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Allergen Immunotherapy Extract Shortages and Their Effects on Clinical Care: A Work Group Report of the AAAAI Immunotherapy, Allergen Standardization, and Allergy Diagnostics Committee

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Allergen immunotherapy (AIT) is the only disease-modifying therapy indicated for treatment of allergic asthma, rhinitis, conjunctivitis, and Hymenoptera hypersensitivity. Manufacturing of the extracts used in AIT involve multistep complex processes as well as regulatory oversight. Furthermore, some source materials are vulnerable to unexpected events of nature. Given these circumstances, allergen extract supply can be disrupted with a potential to adversely impact patient care. A group of members from the American Academy of Allergy, Asthma, and Immunology (AAAAI) Immunotherapy, Allergy Standardization and Allergy Diagnostic Committee formed a workgroup to assess the frequency and effects of allergen extract shortages and associated factors. This workgroup developed a survey that was distributed to a random 20% of the AAAAI membership. In addition, the group also performed a review of the scientific literature on allergen extract supply and shortage. Based on the findings of the survey study and literature review, the workgroup reports frequency and extent of shortages, potential ways to improve communication with suppliers, and need for further guidance in patient care during times of shortage. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:444-52)

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Allergen immunotherapy (AIT) is the administration of increasing amounts of allergens to which the patient has type I immediate hypersensitivity. It is a disease-modifying therapy indicated for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and Hymenoptera hypersensitivity.[1] AIT alters the immune system's reaction to causative allergens and induces long-lasting tolerance to these allergens.[2] In children, AIT can prevent development of asthma.[3] Two commonly used modalities of AIT are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), with SCIT being more commonly practiced compared with SLIT in the United States.[4,5]

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma, and Immunology
ACAAI- American College of Allergy, Asthma, and Immunology
AIT- Allergen immunotherapy
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy
VIT- Venom immunotherapy

An AIT extract can comprise 1 or more allergens, which are obtained from natural source materials. The composition of an extract is influenced by the quality and purity of the source materials, their processing, extraction, and storage conditions. Most commercially available extracts are crude extracts and include all extractable components of the source material.[6]

A wide variety of source materials are used for allergen extract production. Pollens are collected from over 100 species of grasses, weeds, trees, shrubs, and cultivated plants. For mold allergen extracts, fungi (mycelia and/or spores) are used. Allergens of animal origin are mostly isolated from their dander and skin, but saliva, serum, or urine can be used as well. Arthropod materials are used in house dust mite, Hymenoptera venom, and whole-body extracts of imported fire ants. House dust mite allergens are sourced from laboratory cultures. Honeybee venom is collected using direct electrostimulation of live insects, whereas yellow jacket, hornet, and wasp venom is obtained by dissection of their venom sacs. Fire ant extracts are unique in their manufacturing, as their extract is produced from the whole bodies of the insects.[6-10]

Allergen extracts are a mixture of allergenic and nonallergenic molecules, including proteins, glycoproteins, polysaccharides, lipids, nucleic acids, low-molecular-weight metabolites, salts, and pigments. One of the challenges in their production is to preserve the complexity of allergens in an extract, while minimizing the amount of unwanted components, such as destructive proteases. To achieve the optimal product, manufacturing processes involve many steps including defatting (to remove oils, waxes, and oleoresins that can induce type IV hypersensitivity reactions), milling, grinding, homogenizing, centrifugation, and filtration. Removal of low-molecular-weight material is achieved by dialysis, ultrafiltration, or depigmentation.[6]

Once extracts are produced, their characterization and quality control should be performed. For standardized extracts, their composition and potency have been documented, and compliance with these should be ensured for each lot. For some allergen extracts standardization allows the clinician to be relatively certain that a known amount of the important allergen is being delivered to the patient. In addition to this, the risk of inducing a reaction when changing vials or manufacturers is lower due to predictable potency in different lots and producers.[11] Standardized allergen extracts and Food and Drug Administration–approved allergen extracts available for SLIT in the United States are listed in Tables I and II, respectively.

