

Outdated allergens are similar to unexpired extracts for the detection of allergen sensitization

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ABSTRACT

Background: Allergen extracts have relatively short shelf lives, which limits their use and increase financial loss and waste on unused extracts. It is thus important to determine if efficacy persists beyond the expiration date.

Objective: To determine the *in vivo* efficacy and bioavailability of outdated allergen extracts for diagnosis of allergic sensitizations.

Methods: We enrolled 34 participants with allergic rhinitis and 5 participants with Hymenoptera hypersensitivity. After confirming allergen sensitization with the unexpired extracts, each participant had a second skin test with the matched outdated one (up to 7 years after the expiration date). All pairs of extracts were from the same company, stored under identical conditions, and tested for microbiologic contamination. The results of 356 skin-prick tests between expired and 111 unexpired extracts were compared.

Results: None of the extracts had bacterial or fungal contamination. All outdated extracts produced a positive wheal reaction, with an average of 9.4 mm, which was not significantly different than the unexpired allergens. Seven years outdated lyophilized Hymenoptera extracts showed no significant differences in the wheal's size for the intradermal test at 1 µg/mL, between 5 and 9 mm.

Conclusion: Outdated allergen extracts were safe and did not seem to differ in potency and bioavailability from unexpired extracts for the detection of allergen sensitization by skin-prick testing. These results supported our hypothesis that allergen extracts have efficacy and bioavailability that extend beyond the expiry date provided by the manufacturer. For the diagnosis of aeroallergens and Hymenoptera sensitization, it seemed that allergens can be used beyond the expiration date.

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Every year, drugs worth millions of dollars are destroyed when they reach their expiration date.¹ The desire to maintain patient safety and drug effectiveness may stand in opposition to minimize pharmaceutical pollution and health-care system waste. Usually, after the expiration date, the manufacturer is no longer responsible for the efficacy or safety of the drug.² However, several studies^{3,5–7} indicate that, under certain conditions, many drugs may retain efficacy years after the original expiration date published by the manufacturer. The Shelf Life Extension Program was a U.S. Food and Drug Administration (FDA) study performed for the U.S. Army in which >3000 batches of 122 different drugs were tested.³ Eighty-eight percent of the drugs tested in the Shelf Life Extension Program study were acceptable for use even years after the original date of

expiration, with an average extension of 66 months after the original expiry date.³

Toxicity that results from the use of expired drugs is rare. In the 1960s, expired tetracycline resulted in reversible “Fanconi syndrome.”⁴ Recently, we observed a shortage of EpiPen (Mylan N.V., Hatfield, UK) (epinephrine) autoinjectors due to a lack of production as well as a lack of production of Hymenoptera venom extracts. The FDA took additional actions to mitigate shortages of EpiPen autoinjectors by extending the expiration date beyond the approved 20-month shelf life based on stability data.⁵ Studies performed on outdated epinephrine autoinjectors showed that the EpiPen contains at least 90% of the labeled dose up to 24 months, and 84–96% after 2–3 years after the expiry date, and retained at least 50% of labeled strength.^{6,7} For health-care systems, the financial significance of these expiration date extensions is enormous because a significant proportion of its budget is wasted on unused drugs that must be destroyed.

Allergen extracts form the pharmacologic basis for the diagnosis of sensitization to a specific allergen. The skin-prick test (SPT) performed by an allergist who uses allergen extracts is one of the most useful methods for diagnosis of allergy.⁸ However, these extracts are characterized by a short expiry date and relatively high prices. We hypothesized that the *in vivo* efficacy

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and bioavailability of the expired reagents for SPT will extend past the labeled expiry date and that these will be useful for the diagnosis of allergen sensitization in individuals with suspected allergy. In this study, we tested different outdated allergen extracts for their safety and efficacy to determine whether outdated allergen extracts are similar to unexpired extracts for detecting inhaled and Hymenoptera allergen sensitization. Our goal was to compare the same products as we use in clinical practice, without dilutions for potency, and to compare extracts “head to head” up to 7 years after the expiration date.

