporting Tools

The NIH Research Portfolio Online Reporting Tools (NIH RePORTER; <https://report.nih.gov/>) is a query site that contains information on all NIH-funded projects. We searched the following terms for all fiscal years on this site: allergen immunotherapy OR allergy immunotherapy. Grant details were reviewed to ensure that only relevant grants were included. Projects with repeat grants were noted by project unique number, and projects without disclosed grants were not included. We collected the following data for each project: title, start date, recipient's department and organization, location, administering institute, patent, and PI. Number of patents were counted based on patent unique number to avoid redundant citing. Both subprojects and parent projects were included in our search; therefore, to avoid duplication of funding, we did not include subprojects when their parent projects were also present in our search. To account for grant inflation, the U.S. Department of Labor Bureau of Labor Statistics Consumer Price Index Calculator was used to adjust for inflation with 2017 as the standard fiscal year. PI's department was often omitted on the site. In these cases, we conducted an Internet search to identify what department they worked for during the fiscal years that the grants were issued. In addition, we identified the h-index for each PI in this database in a similar way as described for ClinicalTrials.gov.

Statistical analysis

Descriptive analysis was used to identify the frequency of each variable being investigated. Analyses of variance (ANOVAs) and *t* tests were used as appropriate for comparison of continuous variables, with threshold for significance set at $p < 0.05$. SPSS version 20 (IBM Corp., Armonk, NY) was used for statistical analysis.

Results

ClinicalTrials

Our initial ClinicalTrials search yielded 505 results. We excluded 133 results from this initial search; trials were excluded if they were withdrawn, not yet recruiting, or irrelevant to allergen immunotherapy. A total of 372 trials met our inclusion criteria. A majority of these clinical trials were randomized (68.0%), as well as double blind (58.6%). Most of the clinical trials enrolled adults only (62.3%), with 25.2% that enrolled both adults and children, and 19.8% that enrolled only children. Table 1 shows the general characteristics of allergen immunotherapy in Clinicaltrials.gov. Figure 1 shows the number of clinical trials per each year.

Upon examining industry funding trends, we found that the proportion of clinical trials funded by industry has

TABLE 1. General characteristics of allergen immunotherapy in Clinicaltrials.gov

Characteristics	Clinical trials (%)
All trials (n = 372)	
Complete trials	73.1
Industry involvement	58.9
NIH funded	7.3
Pediatric focus	12.4
Adult focus	62.4
Interventional (n = 328)	
Double blind	66.4
Randomized	77.1
Allergen (n = 365)	
Pollen	51.2
Animal	21.1
Food	20.3
Sting	2.2
Phase (n = 298)	
Phase 1	14.1
Phase 1 and 2	9.4
Phase 2	39.9
Phase 2 and 3	4.4
Phase 3	22.1
Phase 4	10.1

Industry involvement and NIH funded are described in Materials and Methods. Out of 372 trials, 328 were interventional. Out of 372 studies, 365 have identifiable allergens. Out of 372 clinical trials, 298 disclosed study phases. NIH = National Institutes of Health.

steadily declined from 2001 to 2016. In 2003, 83% of the allergen immunotherapy clinical trials were funded by industry, compared with only 33% in 2013. Figure 2 shows industry's contribution to allergen immunotherapy clinical trials over a 15-year period ($p < 0.001$).

We categorized the clinical trials by the type of allergen: pollen, animal, food, and sting, and further subcategorized the type of allergen if it represented a significant source of allergy. For example, peanut allergy was included as a subcategory of food allergy, and cat and dust mites are also included in animal allergy. The most research was surrounding pollen allergen immunotherapy (51.2%), followed by animal (21.1%) and food (20.3%). Figure 3 identifies the major trends in investigation of food, animal, and pollen allergy over the 15-year period. Over the past 15 years, although pollen remains the most heavily studied in allergy immunotherapy research, there has been a slow decline in pollen allergy immunotherapy research, while

there has been a small increase in both food and animal allergy immunotherapy research.

A majority of the clinical trials (80.1%) reported their phase; of the clinical trials that reported phase, 14.1% were phase 1, 9.4% were phase 1 and 2, 39.9% were phase 2, 4.4% were phase 2 and 3, 22.1% were phase 3, and 10% were phase 4. Our analysis showed that amount of time needed to complete the clinical trial was related to the phase of the clinical trial, with higher-phase clinical trials on average taking longer to complete. Figure 4 illustrates the amount of time needed to complete each clinical trial, separated by phase.