There are multiple factors to be considered in preparation of allergen extracts for use in AIT. These include speciation, delivery of optimal dose of allergen, use of appropriate diluents, cross allergenicity among allergens, compatibility of extracts, and storing at appropriate conditions.[14]

Given the complexity of allergen extract manufacturing, disruptions in their supply chain can occur. Previously, a prolonged shortage of Hymenoptera venom extracts resulted in interruption or alteration of AIT in many patients. A joint task force formed by American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) published a report to guide management during venom extract shortage. In addition to this, experience with switching venom extract products during venom shortages as well as restarting venom AIT after resolution of disruptions has been reported.[15,16] Such disruptions affect other extracts as well; however, the frequency and effect of such instances have not been previously investigated.

METHODS

The Extract Supply Chain Workgroup within the Immunotherapy, Allergy Standardization, and Allergy Diagnostic Committee of AAAAI developed a survey tool to assess the frequency and effects of allergen extract shortages. This tool comprised 17 survey questions pertaining to allergen extract supply shortages and 8 demographic questions (see Table III for the survey questions). The survey consisted of multiple choice questions. For all questions, responders were instructed to choose the single best answer except for questions 6, 7, 9, 11, 12, 17, and 21, where responders could select all answer choices that applied.

The survey was approved by the institutional review board at Northwell Health System for research on human subjects. In accordance with AAAAI policies, it was sent out via Survey Monkey to 1094 randomly selected members (approximately 20% of AAAAI membership).

Study aims included examining the distribution of responses to survey questions and their association with responses to the 8 demographic questions. Summary statistics were reported as frequencies and percentages based on all responses answered for each survey question. Tests for association were performed using χ^2 or Fisher's exact tests, as appropriate. In tests for association, responses to Q3-Q5 and Q22 were regrouped for ease of analysis. When examining associations with demographics question Q19, the response "Outside of the United States" was excluded. Respondents from the state of MD may have checked that they practice in the Northeast or Southeast, as MD was listed for both responses. A P value of $<.05$ was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

A review of scientific literature was undertaken using PubMed, EMBASE, Web of Science, Scopus, CINAHL, and Google Scholar. Search terms for the review were "allergen extract supply," "allergy extract supply," "allergen extract shortage," "allergy extract shortage," "sublingual immunotherapy extract shortage," and "sublingual immunotherapy extract supply." Results were filtered for relevance.

RESULTS

Survey results were received from 129 members, 3 of whom were excluded because they did not practice AIT. The majority of responders answered all 17 survey questions and 8 demographic questions (n = 104). Table III shows the number of responders who chose each answer for every survey question.

One hundred and eleven responders completed the demographic section. The majority of the responders were 31 to 66 years of age, with 42% (n = 47) in the 31 to 50 range, 41% (n = 45) in the 51 to 65 range, and 15% (n = 17) over 66 years. Two responders (2%) preferred not to answer. All responders had been in practice for at least a year. The majority of them (77%, n = 86) had been practicing more than 10 years.

TABLE I. List of standardized allergen extracts available for subcutaneous immunotherapy in the United States[12]

Allergen source	Extract
Epithelia	Cat hair
	Cat pelt
Dust mite	*Dermatophagoides pteronyssinus*
	Dermatophagoides farinae
Pollen	Short ragweed
	Bermuda grass
	Kentucky blue grass
	Perennial rye grass
	Orchard grass
	Timothy grass
	Meadow fescue grass
	Redtop grass
	Sweet vernal grass
Hymenoptera venoms	Yellow jacket
	Honeybee
	Paper wasp
	Yellow hornet
	White faced hornet
	Mixed vespids

TABLE II. List of allergen extracts Food and Drug Administration approved for use as sublingual immunotherapy tablets in the United States[13]

Combination *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*
Short ragweed
Combination Sweet vernal, orchard, perennial rye, timothy, Kentucky blue grass
Timothy grass

The majority of responders practiced in the United States (92%, n = 102). Nine of the participants (8%) practiced outside of the United States. Figure 1 shows geographical distribution of participants practicing in the United States.