METHODS

Study Cohort

The study was performed after obtaining the Helsinki Committee approval from the E. Wolfson Medical Center, Holon, Israel (0018-16-WOMC) to perform outdated SPT. During the year 2017, individuals underwent clinical evaluation and SPT with the unexpired extracts, and were enrolled after providing signed informed consent. The study included 34 patients, ages 18–57 years, with allergic rhinitis or asthma; in addition, 5 patients with Hymenoptera hypersensitivity were included. Patients who were treated with oral antihistamine during the 7 days before the visit were excluded from the study.

M.L. Stein designed the research, took clinical care of the patients, enrolled individuals for the research, performed acquisition, analyzed and interpreted data, drafted and reviewed the manuscript, and gave final approval of the draft version. L. Ramikhanov

performed blinded SPTs and clinical evaluation of the individuals, and gave final approval of the drafted version. M. Boaz performed statistical data analysis, interpretation of data, drafted and reviewed the manuscript, and gave final approval of the draft version. O. Schwartz performed all the bacteriologic and fungal evaluations of the reagents, data analysis, and interpretation of bacteriologic results, and gave final approval of the draft version. Y. Faitelson provided clinical care of patients, enrolled individuals for the research, analyzed and interpreted the data and draft of the manuscript, and gave final approval of the draft version.

Allergen Extracts

All the allergen extracts (outdated and unexpired) were glycerinated and from a single company, (ALK-Abelló, Inc., Hørsholm, Denmark), being standardized for dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, 10,000 AU/mL), cat (10,000 BAU/mL), and grasses (timothy 100,000 BAU/mL, Bermuda 10,000 BAU/mL, mixed grasses 100,000 BAU/mL), and nonstandardized (1:20 weight/volume) for mold, weeds, Johnson grass, sagebrush, *Parietaria*, and trees, and were stored at 2°C–8°C, as recommended by the manufacturer. We used different outdated extracts for each allergen as depicted in Table 1. Histamine at 1 mg/mL was used as the positive control test for SPT and was compared with outdated histamine from year 2016.

Hymenoptera extracts (ALK-Abelló, Inc., Hørsholm, Denmark) included honey bee (HB), yellow jacket

Table 1 Characteristics of positive skin-prick test sensitizations for unexpired and outdated allergens

Allergen	Individuals with Positive Skin-Prick Test Responses, no. (%) (N = 34)						
	Unexpired Extracts*		Outdated Allergen Extracts [#]				
	2017	2016	2015	2014	2013	2012	2010
House-dust mites	28 (82)	28 (100)	27 (96)	NA	27 (96)	NA	28 (100)
Olive tree	22 (65)	22 (100)	22 (100)	22 (100)	NA	NA	NA
Grasses, mixed	14 (41)	NA	14 (100)	NA	NA	13 (93)	12 (86)
Cat	12 (35)	NA	12 (100)	12 (100)	NA	NA	NA
Sagebrush	9 (26)	NA	8 (89)	8 (89)	NA	8 (89)	9 (100)
Weeds	8 (24)	8 (100)	8 (100)	NA	NA	8 (100)	6 (75)
Pecan tree	7 (21)	NA	NA	6 (86)	NA	7 (100)	NA
Cypress	5 (15)	NA	5 (100)	5 (100)	NA	NA	NA
<i>Parietaria judaica</i>	3 (9)	3 (100)	NA	NA	NA	NA	NA
Molds	3 (9)	NA	NA	3 (100)	NA	NA	NA
Histamine	34 (100)	33 (97)	NA	NA	NA	NA	NA

NA = Not available.

*Characteristics of allergic sensitizations in the cohort of 34 individuals to the different aeroallergens for the current unexpired extracts (year 2017).

[#]Years of expiration date; positive skin-prick test responses of the outdated extracts compared with the unexpired matched extracts from year 2017.

(YJ), and wasp (W), and were kept lyophilized in the original flacons with the expiration date labeled for the year 2010. These outdated extracts were diluted 7 years later, during the year of our study (2017), for the comparison with the unexpired Hymenoptera venom extracts. Intradermal skin testing was performed in an open-labeled way, at concentrations from 0.01 to 1 $\mu\text{g}/\text{mL}$.