Additionally, we examined the method of delivery for the allergen immunotherapy. Of the clinical trials that reported the method of delivery (90.0%), 46.9% delivered the allergen immunotherapy via shot (ie, subcutaneous immunotherapy), 30.0% via sublingual administration, 16.4% via oral administration, 3.3% via patch administration, 3.0% via intralymphatic administration, and 0.6% via intranasal administration. Figure 5 shows the number of clinical trials per delivery method per year.

The variety of academic departments of the PIs reflected the multidisciplinary treatment of allergic disease, with the majority of studies in departments of allergy and immunology, pediatric allergy and immunology, pulmonology, dermatology, and otolaryngology. The number of clinical trials per specialty, as well as the number of PIs per specialty, are illustrated in Figure 6.

NIH RePORTER

Our initial NIH RePORTER search yielded 128 results. Each individual result corresponds to a single funding year of a project. We excluded 10 studies from this initial search that did not disclose the grant amount. Thus, 118 results met criteria and were included in the study. A total of 40 unique projects met inclusion criteria spanning 118 total funding years and attributable to 40 PIs. Table 2 outlines the general characteristics of NIH grants for allergen immunotherapy. Table 3 shows the types of grants awarded for allergen immunotherapy. Seventy (59.3%) of the grants were research grants (R series), 15.2% of the grants were cooperative agreement grants (U-series), and 12.7% of the grants were for general clinical research centers programs (M-01 grants).

There was a total adjusted funding of \$74,986,125 for the 118 total funding years. Figure 7 shows the aggregate funding and number of grants per year sponsored by the NIH over a 15-year period ($p < 0.01$). There was significant regional difference in overall funding for allergen immunotherapy. The East North Central region had the most adjusted funding dollars over the 15-year period (\$33,926,392, 45.2%), followed closely by the Pacific region (\$15,142,257, 20.2%), and by the South Atlantic region (\$14,525,593, 19.4%).

The vast majority of the NIH funding for allergen immunotherapy was provided through the National

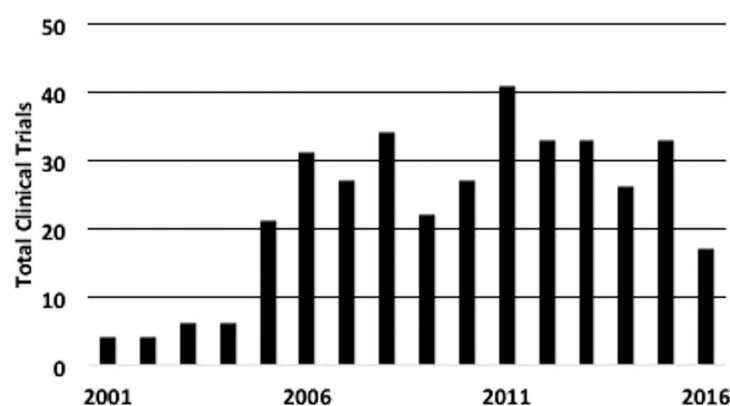


FIGURE 1. Number of clinical trials per year.

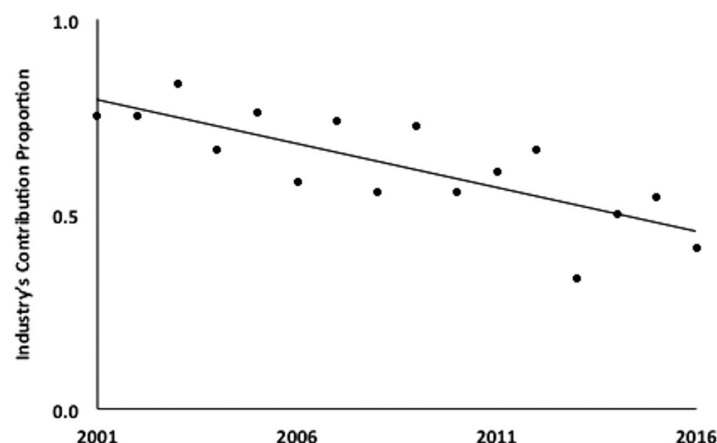


FIGURE 2. Industry contribution to allergen immunotherapy clinical trials over 15-year period.