Most responders were physicians (83%, n = 92), 14% were RN/PA/LPNs (n = 15), and 4% (n = 4) were staff/other. Of the 89 physicians who passed at least 1 specialty board, 97% (n = 86) passed the allergy and immunology board, 45% (n = 40) passed the internal medicine board, and 38% (n = 34) passed the pediatric board. Most responders (61%, n = 67 of 110) practiced in a group setting, whereas 36% (n = 40 of 110) were in solo practice and 3% (n = 3 of 110) were federal government employees. Of the 108 responders who were not federal employees and completed this question, 76% (n = 82) were in private practice, and 24% (n = 26) were in academic practice.

About two-thirds of responders who practiced immunotherapy had over 100 patients on SCIT (66%, n = 83), whereas 22% (n = 28) had 26 to 100 patients and 11% (n = 14) had 1 to 25 patients.

Ninety-seven percent (n = 120) of responders experienced extract shortages with a majority of them (61%, n = 75) reporting shortages a few times a year or more. Among the responders who also answered all of the demographic questions, the frequency of extract shortages was not significantly associated with responders' geographic location, years of practice, or whether or not the practice was private or academic ($P = .39$ [n = 102], $P = .35$ [n = 111], and $P = .07$ [n = 108], respectively).

In addition, approximately 95% (n = 113) of responders also reported that the supply chain disruptions affected patient care. Forty-three and 24 of the responders (36% and 20%) thought that this impact was "a moderate amount" and a "great deal," respectively. Among those responders who answered the demographic questions, no significant association was observed between the perception of impact on patient care with geographic location, years of practice, or whether or not the practice was private or academic ($P = .763$ [n = 102], $P = .573$ [n = 111], and $P = 1$ [n = 108], respectively).

Of those responders who thought that supply chain disruptions affected their patients' care, 74% (n = 81) reported that the shortage affected patient care at least yearly or more. Again, this frequency was not found to be associated with responders' geographic location, years of practice, or whether or not the practice was private or academic ($P = .83$ [n = 98], $P = .581$ [n = 107], and $P = .414$ [n = 104], respectively).

When asked about the types of extracts affected by shortages, 109 responders checked at least 1 option, with 72% of them identifying venom extract as a concern, 50% identifying pollen (tree, grass, and weeds about equally), and 45% identifying mold spores. Responders also felt that the extracts for animal dander (36%, n = 39), dust mites (19%, n = 21), cockroach (6%, n = 7), and other extracts (3%, n = 3) were affected. Responders practicing in a private setting experienced significantly more pollen extract shortages compared with the responders in academia ($P = .034$, n = 103). No significant difference was observed between these different settings in regard to other allergen extract shortages. Mold spores were checked by a higher than expected percentage of responders from the Midwest and a lower than expected percentage of responders from the Southwest ($P < .009$, n = 97), and venom was checked by a lower than expected percentage of responders from the West ($P < .007$, n = 97). No significant association was observed between geographic location and pollen, animal dander, dust mites, or cockroach.

Of the 110 responders who checked at least 1 response to question 7, 89% (n = 97) obtained information for AIT extract shortages "by the company upon ordering the extract" and 21% (n = 23) "by the company prior to ordering the extract." Only 2 responders reported information from "in the news."

Half of the 110 responders who answered question 8 were not informed of the expected duration of shortage. The remaining half were provided information on expected duration of shortage of venom, pollen, mold spores, animal dander, dust mites, and cockroach, in descending order. Overall, for each specific extract, less than a quarter of the practitioners were informed of duration of shortage.