Assessment of Contamination of Allergen Extracts

A sample (0.1 mL) collected from each extract solution was aseptically cultured in duplicate on three culture media: chocolate agar (BD, Sparks (BD Diagnostics, Sparks Glencoe, MD)) and blood agar (Hy-Lab Ltd, Rehovot, Israel) for bacteria, and Sabouraud dextrose agar (Hy-Lab) for fungi. The plates were incubated for a week at 35°C in an atmosphere that contained 5% CO₂, except the Sabouraud dextrose agar, which was incubated at 26°C. The procedures were performed by the microbiology laboratory personnel of E. Wolfson Medical Center.

SPT Procedure

Skin testing was performed in two steps. The first step was performed by using the unexpired allergens. SPTs were done as previously described.⁹ For the Hymenoptera venom extracts, each participant underwent SPT and intradermal testing with unexpired and with outdated extracts. Positive reactions were defined as a wheal of ≥ 3 mm. After diagnosing the individuals with allergy and with the positive reactive allergens, a second step was done blindly for the outdated relevant extracts. Vials for the outdated allergen extracts were masked with code numbers for the different outdated years of the same allergen. Allergens causing positive reactions that were identified in the first step with the unexpired allergens were used in the second step with the relevant outdated ones. The second step was done immediately after the first step, within 20–40 minutes, in the opposite arm of the participating individual. SPT wheal and flare were measured in both steps by the same nurse (L.R.), who was blinded to the expiration dates. The results were recorded on an Excel spreadsheet (Microsoft, Washington). Only the principal investigator (M. S.) had the code key for the expiration dates.

Statistical Analysis

Statistical analysis was performed by using GraphPad Prism for Windows version 4.0 (GraphPad Software, San Diego, CA). Data were assessed for normality by using the Kolmogorov-Smirnoff test. Normally distributed data are expressed as mean $\pm$ standard deviation. Data with distributions that significantly deviated from normal are presented as median (interquartile range). The outdated allergen extracts were compared with the

matching unexpired one by using the *t*-test for paired samples or the Wilcoxon signed rank test, as appropriate. Tests were considered significant at $p < 0.05$.

RESULTS

Sterility and Safety of Outdated Allergen Extracts

For our study, we used outdated allergen extracts that were between 2 and 7 years after the expiration dates. Testing for bacterial and fungal contamination was performed for all the outdated allergen extracts and for the histamine control before being used. After 1 week of incubation, no growth was observed on any one of the three cultured media. None of the participants had any adverse effects from the SPT or the extracts.

Study Population and Clinical Characteristics

During the study period, we enrolled 34 individuals, 16 women and 18 men, mean age 21 years (range, 17–57 years), all with allergic rhinitis. Two participants were also diagnosed with asthma and two with atopic dermatitis. The most common aeroallergens sensitizations were to house-dust mite (82%), followed by olive pollen (65%) and grasses (41%). Multiple sensitizations were observed in 25 of the individuals (74%), with a median of three different allergens per individual. The characteristics of allergic sensitizations to the different aeroallergens and their SPT responses for the unexpired and all the outdated allergens are depicted in Table 1. For most of the allergens, SPTs were performed for two or more different outdated years, but, for *Parietaria* and molds, only one outdated extract was available. Overall, 356 SPTs of the outdated extracts were compared with the matched 111 SPTs of unexpired extracts, as described in the methods section.

SPT Responses to Outdated Aeroallergens

All the outdated allergens produced a positive, >3 mm, result with an average $\pm$ SD of 9.4 ± 4.9 mm, which was not significantly different from the unexpired allergens, average $\pm$ SD of 9.8 ± 5.4 mm, and compared with histamine average $\pm$ SD wheal reaction of 5.4 ± 1.6 mm and 5.8 ± 1.5 mm for outdated and the unexpired histamine positive controls respectively (Fig. 1, A–D). The analyses of the different allergens are depicted in Fig. 2, A–H and the Online Supplemental Fig. 1. No significant differences were observed between the unexpired and outdated extracts in terms of wheal size for any of the allergens, with the exception of one batch of weed extract from December 2016 that produced a mildly, but statistically significant, smaller average wheal of 4 mm compared with 7 mm of the unexpired extract. Nevertheless, this difference showed a wheal reaction that was still positive for the diagnosis of allergic rhinitis due to weeds.

