

Dose Adjustment After Gaps in Administration of Subcutaneous Immunotherapy From a Past Survey: Work Group Report of the AAAAI Allergen Standardization and Allergy Diagnostics Committee



Désirée Larenas-Linnemann, MD^{a,*}, Punita Ponda, MD^{b,c,d,e,*}, Peter Creticos, MD^{f,g}, David Bernstein, MD^h, Tolly Epstein, MD^{i,j}, and Paul Williams, MD^{k,l} *Mexico City, Mexico; Manhasset, NY; Baltimore, Md; Crownsville, Md; Cincinnati, Ohio; Indianapolis, Ind; Seattle, Wash; and Everett, Wash*

“AAAAI Position Statements, Work Group Reports, and Systematic Reviews are not to be considered to reflect current AAAAI standards or policy after five years from the date of publication. The statement below is not to be construed as dictating an exclusive course of action nor is it intended to replace the medical judgment of healthcare professionals. The unique circumstances of individual patients and environments are to be taken into account in any diagnosis and treatment plan. The statement reflects clinical and scientific advances as of the date of publication and is subject to change.”

The allergen immunotherapy practice parameters third update recommendations on dose adjustment after a gap in administration during the build-up are based solely on expert opinion, and no recommendations for gaps during maintenance are given. In a previous survey among American Academy of Allergy, Asthma & Immunology (AAAAI) members on subcutaneous allergen immunotherapy, this was addressed, but details were never published. Members of the Immunotherapy, Allergen Standardization, and Allergy Diagnostics Committee of the AAAAI convened a workgroup to address this issue and reanalyze results on the particular survey section. Build-up: many practitioners start dose-adjusting if a patient comes in

14.1/14 days (mean/median) after the last dose and restart immunotherapy after an interruption of 85/90 days. Dosing frequency during maintenance is generally every 3 (12%) to 4 weeks (73%). Maintenance: allergists start dose-adjusting if a patient comes in 5.1/5 weeks (mean/median) after the last dose and completely restart after an interruption of 16/12 weeks (some replied in days [90.4/90 days] or months [4.43/4 months]). Subgroups: physicians with ≥ 11 years in practice in nonacademic centers or rural/suburban settings tolerate longer gaps before restarting subcutaneous immunotherapy (SCIT). There is no uniform dose-adjustment protocol after gaps in SCIT administration. Prospective studies shall have to help find

^aCenter of Excellence in Asthma and Allergy, Medica Sur Clinical Foundation and Hospital, Mexico City, Mexico

^bDivision of Allergy & Immunology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Great Neck, NY

^cDepartment of Pediatrics, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, New Hyde Park, NY

^dDepartment of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Northwell Health System, Manhasset, NY

^eInstitute of Health System Science, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY

^fDivision of Allergy & Clinical Immunology, The Johns Hopkins University School of Medicine, Baltimore, Md

^gCreticos Research Group, LLC, Crownsville, Md

^hDivision of Pneumology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, Ohio

ⁱDivision of Immunology, Allergy & Rheumatology, University of Cincinnati School of Medicine, Cincinnati, Ohio

^jAllergy Partners of Central Indiana, Indianapolis, Ind

^kDepartment of Pediatrics, Division of Allergy/Inflammation, University of Washington School of Medicine, Seattle, Wash

^lNorthwest Asthma and Allergy Center, Everett, Wash

*These authors contributed equally to this work.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 7, 2022; revised September 29, 2022; accepted for publication October 3, 2022.

Available online November 25, 2022.

Corresponding author: Désirée Larenas-Linnemann, MD, Hospital Médica Sur, Torre 2, cons. 602, Puente de Piedra 150, Col. Toriello Guerra, Del. Tlalpan, 14050 México D.F., Mexico. E-mail: Marlar1@prodigy.net.mx.