Furthermore, 74% (n = 81 of 110) of the responders were not informed of the reason for the shortage, and of those who were informed, only half knew of the reasons for venom shortages. Only 1 in 5 of those who were informed knew of reasons for shortages of all the other extracts. When asked to conjecture about the 3 main reasons for the disruptions, responders thought that cost of production, high demand, pollen collection or mold culture techniques, lack of standardization of extracts, and regulatory oversight procedures were approximately equally to blame. However, these were the 5 choices given in the multiple choice question. The most likely causes to be picked were high

TABLE III. Complete survey results

Questions	Answer choices	Responses	Association with demo factors	*P* value
Q1. Do you practice allergen immunotherapy? (select one)	Total	129		
	Yes	126 (97.7%)		
	No	3 (2.3%)		
Q2. Approximately how many patients in your practice are on subcutaneous immunotherapy for allergic rhinoconjunctivitis, allergic asthma, and/or Hymenoptera hypersensitivity? (select one)	Total	126		
	0 patients	1 (0.8%)		
	1-25 patients	14 (11.1%)		
	26-100 patients	28 (22.2%)		
	>100 patients	83 (65.9%)		
Q3. How often do you experience extract shortage? (select one)	Total	124		
	Never	4 (3.2%)		
	<1 y	16 (12.9%)		
	Yearly	29 (23.4%)		
	Few times/y	63 (50.8%)		
	Monthly	5 (4.0%)		
	More than monthly	7 (5.7%)		
Q4. How much, if at all, do you think supply chain disruptions in allergen immunotherapy extracts are impacting patient care? (select one)	Total	120		
	Not at all	6 (5.0%)		
	A little	46 (38.3%)		
	A moderate amount	43 (35.8%)		
	A great deal	24 (20.0%)		
	Don't know	1 (0.8%)		
Q5. How often does the allergen immunotherapy extract shortage affect your patient care? (select one)	Total	110		
	Less than every year	29 (26.4%)		
	Yearly	26 (23.6%)		
	Few times/y	48 (43.6%)		
	Monthly	4 (3.6%)		
	More than monthly	3 (2.7%)		
Q6. Which allergens do you perceive to be affected by supply chain disruptions? (select all that apply)	Total (*multiple choice*)	109		
	Pollen (tree, grass, weed)	55 (50.5%)	Yes	.03*
	Mold spores	49 (45.0%)	Yes	.009†
	Animal dander	39 (35.8%)		
	Dust mites	21 (19.3%)		
	Cockroach	7 (6.4%)		
	Venom	77 (70.6%)	Yes	.007†
	Other‡	3 (2.8%)		
Q7. How are you informed in general of the allergen immunotherapy extract shortage? (select all that apply)	Total (*multiple choice*)	110		
	In the news	2 (1.8%)		
	By manufacturer before ordering extract	23 (20.9%)		
	By manufacturer upon ordering extract	97 (88.2%)		
Q8. Are you informed of the expected duration of the allergen immunotherapy extract shortage for any of the extracts? (select one)	Total	110		
	Yes	55 (50.0%)		
	No	55 (50.0%)		

(continued)