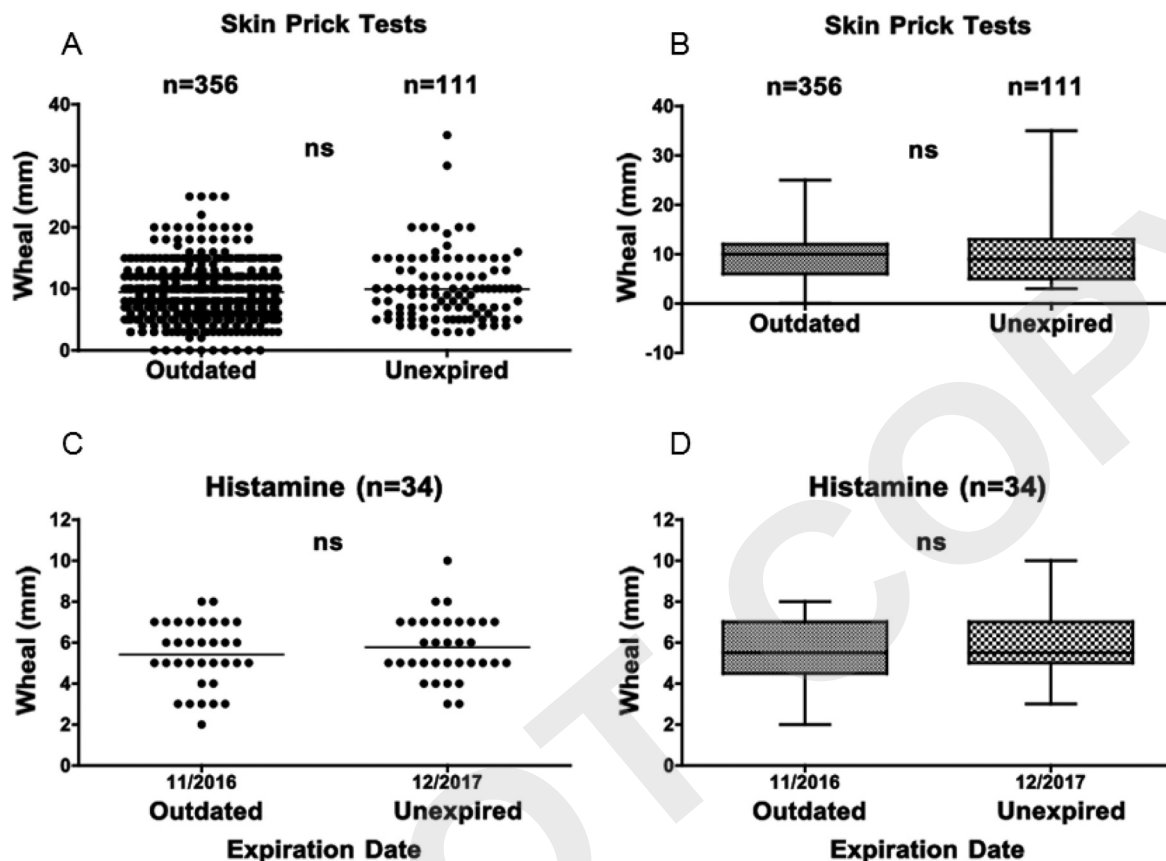


Figure 1. Skin-prick test responses to outdated and unexpired extracts. The wheal responses measured for the different outdated extracts are compared with the unexpired ones. (A) Allergens are represented as group distribution, with the mean shown by the horizontal line, and (B) by box-and-whisker plots with interquartile and median values. (C, D) Outdated histamine positive control test, at 1 mg/mL for outdated and current unexpired reagents are shown. NS = Not significant.