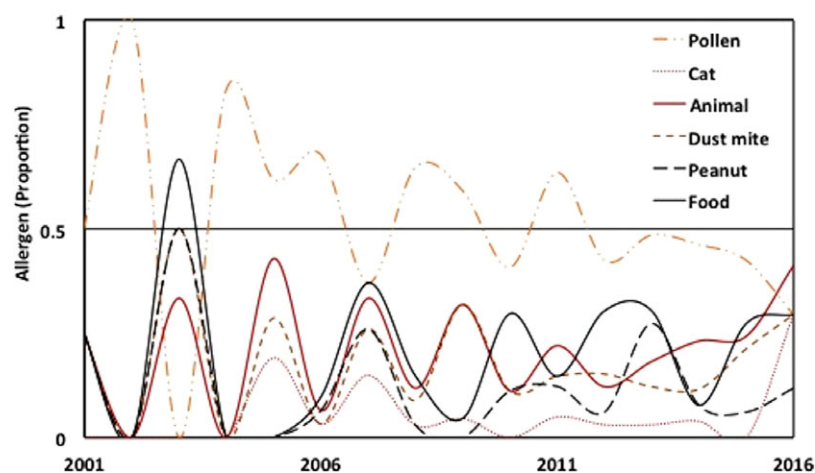


FIGURE 3. Trends in investigation of food, animal, and pollen allergy over 15-year period. Peanut is included in food allergy, and cat and dust mite are included in animal allergy.

Institute of Allergy and Infectious Diseases (NIAID) (96.8%). Of 43 grants connected to clinical trials, 32 projects and 5 subprojects were sponsored by NIAID. The remaining 3.2% of NIH funding was provided by the National Cancer Institute (NCI), National Center for Complementary and Integrative Health (NCCIH), National Center

for Research Resources (NCRR), and National Institute of Child Health and Human Development (NICHD).

Discussion

Due to its rising incidence and immense negative health and financial consequences, allergic disease represents an

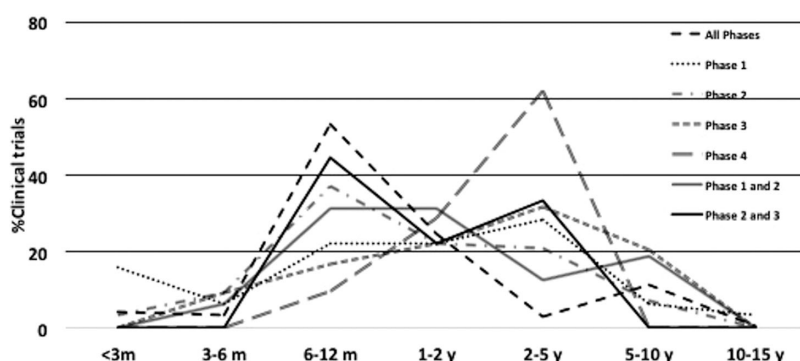


FIGURE 4. The amount of time needed to complete each phase of the clinical trials.

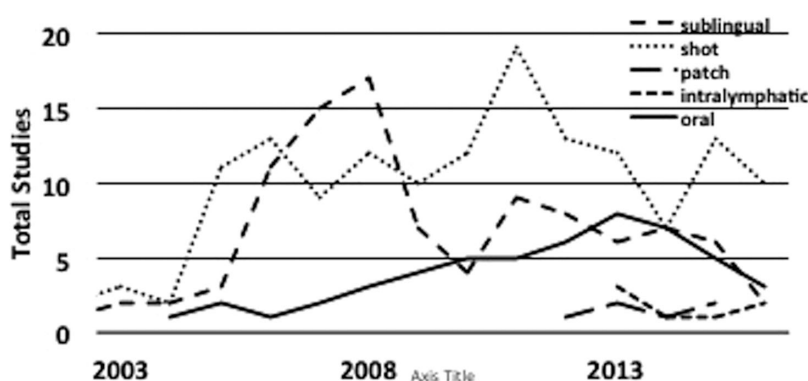


FIGURE 5. Number of clinical trials per delivery method per year.

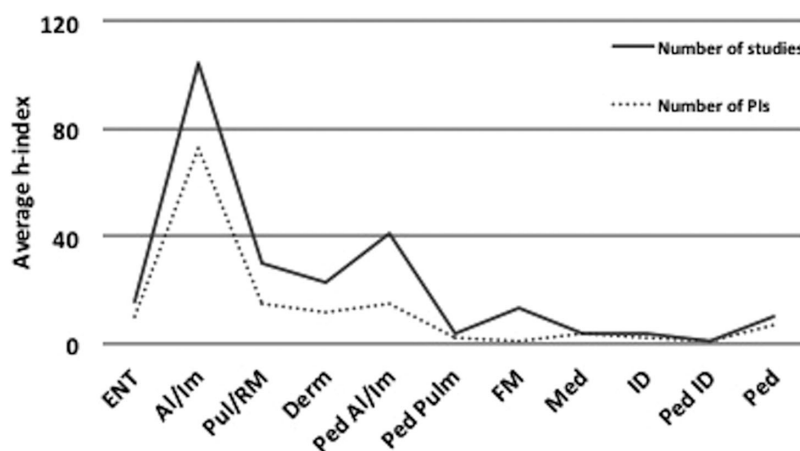


FIGURE 6. Number of clinical trials as well as number of PIs by specialty. All/Im = allergy and immunology; Derm = dermatology; ENT = otolaryngology; FM = family medicine; ID = infectious disease; PED = pediatrics; Ped All/Im = pediatric allergy and immunology; Ped ID = pediatric infectious disease; Ped Pulm = pediatric pulmonology; PI = principal investigator; Pul/RM = pulmonology and respiratory medicine.