2213-2198

© 2022 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2022.10.036>

Abbreviations used

AAAAI- American Academy of Allergy, Asthma & Immunology
 AIT- Allergen immunotherapy
 CI- Confidence interval
 SCIT- Subcutaneous immunotherapy

the best trade-off between safety (dose reduction) without giving in on efficacy (too much dose reduction). © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:145-8)

Key words: Allergen immunotherapy; Subcutaneous immunotherapy; Adverse reactions; Dose adjustment; Adherence; Practice patterns

Subcutaneous immunotherapy (SCIT) has been practiced by allergists for over a century and is effective in the treatment of allergic rhinitis, allergic conjunctivitis, asthma, and venom hypersensitivity. Allergen immunotherapy (AIT) is recognized as the standard of care when medical management fails and/or when preferred over pharmacotherapy by an allergic patient. The immunotherapy practice parameters provide recommendations on patient selection, extract selection, extract preparation, route of delivery, therapeutic dose range, and other practices for the safe and effective administration of immunotherapy. However, there is very little currently available data that can be used to determine the ideal dose-adjustment schedule after a gap in administration. The immunotherapy practice parameters third update recommendations on dose adjustment after a gap in administration during the build-up are based solely on expert opinion. Although a survey and a retrospective study^{1,2} implied the need for standardization of dose-adjustment protocols after gaps in aeroallergen immunotherapy, the recommendations for adjustment after gaps during maintenance were not addressed in the last practice parameters update.³

The largest dataset on practice patterns of dose adjustment comes from a survey of American Academy of Allergy, Asthma & Immunology (AAAAI) members that was published in 2012.^{4,5} However, as the survey included multiple issues related to the practice of SCIT, detailed results on how allergists handle dose adjustment after gaps were not included in the publication.⁴

As we continue to wrestle with the impact of the COVID-19 pandemic on our clinical practices, many patients on AIT are experiencing prolonged gaps in their administration schedule. Without evidence-based guidance on how to adjust the SCIT dose for a patient who is late for a scheduled injection, the collective experience of our allergists may provide valuable insight into defining a standardized approach that effectively balances safety with optimization of dose.

We here present a reanalysis of the section of the 2012 SCIT (or AIT) survey that relates to a gap in dose adjustments, anticipating that this will increase our knowledge and identify unmet needs.

METHODS

Electronic surveys on practice patterns of SCIT were sent out by email in September 2010 to 4870 AAAAI members. Part of the questionnaire contained questions related to dose adjustment after

TABLE I. Demographic details of the participating physicians (n = 560)

	n	%
Years in practice		
≤5	110	20
6-10	74	13
11-15	64	11
>15	312	56
Academic center		
Yes	161	29
No	399	71
Setting of your clinic		
Rural	33	6
Suburban	307	55
Urban	220	39

gaps in administration during build-up (in days) and during the maintenance phase (in weeks); see the original article.⁴ The detailed results including analysis of subgroups, not available in the original publication, are presented here. Some interval questions were clearly misunderstood and replied in days instead of weeks or vice versa. These replies were corrected before analysis (see this article's Online Repository at www.jaci-inpractice.org); 2 replies of 0 were eliminated.

RESULTS

From the 1201 respondents, 560 replied in relation to dosing gaps (Table I). After a gap in dosing, 79% of the responders dose-adjust based on time elapsed since the last administration. During *build-up*, many practitioners start dose-adjusting if a patient comes in 14.1/14 days (mean/median) after the last dose. Table II shows how dose adjustment is accomplished. Most allergists adjust doses when the interval between doses is 14 days or more. In this case most (82%) opt for repeating the last dose. However, with longer gaps, most practitioners (62%-66%) prefer to decrease doses in categorical intervals, stepping down via the same stepwise protocol that was followed for up-dosing. However, a fair minority (16%-21%) chose to decrease doses using volume as a continuous interval by percent decrease (see Table II for further explanation). Most responders (83%) would restart immunotherapy for prolonged gaps: 12% restarting within 30 days, 24% within 60 days, and 30% with 90 days (mean/median 79/90 days).

Dosing frequency during *maintenance* is generally every 3 (12%) to 4 weeks (73%), but 4% gradually spaces dosing intervals starting from every 1 to 2 weeks the first year to every 4 weeks during the third year. Allergists start dose-adjusting if a patient comes in 5.1/5 weeks (mean/median) after the last dose. Just as during the build-up phase, the technique used to reduce dosing after prolonged gaps by about half of the physicians is going back 1 dose, 2 doses, and so on, whereas about a quarter prefer to reduce dosage by a certain percentage. Table III shows further details on how dose adjustment is accomplished during the maintenance phase.