Failure to Detect Sensitization with Outdated Allergens

Although there were no statistically significant differences between unexpired and outdated allergens in the whole cohort, false-negative responses were found in 11 of 356 SPTs (3%), such that false-negative responses were observed in only one individual each for dust mites, grasses, sagebrush, and pecan tree, and in two individuals for outdated weed extracts. No false-negative responses were found for cat, mold, *Parietaria judaica*, and olive and cypress trees. There were no false-negative responses for any outdated extracts at 2 years after the expiration date, except for one individual, who had negative SPT results for dust mites and sagebrush but had a positive SPT result for the 7 years outdated dust mites and sagebrush extracts. Interestingly, some of the outdated extracts produced larger wheal reactions than the unexpired ones. All of the individuals had positive SPT results at 1 or 2 years of expiration date for all of the outdated allergen extracts. Characteristics of the outdated extracts that failed to detect sensitization by SPT are depicted in Table 2.

Outdated Hymenoptera Extract Sensitizations

The group with Hymenoptera allergy included five men, with an average $\pm$ SD age of 18.6 ± 2.7 years. Hypersensitivity reactions were found in three patients for HB, three for YJ, and two for W. Two individuals had multiple sensitizations. We compared the wheal reactions of the five individuals who had positive Hymenoptera sensitizations to extracts at 1 μ g/mL for the year 2017 with the outdated extracts from 2010 being 6.8 ± 1.8 mm and 8.4 ± 1.5 mm, respectively (Fig. 3). Two individuals were highly sensitized at 0.01 μ g/mL, one for HB and one for YJ. Their wheal responses were 5 and 8 mm for the unexpired extracts and were 4 and 8 mm for the outdated extracts, respectively. One individual who was sensitized to YJ at 0.1 μ g/mL did not show a sensitization response for the outdated extract but did show a positive response for W sensitization for both unexpired and outdated extracts at 1 μ g/mL.

Outdated Histamine Positive Control

One year outdated histamine at 1 mg/mL did not show any significant differences in SPT wheal compared