important target for intervention by physicians, and allergen immunotherapy represents the forefront of such interventions. With this new treatment modality comes an obligation to scrutinize effectiveness and safety, explore novel administration methods, and help advance the field. Nonetheless, there remains a lack of literature examining the current trends in allergen immunotherapy clinical trials. Additionally, although the NIH remains the principal

public funder of medical research in the United States,¹⁷ no previous studies have assessed the funding landscape in allergen immunotherapy research.

This analysis demonstrates that the proportion of allergen immunotherapy clinical trials funded by industry has been steadily decreasing over the past 15 years, as illustrated in Figure 2. This decrease in industry funding may reflect industry choice, as allergen immunotherapy

TABLE 2. General characteristics of NIH grants for allergen immunotherapy

Grant characteristics	n
Projects total	40
Patents associated	31
Projects with patents	7
Recipient profile	118
Domestic for higher education	84
Domestic for profits	16
Research institute	14
Independent hospital	4
PIs total	40
PIs with one project	31
PIs with two projects	7
PIs with three projects	2
PIs who worked for two institutes	2
Department	118
Medicine	54
Pediatrics	35
Dermatology	1
Other ^a	28

^aIncludes industry-sponsored and research institute-sponsored projects. All but two grants of the medicine and pediatric departments have PIs with subspecialty in allergy and immunology.
 NIH = National Institutes of Health; PI = principal investigator.

TABLE 3. Types of grants awarded for allergen immunotherapy (n = 118)

Grant types/series	Grants (n)	(%)	Studies (n)
R series	70	59.3	25
R01	47	39.8	14
U series	18	15.2	8
M-01	15	12.7	6
K series	8	6.8	3
Z series	2	1.7	1
P series	0	0	0
Other	17	14.4	8

research may have lower economic potential compared to conventional medication (since it represents a potential cure), or it may reflect a concern regarding the public's distrust of the industry ties to medical research.¹⁸ However, as industry funding is shown to be correlated with greater scientific publications,¹⁹ it can also be argued that industry-sponsored research promotes scientific progress

and ultimately benefits patients.²⁰ Recent research shows that a majority of U.S. survey respondents distrust government officials and company representatives with respect to conflict of interest, while they trust physicians and their professional societies the most.²¹ Surprisingly, the results of this research showed that the public endorses and trusts industry-sponsored research, but only if it also had strong physician involvement; most respondents felt that industry-sponsored research could be both objective and beneficial to patients if physicians were involved. Although industry-sponsored allergen immunotherapy has been declining over the past 15 years, physicians should not be so quick to sever ties with industry; it may be prudent to continue to have physician-industry ties to advance scientific Progress.

Additionally, this analysis showcased the pronounced interest in allergen immunotherapy research, with almost \$75 million of NIH funding allocated for this discipline. Figure 7 demonstrates the aggregate funding and number of grants per year sponsored by the NIH over a 15-year period; importantly, this chart shows a steady rise in funding per year, which implies that this trend of increased funding for allergen immunotherapy is likely to continue in the next few years. This increased funding may be reflective of the recent interest in allergen immunotherapy by the scientific community at large.

This analysis also characterizes the various methods of delivery of allergen immunotherapy. These clinical trials included 6 different methods of allergen immunotherapy: subcutaneous, sublingual, oral, patch, intralymphatic, and intranasal. While subcutaneous immunotherapy is the only delivery method that is currently accepted by the scientific community at large, our research shows that clinical research is fervently exploring new allergen immunotherapy routes of administration, and these methods may soon become as mainstream as subcutaneous immunotherapy. Of note, while a large percentage of clinical trials focused on subcutaneous immunotherapy (46.8%), a sizeable percentage of clinical trials also focused on sublingual immunotherapy (30.0%). The variety of delivery methods of allergen immunotherapy is important for many reasons. First, allergen immunotherapy may also have a site-dependent effect, as in the case of some vaccines that generate higher immunogenicity at sites closer to the site of infection.²² In the case of allergen immunotherapy research, this could be done by tailoring the intranasal route for allergic rhinosinusitis, or the oral route for food allergy. Additionally, certain methods, such as patch or oral, may be easier to administer for healthcare practitioners who are not specifically trained in allergy, which may increase access to these vital therapies. The variety of delivery methods is projected to be an exciting direction of allergen immunotherapy.²³ Future systematic reviews and meta-analyses are needed to ascertain whether these methods are as efficacious and safe as subcutaneous immunotherapy, and to determine whether they can offer additional benefits over subcutaneous immunotherapy.²⁴