TABLE III. *(Continued)*

Questions	Answer choices	Responses	Association with demo factors	*P* value
Q9. For which extracts? (if answered "yes" to Q8, select all that apply)	Total (*multiple choice*)	55		
	Pollen	20 (36.4%)		
	Mold spores	11 (20.0%)		
	Animal dander	10 (18.2%)		
	Dust mites	3 (5.5%)		
	Cockroach	2 (3.6%)		
	Venom	22 (40.0%)		
	All extracts	7 (12.7%)		
	Other	3 (5.4%)		
Q10. Are you informed of the reason for the allergen immunotherapy extract shortage for any of the extracts? (select one)	Total	110		
	Yes	29 (23.4%)		
	No	81 (73.6%)		
Q11. For which extracts? (if answered "yes" to Q10, select all that apply)	Total (*multiple choice*)	29		
	Pollen	5 (17.2%)		
	Mold spores	6 (20.7%)		
	Animal dander	4 (13.8%)		
	Dust mites	4 (13.8%)		
	Cockroach	1 (3.4%)		
	Venom	14 (48.3%)		
	All extracts	3 (10.3%)		
	Other	0 (0.0%)		
Q12. What do you think are the top 3 main causes of supply chain disruptions? (in order of most likely cause (1) to least (3))	Total (*multiple choice*)			
	Cost of production	67		
	1—Most likely	30 (44.8%)		
	2	19 (28.4%)		
	3—Least likely	18 (26.9%)		
	High demand	78		
	1—Most likely	30 (38.5%)		
	2	27 (34.6%)		
	3—Least likely	21 (26.9%)		
	Pollen collection/mold culture technique	75		
	1—Most likely	31 (41.3%)		
	2	24 (32.0%)		
	3—Least likely	20 (26.7%)		
	Lack of extracts standardization	51		
	1—Most likely	17 (33.3%)		
	2	20 (39.2%)		
	3—Least likely	14 (27.5%)		
	Regulatory oversight procedures	65		
	1—Most likely	24 (36.9%)		
	2	20 (30.8%)		
	3—Least likely	21 (32.3%)		
	Other	18		
Q13. How knowledgeable do you feel about the process by which allergen immunotherapy extracts are created from raw material? (select one)	Total	107		
	Not at all	24 (22.4%)		
	Modestly	54 (50.5%)		
	Moderately	23 (21.5%)		
	Very	6 (5.6%)		

(continued)

TABLE III. *(Continued)*

Questions	Answer choices	Responses	Association with demo factors	*P* value
Q14. Are you informed of the available alternatives to the allergen immunotherapy extract that is not available? (select one)	Total	107		
	Yes	53 (49.5%)		
	No	54 (50.5%)		
Q15. Do you use the suggested extract alternative (If answered "yes" to Q14, select one)	Total	53		
	Yes	37 (69.8%)		
	No	16 (30.2%)		
Q16. How closely do you work with representatives from manufacturers in anticipating supply chain disruptions? (select one)	Total	107		
	Not at all	41 (38.3%)		
	Somewhat closely	42 (39.3%)		
	Very closely	16 (15.0%)		
	Extremely closely	8 (7.5%)		
Q17. Which of the following resources, if any, would be helpful to you in foreseeing supply chain disruptions and thus mitigate their effects on clinical care? (select all that apply)	Total (*multiple choice*)	109		
	Periodic bulletins	78 (71.6%)		
	Continuing medical education on AIT extract manufacturing process	37 (33.9%)		
	Gaining real-time inventory visibility	63 (57.8%)		
	Other	7 (6.4%)		
Q18. What is your age? (select one)	Total	111		
	18-30 y	0 (0.0%)		
	31-50 y	47 (42.3%)		
	51-65 y	45 (40.5%)		
	Over 66 y	17 (15.3%)		
	No answer	2 (1.8%)		
Q19. Where do you practice? (select one)	Total	111		
	West	12 (10.8%)		
	Southwest	13 (11.7%)		
	Midwest	25 (22.5%)		
	Northeast	31 (27.9%)		
	Southeast	21 (18.9%)		
	Outside of the United States	9 (8.1%)		
Q20. Which of the following best describes your role as a health care provider? (select one)	Total	111		
	Physician	92 (82.9%)		
	RN/PA/LPN	15 (13.5%)		
	Staff/Other	4 (3.6%)		
Q21. Which medical specialty boards have you passed (if answered "physician" for Q20, select all that apply)	Total (*multiple choice*)	89		
	Allergy and immunology	86 (96.6%)		
	Internal medicine	40 (44.9%)		
	Pediatrics	34 (38.2%)		
	Pulmonary	0 (0.0%)		
	None	0 (0.0%)		
	Other	2 (2.25%)		
Q22. How long have you been practicing? (select one)	Total	111		
	<1 y	0 (0.00%)		
	1-5 y	17 (15.3%)		
	6-10 y	8 (7.2%)		
	>10 y	86 (77.5%)		

(continued)