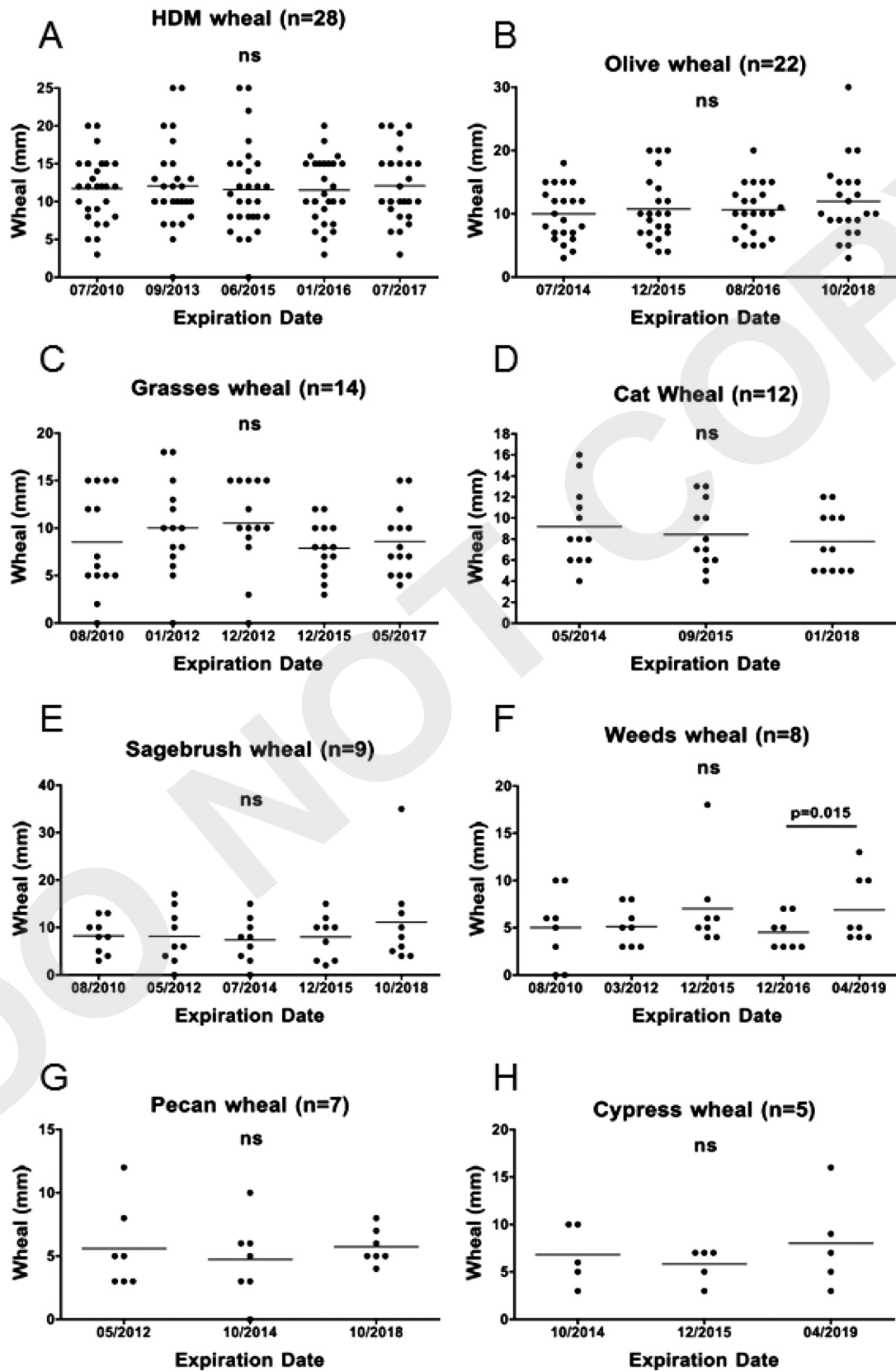


Figure 2. Skin-prick test to outdated extracts allergen sensitizations (A–H). The wheal responses measured for the different outdated extracts are compared with the matching unexpired one. Allergens are represented as group distribution, with the mean shown by the horizontal line. NS = Not significant.

Table 2 Characteristics of outdated extracts that failed to detect sensitization

Allergen	Outdated SPT (N = 356)	
	Number of SPT performed with the outdated allergen	Number (%) of false negative SPT with the outdated allergen
House-dust mites	112	2 (1.8)*
Olive tree	66	0
Grasses, mixed	56	3 (5.4)*
Cat	24	0
Sagebrush	36	3 (8.3)*
Weeds	32	2 (6.3)
Pecan tree	14	1 (7.1)
Cypress	10	0
<i>Parietaria judaica</i>	3	0
Molds	3	0
Total allergens	356	11 (3.1)
Histamine	34	1 (2.9)

SPT = Skin-prick test.

*SPT in the same individual at different outdated years.

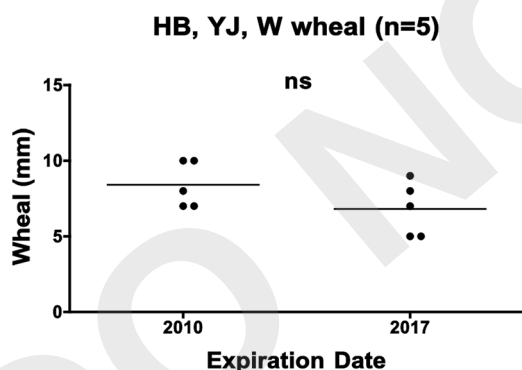


Figure 3. Hymenoptera outdated intradermal test. Intradermal skin testing at 1 μ g/mL, for honey bee venom (HB), yellow jacket (YJ), and wasp (W) outdated year 2010 and current unexpired year 2017 venom extracts. Hymenoptera venom extracts are represented as group distribution, with the mean shown by the horizontal line. NS = Not significant.

with the unexpired 2017 reagent, at 5.4 ± 1.6 and 5.8 ± 1.5 mm for outdated and unexpired responses, respectively. One individual did not respond to the outdated test (Table 1 and Fig. 1, C and D).