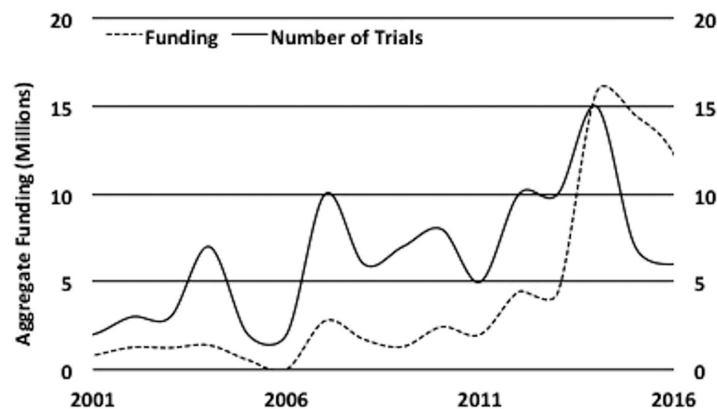


FIGURE 7. Aggregate funding and number of grants sponsored by NIH over the 15-year period. NIH = National Institutes of Health.

A primary objective was to describe the present trends of NIH funding for allergen immunotherapy research and recognize the role of otolaryngologists in clinical trials. To contextualize this, otolaryngologists represent 1.1% of active physicians, and receive a total of 0.74% of total NIH funding. Allergen immunotherapy research is a growing field that attracts medical and scientific researchers from all fields, especially otolaryngology and allergy and immunology, but also dermatology, pulmonology, and family medicine. Our study shows that researchers have received nearly \$75 million in NIH research funding for allergen immunotherapy since 2003 alone. Despite the relevance of allergen immunotherapy to the field of otolaryngology, this analysis demonstrates that otolaryngologists only represented 6.4% of the overall clinical trials as PIs. This is in comparison to allergy and immunology and pediatric allergy and immunology specialists, who led 41.6% and 16.4% of the clinical trials, respectively. This may be partly explained by the fact that only pollen allergies would typically be considered under the scope of practice for otolaryngologists, as food and animal allergies are typically not addressed by otolaryngologists. Nevertheless, as 51.2% of the clinical trials in our analysis were looking at pollen allergies, one would expect a greater degree of otolaryngologist involvement. Our analysis highlights one potential area of growth in the field of allergen immunotherapy; otolaryngologists must be active in leading clinical trials in order to facilitate greater scholarship in this field.

The present study has several limitations. First, there are other sources of research funding for physicians and other scientists that are not included in the NIH RePORTER system. However, as the NIH is the largest supporter of biomedical science, it is the best representation of national funding among all specialties for allergen immunotherapy. Nevertheless, the NIH RePORTER database itself has some

limitations, as funding totals are not available for funding issued before the year 2000, which limits the study period. Even with this limitation, however, we were able to analyze 15 years of NIH funding data.

Additionally, although we believe that the number of trials registered on ClinicalTrials.gov reflects the current landscape of scientific interest, another possible limitation is that these data do not fully represent recent research trends, as there remain some questions regarding the impact of such studies, especially with a high non-publication rate.

Another limitation to our study is that there were only 16 studies which were led by otolaryngologists, with only 10 distinct otolaryngology PIs. This small number makes it difficult to draw many conclusions regarding the characteristics of such otolaryngologists. Furthermore, it is likely that these otolaryngologists are more involved with the clinical trials as either contributing faculty members or co-authors, but our dataset does not capture any other role besides PI.

Conclusion

Despite the high prevalence of allergy-mediated respiratory disorders, there has been a paucity of literature regarding the current state of allergen immunotherapy clinical trials and a lack of information describing patterns in NIH support. This analysis highlights that there is immense interest in allergen immunotherapy today, with nearly \$75 million in NIH funding allocated to allergen immunotherapy research over the covered time period. These trends could help direct future resource allocation for allergen immunotherapy. Importantly, these findings highlight a potential area of growth in the field of allergen immunotherapy; otolaryngologists must be active in leading clinical trials in order to facilitate greater scholarship in this field. 🌐

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