When asked about when they would completely restart immunotherapy after an interruption during the maintenance phase, most replied (mean/median) in weeks (16/12 weeks), some in days (90.4/90 days), and others in months (4.4/4 months).

TABLE II. During build-up: how would you dose-adjust after missed doses?

After 1 missed dose* (N = 445)		After 2 missed doses† (N = 427)		After 3 missed doses‡ (N = 395)	
Adjustment made	n (%)	Adjustment made	n (%)	Adjustment made	n (%)
Repeat last dose	364 (81.8)	Reduce dose (2 doses back)	282 (66.0)	Reduce dose (3 doses back)	243 (61.5)
Lower by X percent: X = 29/25% (mean/median)	22 (4.9)	Lower by Y percent: Y = 35/25% (mean/median)	67 (15.7)	Lower by Z percent: Z = 49/50% (mean/median)	84 (21.3)
Lower by 2 doses	25 (5.6)	Reduce dose (3 doses back)	21 (4.9)	Reduce dose (2 doses back)	0
Other	34 (7.7)	Repeat last dose	0	Repeat last dose	0

Bolded row holds the most frequently given reply.

*The survey question did not refer to a certain time, but it would likely be 2 to 4 weeks after the last dose.

†The survey question did not refer to a certain time, but it would likely be 3 to 5 weeks after the last dose.

‡The survey question did not refer to a certain time, but it would likely be 4 to 6 weeks after the last dose.

TABLE III. During the maintenance phase: how would you dose-adjust after missed doses?

After 1 missed dose* (N = 402-403)		After 2 missed doses† (N = 374-375)		After 3 missed doses‡ (N = 353-354)	
Adjustment made	n (%)	Adjustment made	n (%)	Adjustment made	n (%)
Repeat last dose	218 (54.2)	Reduce to prior dose (2 doses back)	193 (51.6)	Reduce to prior dose (3 doses back)	176 (49.9)
Lower by X percent: X = 29.9/25% (mean/median)	69 (17.2)	Lower by Y percent: Y = 43.4/50% (mean/median)	103 (27.5)	Lower by Z percent: Z = 57.3/50% (mean/median)	92 (26.1)
Reduce volume by X mL: X = 0.13/0.1 (mean/median)	29 (7.2)	Reduce volume Y mL: Y = 0.19/0.2 (mean/median)	26 (6.9)	Reduce volume by Z mL: Z = 0.28/0.3 (mean/median)	19 (5.4)
Other	38 (9.4)	Other	41 (10.9)	Other	56 (15.8)
No dose adjustment	31 (7.7)	No dose adjustment	7 (1.9)	No dose adjustment	2 (0.6)
No plan for dose adjustment	17 (4.2)	No plan for dose adjustment	4 (1.1)	No plan for dose adjustment	8 (2.3)

Bolded row holds the most frequently given reply.

The survey question did not refer to a certain time. As 85% of responders dose every 3 to 4 weeks during maintenance, approximations might be:

*This should be 4 to 7 weeks after the last dose.

†This should be 7 to 11 weeks after the last dose.

‡This should be 8 to 15 weeks after the last dose.

Subgroup analyses

We carried out some subgroup analyses on the subgroups in Table I. The first one on how dosing adjustment is accomplished: calculating from the date of the last administered dose or from the date of the first missed dose. In this sense we did not see any remarkable differences between the groups, with 72%-88% calculating the gap since the last administered dose; see this article's Online Repository at www.jaci-inpractice.org.

The following 2 subgroup analyses were in relation to the gap that would oblige the physician to completely restart AIT, during the build-up and during the maintenance phase. Here, we did find some remarkable differences. During the build-up phase, physicians with more years in practice tolerate longer gaps before they decide to restart AIT than physicians with a shorter working experience: 83 days for ≥11 years in practice versus 68 days for ≤10 years in practice (difference 15.0 [95% confidence interval (CI): 5.3-24.6] days, $P < .005$). However, during the maintenance phase, the difference is only minimal and not significant: 17.3 weeks versus 16.2 weeks (Tables E1 and E4, available in this article's Online Repository at www.jaci-inpractice.org).