DISCUSSION

The use of allergen extracts for the diagnosis and treatment of allergic disorders encourages the clinicians to have a constant supply of reagents. Extracts are not always available in some countries, and the

relatively short shelf life of the products forces clinicians to buy larger quantities of reagents. These are not always used, which increases expenses and waste because many extracts are discarded before they are completely used.

In this study, we tested different outdated allergen extracts for their safety and efficacy. We observed no adverse reactions and no bacterial or fungal contaminations up to 7 years after the expiration date in extracts stored according to manufacturer recommendations. Outdated allergen extracts did not significantly differ in terms of potency and bioavailability from unexpired ones for detecting aeroallergens and Hymenoptera venom sensitization. It is tempting to conclude that outdated allergen extracts are also effective for immunotherapy, but this conclusion cannot be made based on our data, and we do not suggest that, because further studies that address this issue need to be done. Another limitation of our study was that we could not get older outdated extracts to learn how many more years are needed from the expiry date for an extract to lose its potency.

The present study used an *in vivo* human real-life model in which SPT was performed in the same individual by using unexpired and the outdated matched allergen extracts. By using the individual as his or her own control for each allergen tested, we isolated extract variability from between-person variability. This eliminated the need to perform *in vitro* studies, extract competition, enzyme-linked immunosorbent assay, or dilutional titration of extracts to prove our hypothesis. Each pair of unexpired and outdated extracts were manufactured by the same company, which eliminated by-company differences in manufacturing that could influence potency. This strengthened our conclusion that outdated reagents have longer shelf-life activity than the labeled date. Furthermore, in our study, all outdated extracts produced a positive wheal reaction, which did not significantly differ from the unexpired allergens (9.4 ± 4.9 versus 9.8 ± 5.4 ; $p = 0.78$). Similarly, unexpired histamine 1 mg/mL as a positive control produced a wheal reaction that did not significantly differ from the reaction produced by histamine 1 year after the expiration date (5.8 ± 1.5 mm and 5.4 ± 1.6 mm, respectively; $p = 0.3$).

False-negative responses were observed in 11 of 356 outdated SPTs (3%). These occurred in only one individual for SPT for dust mites, mixed grasses, sagebrush, and pecan tree, and in two individual SPTs for weeds. In the few participants with false-negative results, the size of the wheal produced by the unexpired extract was relatively small (3–4 mm). This can be attributed to low sensitization in a given individual and possibly to technical error when performing the SPT because we did not repeat a second outdated SPT. Interestingly, the other outdated extracts in the same

individuals were positive for those allergens, and some of the outdated extracts produced larger wheal reactions than the unexpired extracts. No false-negative responses were found up to 2 years of the expiration date for all the outdated extracts. Notably, 100% of the SPT responses after the expiration date of the outdated extracts were found at 7 years for house-dust mites and sagebrush; at 5 years for pecan tree and weeds; at 3 years for olive and cypress trees, cat, and molds; and at 2 years for grasses (Table 1).

Pharmaceutical companies provide an expiry date for the period in which the drug has been proven to be safe and effective.¹⁰ However, studies performed by using outdated drugs showed similar potency and activity as unexpired drugs.^{11,12} Outdated epinephrine autoinjectors have shown at least 90% of the labeled dose up to 24 months after the expiry date.^{6,7,12} For nonstandardized extracts, the FDA defines expiration dates for products in 50% glycerin to be 3 years after shipping and allows the manufacturer up to 3 years refrigerated storage for a total of 6 years.^{13–15} However, a web site search for manufacturer recommendations for some standardized extracts indicated that the shelf life is only 3 years, and, once opened, a maximum of 6 months storage is recommended.¹⁶

In addition, for Hymenoptera extracts, the recommended shelf life according to the manufacturer's leaflet brochures decreased over the years, being 12 and 6 months for the years 2010 and 2017, respectively, for a 100- μ g/mL concentration. Furthermore, for 1–10 μ g/mL, the manufacturer's recommendation was 1 month from the day of dilution for a lot from year 2010, but only 24 hours for a lot from the year 2017 (Online Supplemental Fig. 2). The company indicates that the venom protein extracts are stable and did not change throughout the years.^{13–15} The recent lack of Hymenoptera venom extracts could be prevented by extending their shelf life. This would decrease the possibility that patients would be affected by this shortage. Our findings indicate that outdated lyophilized extracts 7 years after expiry showed no significant differences in intradermal wheal reactions compared with unexpired extracts.