TABLE III. *(Continued)*

Questions	Answer choices	Responses	Association with demo factors	*P* value
Q23. Which of the following best describes your practice setting? (select one)	Total (*multiple choice*)	110		
	Federal	3 (2.7%)		
	Group practice	67 (60.9%)		
	Solo practice	40 (36.4%)		
Q24. Which solo practice? (if answered "solo practice" for Q23, select one)	Total	41		
	Academic	36 (87.8%)		
	Private	5 (12.2%)		
Q25. Which group practice? (if answered "group practice" for Q23, select one)	Total	67		
	Academic	21 (31.3%)		
	Private	46 (68.7%)		

AIT, Allergen immunotherapy.
*Association with practice setting (academic vs private, n = 103).
†Association with geographic demographics (n = 97; note: the category, "Outside of the United States" was excluded from analysis).
‡Some free text responses in the "other" category were regrouped into other responses if appropriate.

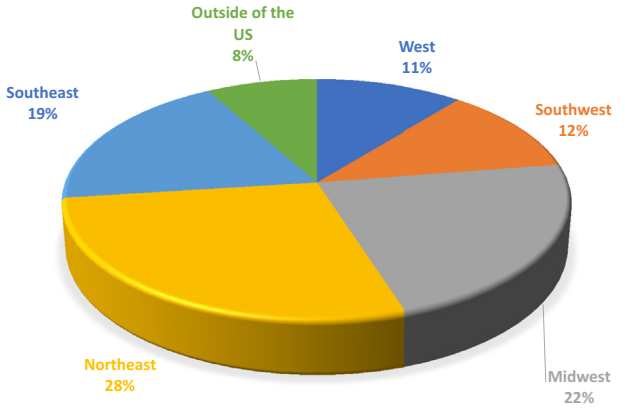

FIGURE 1. Geographic distribution of responders (n = 111) grouped into 6 categories. West: AK, CA, CO, HI, ID, MT, NV, OR, UT, WA, WY; Southwest: AZ, NM, OK, TX; Midwest: IA, IL, IN, KD, MI, MN, MO, ND, NE, OH, SD, WI; Northeast: CT, DC, DE, MA, MD, ME, NH, NJ, NY, PA, RI, VT; Southeast: AL, AR, FL, GA, KY, IA, MD, MS, NC, SC, TN, VA, WV; Outside of the United States: Canada, Cuba, Dominican Republic, Qatar, Taiwan, Thailand.

demand, pollen collection/mold culture technique, and cost of production, in descending order.

Slightly less than a quarter of the responders (n = 24 of 107) did "not feel knowledgeable at all" about the manufacturing process of allergen extracts, whereas only 6 practitioners (6%) felt "very knowledgeable." There was no significant association between how knowledgeable responders felt and their age ($P = .155$, n = 105), geographic location ($P = .281$, n = 98), years in practice ($P = .122$, n = 107), or practice setting ($P = .462$, n = 104).

Only half of the 107 responders who also answered demographic questions and question 14 were informed about the alternatives to the allergen extract that was affected by the shortage. The majority of the responders (70%, n = 37 of 53) who were offered an alternative extract reported using the suggested product. No significant association was observed between responders' practice setting and being offered ($P = .067$, n = 104) or using an alternative extract ($P = .24$, n = 51).

When asked how closely they work with representatives from manufacturers, equal numbers of responders reported working "somewhat closely" and "not at all" (39% and 38% of 107, respectively), although 15% work "very closely" and 7% work "extremely closely" with manufacturer representatives. No significant difference was observed in how closely responders worked with representatives in academic or private practice ($P = .682$, n = 104).

When asked about preference of helpful resources in foreseeing supply chain disruptions and thus to mitigate their effects on clinical care, of the 109 responders who checked at least 1 response, 72% (n = 78) chose "periodic bulletins," 33% (n = 37) chose "continuing medical education on AIT extract manufacturing process," 58% (n = 63) chose "gaining real-time inventory visibility," and 6% (n = 7) chose "other." Please refer to Table III for the free text responses to this question.