Interestingly, 24% of the allergists with ≥11 years in practice would tolerate a gap of 6 months or more before restarting.

Colleagues working in an academic setting more rapidly restart AIT from vial 1 after a gap in administration as compared with nonacademic physicians. This holds true during both the build-up and the maintenance phase. During build-up the difference between academics, restarting after 62.3 days, and nonacademics, restarting AIT from the start after 84.3 days, is 22 days (CI: 12.1-31.9 days, $P < .0001$), with nonacademics holding on 22 days more after a patient comes in late, before they decided to restart from vial 1; also during maintenance academics restart after 14.5 weeks as opposed to the 17.4 weeks of nonacademics (difference of 2.9 weeks [95% CI: 1.1-4.7 weeks], $P < .005$; Tables E2 and E5, available in this article's Online Repository at www.jaci-inpractice.org).

Also, colleagues working in an urban setting more rapidly restart AIT from the beginning after a gap in administration. During the build-up phase, urban colleagues restart after 68 days, and rural and suburban colleagues do this after 85 days (difference of 17 days [95% CI: 7.0-27 days], $P < .001$). The same

holds true during the maintenance phase where urban colleagues also start AIT all over again after a shorter gap in administration as compared with colleagues working in the suburban or rural areas. Urban physicians do this after a mean of 15 weeks after the last administered dose, whereas colleagues in suburban-rural centers restart maintenance from zero after 17.6 weeks, with a difference of 2.6 weeks (95% CI: 0.99-4.2 weeks, $P < .005$; Tables E3 and E6, available in this article's Online Repository at www.jaci-inpractice.org). This is also reflected in the difference between the median values.

DISCUSSION

Based on the results from the survey, which had replies from over 900 US practitioners who use AIT, it is observed that there is considerable variability in the frequency of SCIT dosing, and furthermore, that allergists adjust doses in a variety of ways after a gap in treatment. However, some underlying principles can be noted from these data.

During the *maintenance* phase (Table III), most responders stated that they would dose-adjust if the dose interval was greater than 4 to 7 weeks, consistent with the practice parameters that give a range of 2 to 6 weeks as an acceptable maintenance dosing interval. Only half of the responders used categorical step-down dosing, as a significant minority (17%-28%) decreased doses by percent of the last dose. A smaller number decrease the dose by volume (Table II). However, because the volume of the maintenance dose may be different between clinics, this further demonstrates the heterogeneity in dosing and dose adjustments. With a gap of more than 8 to 15 weeks, most responders (76%) would either decrease IT doses in 3 steps in their dosing protocol or decrease doses by an average of almost 60%.

Colleagues with longer working experience, those in nonacademic centers, and those working in suburban or rural areas tolerate longer dosing intervals during build-up and maintenance until they decide to restart SCIT.

The safety and long-term efficacy of specific dosing strategies after gaps is not known. Given the wide variability in dosing methods for routine build-up and maintenance SCIT, it is possible that dosing intervals could safely be extended during times such as the COVID-19 pandemic. Safety of larger gaps has been shown for venom immunotherapy, where dosing intervals can be successfully increased up to 3 months⁶ but not 6 months during maintenance.⁷ This emphasizes a meaningful opportunity to now study the safety and efficacy of *gap dosing* for aeroallergen immunotherapy.

The limitations of the work presented here are that the original data are 10 years old and it is very well possible that practices may have changed during the pandemics.

The AAAAI SCIT surveillance study has been capturing safety data in the United States, and no fatalities have been attributed to dosing gaps. Although this is encouraging, associations with grade 3 to 4 systemic reactions are unknown.⁸ The surveillance study is ongoing and has added gap-dosing questions, making it an extremely useful tool to capture safety data on this issue.⁹ We encourage all practitioners administering SCIT to participate (<https://tinyurl.com/AITAnnualSurvey>).

The long-term clinical efficacy of SCIT when given at the maintenance dose has been established, but it is not known if treatment gaps reduce long-term efficacy. Short-term clinical efficacy during build-up has been debated and is unlikely to occur until maintenance doses are achieved. Gaps in treatment can slow this process, and the amount of dose reduction can play a role in both short- and long-term efficacy. Ultimately, to truly address safety and efficacy of gap dosing, a prospective clinical trial would be ideal.