CONCLUSION

We performed 356 SPT in a head-to-head comparison of expired and unexpired extracts by comparing pairs of extracts in the same individual, and concluded that expired extracts were potent beyond the expiration date labeled. Further, these expired extracts produced no adverse events. It thus seemed that extracts were safe and effective to use at least 2 to 7 years after the expiry date recommended by the manufacturer. We suggest that procedures for determining expiration

dates be reevaluated as has been done for other drugs.¹⁷ This could reduce costs to health-care systems and prevent product shortages and minimize pharmaceutical waste.

REFERENCES

1. Tchen J, Vaillancourt R, Pouliot A. Wasted medications, wasted resource. *Can Pharm J* (Ott). 2013; 146: 181–182.
2. Drugs past their expiration date. *JAMA*. 2016; 315:510–511.
3. Lyon RC, Taylor JS, Porter DA, Prasanna HR, Hussain AS. Stability profiles of drug products extended beyond labeled expiration dates. *J Pharm Sci*. 2006; 95:1549–1560.
4. Frimpter GW, Timpanelli AE, Eisenmenger WJ, Stein HS, Ehrlich LI. Reversible “Faconi syndrome” caused by degraded tetracycline. *JAMA*. 1963; 184:111–113.
5. Eisenman T. FDA In Brief: FDA takes additional action to mitigate shortages of EpiPen by extending expiration date for specific lots of medication, August 21, 2018 [cited]. Available from: <https://www.fda.gov/news-events/fda-newsroom/fda-brief>.
6. Simons FE, Gu X, Simons KJ. Outdated EpiPen and EpiPen Jr autoinjectors: past their prime? *J Allergy Clin Immunol*. 2000; 105:1025–1030.
7. Rachid O, Simons FE, Wein MB, Rawas-Qalaji M, Simons KJ. Epinephrine doses contained in outdated epinephrine autoinjectors collected in a Florida allergy practice. *Ann Allergy Asthma Immunol*. 2015; 114:354–356.e1.
8. Bernstein IL, Storms WW. Practice parameters for allergy diagnostic testing. Joint Task Force on Practice Parameters for the Diagnosis and Treatment of Asthma. The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 1995; 75(Pt 2):543–625.
9. Bernstein IL, Li JT, Bernsetin DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008; 100 (Suppl 3):S1–S148.
10. International Conference on Harmonization. Guidance for industry Q1A(R2) stability testing of new drug substances and products, November 2003 [cited 2015 July 23]. Available from: <http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm073369.pdf>.
11. Cantrell L, Suchard JR, Wu A, Gerona RR. Stability of active ingredients in long-expired prescription medications. *Arch Intern Med*. 2012; 172:1685–1687.
12. Cantrell FL, Cantrell P, Wen A, Gerona R. Epinephrine concentrations in EpiPens after the expiration date. *Ann Intern Med*. 2017; 166:918–919.
13. Plunkett G. Stability of allergen extracts used in skin testing and immunotherapy. *Curr Opin Otolaryngol Head Neck Surg*. 2008; 16:285–291.
14. Plunkett GA, Mire B. How stable are allergenic extracts? *J Allergy Clin Immunol*. 2015; 135:AB58. <https://doi.org/10.1016/j.jaci.2014.12.1122>.
15. Plunkett G. Update: stability of allergen extracts to establish expiration dating. *Curr Opin Otolaryngol Head Neck Surg*. 2016; 24:261–269.
16. Summary of product characteristics. Alk Abelo. Soluprick SQ *Phleum pratense* DK/H/1263/001/R/001, May 2012. https://mri.cts-mrp.eu/download/DK_H_1263_001_FinalSPC.pdf.
17. Search List of Extended Use Dates to Assist with Drug Shortages. <https://www.fda.gov/drugs/drug-shortages/search-list-extended-use-dates-assist-drug-shortages>. Accessed 11 November 2019. □

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