A review of scientific literature through PubMed, EMBASE, Web of Science, Scopus, CINAHL, and Google Scholar revealed 355 publications that mentioned allergen extract supply or shortage (Figure 2). After removal of duplicates and screening for relevance, 11 publications remained. Of these, 1 was an AAAAI/ACAAI joint task force report on venom extract shortage,[17] 4 discussed transitioning products during venom extract shortage,[15,16,18,19] 3 were perspective articles discussing potential effects of single venom extract supplier and related reimbursement issues,[20-22] 1 was a review of literature on venom immunotherapy (VIT),[23] and 1 discussed restarting VIT after discontinuation due to a shortage.[24] There was only 1 publication that discussed allergen extract supply besides venom extract in the context of commercial laboratory preparation of individual immunotherapy vials.[25] There were no studies about extract supply or shortage in relation to SLIT.

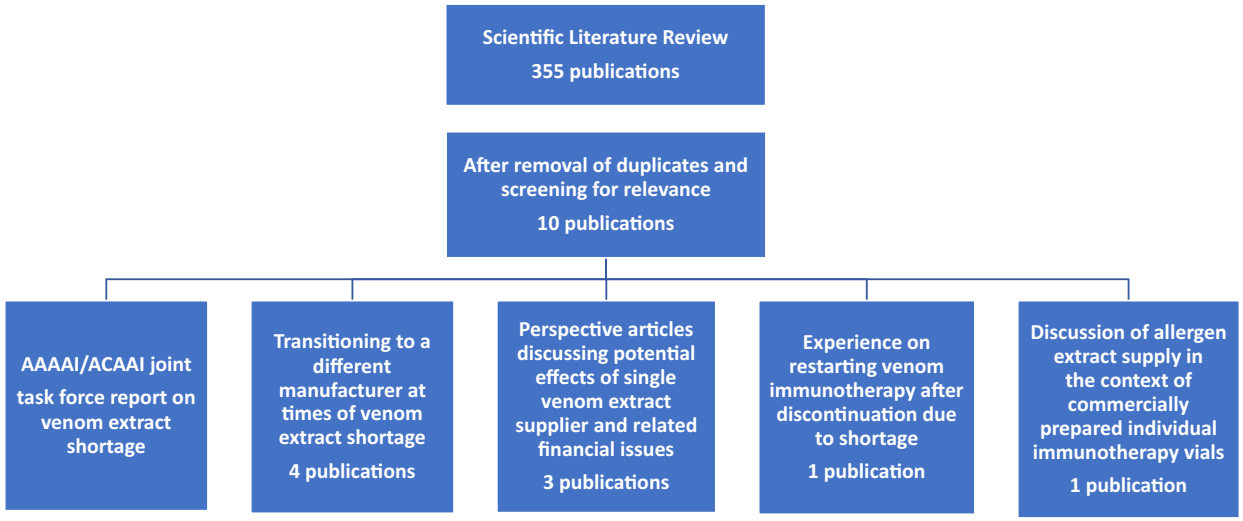

FIGURE 2. Scientific literature review was conducted using PubMed, EMBASE, Web of Science, Scopus, CINAHL, and Google Scholar with search terms "allergen extract supply," "allergy extract supply," "allergen extract shortage," "allergy extract shortage," "sublingual immunotherapy extract shortage," and "sublingual immunotherapy extract supply." *AAAAI*, American Academy of Allergy, Asthma, and Immunology; *ACAAI*, American College of Allergy, Asthma, and Immunology.

DISCUSSION

The prevalence of allergic rhinitis, allergic conjunctivitis, and asthma has been on the rise in recent decades, especially in developed countries and urban areas.[26-28] As AIT is the only disease-modifying therapy for these conditions, their increased prevalence could lead to a greater demand for AIT. The combination of complexity of sourcing and manufacturing, regulatory processes, and limited number of manufacturers makes allergen extracts vulnerable to shortages. Increasing demand coupled with changes in weather patterns will likely strain the supply chain further.

Stability of the supply chain is an important detail in ensuring that patients receive uninterrupted care. Although the effects of disruption in AIT are not well studied, one could theoretically surmise that not receiving AIT for an asthmatic may increase risk for asthma exacerbations. Similarly, for venom allergic patients, lack of treatment can increase risk for severe allergic reactions on subsequent stings. Oversight by regulatory bodies or manufacturers could be helpful in ensuring that patient safety is not at risk.

There is consensus that AIT should consist of 3 to 5 years of maintenance therapy.[29] Although benefits are observed during the first year of therapy, evidence suggests that discontinuation at 2 years leads to short-lived beneficial effects.[30] Additional effects of disruptions on maintaining AIT regimens and overall efficacy remain to be explored.

Our survey response rate was 12%, which was within the expected range of 10% to 15% (based on prior similar surveys distributed among AAAAI membership[31,32]). Most of the responders were practicing in the United States; therefore, results are mostly reflective of the United States supply chain. An overwhelming majority of responders experienced allergen extract shortages, and for most of them, shortages occurred more than a few times a year. In addition, an overwhelming majority of the participants also indicated that shortages affect patient care in varying degrees.

Responders practicing in a private setting experienced more pollen extract shortages compared with the ones from academia. This could be explained by the higher patient volume of private practices and resulting higher demand and use of AIT. However, this effect was not observed for other allergen extract types. Thus, it is possible that the number of patients treated with pollen extracts by private practitioners is higher and warrants additional evaluation. Future work to examine difference in approaches to AIT practices between academia and private practice can provide further insight into other potential causes.

Mold extract shortages showed significant geographic variance. They were affected more in the Midwest, whereas their shortage was experienced less in the Southwest. In addition, venom extract shortage was reported less by participants from the West. However, when evaluating this finding, the number of participants from this area should be kept in mind ($n = 12$, with 3 indicating venom extract as affected by shortages). All other extracts were affected similarly by supply chain disruptions among different parts of the United States. It is unclear if this is because of a higher supply of venom in the West, or decreased demand.

Our study findings suggest that there is definite room for improvement in communication between suppliers and health care providers. There is a clear impact on patient care as most of the participants learned of the extract shortage when placing an order of the needed allergen extract. In addition, about half of the responders were not informed about expected duration of the shortage, and three-quarters of the participants did not know the reason for the shortage, although this information tended to be more available for venom extracts.

Even though most allergists use allergen extracts in their practice routinely, up to a quarter of the participants reported not being knowledgeable at all about the allergen extract manufacturing process, and a mere 6% felt very knowledgeable, revealing a knowledge gap that should be addressed. Although manuscripts such as a recent review by Goodman et al[14] are helpful, this is a topic that should be covered more closely during

fellowship training and in the scientific literature in general. Coverage of this subject by the AAAAI programming could be helpful in addressing the knowledge gap.

Our literature review showed multiple research and quality improvement studies undertaken during venom extract shortage. These studies as well as the AAAAI/ACAAI joint task force report from 2017 provide valuable information in guiding the clinician through times of venom extract shortage. Interestingly, there was a lack of similar guidance for other allergen extracts. There were no articles regarding SLIT extract supply or shortages. Future studies are needed to identify ways to better navigate shortages of allergen extracts besides venom. In addition, extract shortages and their effects on SLIT remain to be investigated.

Our study has limitations. A small number of providers who practice AIT were surveyed. Participation was voluntary; thus providers who have been affected by shortages could be more likely to participate than those who have not been. As majority of the responders were from the United States, results might not be applicable for other countries. There were multiple questions relying on respondent recall; however, the overall conclusions are illuminating. Allergen extract shortages were experienced by an overwhelming majority of participants, suggesting that they are a common occurrence in the practice of AIT. Communication between suppliers and AIT providers can be improved, and as suggested by the responders, periodic bulletins or a central database providing real-time information about inventory may be helpful.

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