REFERENCES

1. Montgomery JR. The need for standardizing the aeroallergen immunotherapy missed-dose adjustment protocol. *Allergy Asthma Proc* 2008;29:425-6.
2. Webber CM, Calabria CW. Assessing the safety of subcutaneous immunotherapy dose adjustments. *Ann Allergy Asthma Immunol* 2010;105:369-75.
3. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127(Suppl):S1-55.
4. Larenas-Linnemann DE, Gupta P, Mithani S, Ponda P. Survey on immunotherapy practice patterns: dose, dose adjustments, and duration. *Ann Allergy Asthma Immunol* 2012;108:373-8.e3.
5. Ponda P, Mithani S, Kopyltsova Y, Sison C, Gupta P, Larenas D, et al. Allergen immunotherapy practice patterns: a worldwide survey. *Ann Allergy Asthma Immunol* 2012;108:454-9.e7.
6. Cavallucci E, Ramondo S, Renzetti A, Turi MC, Di Claudio F, Braga M, et al. Maintenance venom immunotherapy administered at a 3-month interval preserves safety and efficacy and improves adherence. *J Investig Allergol Clin Immunol* 2010;20:63-8.
7. Goldberg A, Confino-Cohen R. Effectiveness of maintenance bee venom immunotherapy administered at 6-month intervals. *Ann Allergy Asthma Immunol* 2007;99:352-7.
8. Epstein TG, Liss GM, Berendts KM, Bernstein DI. AAAAI/ACAAI subcutaneous immunotherapy surveillance study (2013-2017): fatalities, infections, delayed reactions, and use of epinephrine autoinjectors. *J Allergy Clin Immunol Pract* 2019;7:1996-2003.e1.
9. Dhamija Y, Epstein TEG, Bernstein DI. Systemic allergic reactions and anaphylaxis associated with allergen immunotherapy. *Immunol Allergy Clin North Am* 2022;42:105-19.

ONLINE REPOSITORY

DATA CLEARING

As the question on the dosing gap that calls for a dose adjustment during build-up was asked in days and that during the maintenance phase was asked in weeks, there were a significant number of physicians replying to the first question in weeks (eg, 3, 4, and 5) and vice versa to the second question in days (eg, 60, 90, and 120). We analyzed all replies given to these 2 questions, one on the side of the other, and looked for the plausible correction whenever the dosing interval to restart AIT during build-up was larger than the gap in administration during the maintenance phase. Also, replies as exemplified above, where it is clear that the physician refers to weeks and not days or days and not weeks, were corrected.

These interval corrections were carried out on the full dataset, blinded for subgroups.

I When a patient comes in late, dose adjustment is based on....

In relation to years in practice we could not find any difference between subgroups. In general, 72% to 81% bases the dose adjustment on the time elapsed since the last given dose, whereas around 17% to 27% calculates depending on the time elapsed since the last missed dose (Figure E1).

As for the comparison between academic and nonacademic settings, we see the same pattern, with no difference between both. Between 75% and 80% bases the dose adjustment on the time elapsed since the last given dose (Figure E2).

As for urban versus rural settings, clinics situated in rural settings tend to base the dose adjustment after missed doses more frequently on time elapsed since the last administered dose (88%), although this difference is not significant ($P = .12$) (Figure E3).

II When to completely restart AIT after a gap during build-up

During build-up colleagues would completely restart AIT after a gap in administration of 60-90 days, depending on years in practice. Below 10 years of experience shows that the longer the years in practice, the longer the interval after the last given dose before the physician decides to restart AIT from zero. These differences are different with statistical significance: <5 years' versus >15 years' experience; the mean differs by 14.6 days ($P = .017$) (Table E1). When dividing the physicians into only 2 groups, ≤ 10 years' or ≥ 11 years' experience, the difference is 15.0 (95% CI: 5.3-24.6) days and the statistical significance rises to $P < .005$.

Colleagues working in an academic setting more rapidly restart AIT from the beginning after a gap in administration

during build-up. They do this after a mean of 62.3 days after the last administered dose, whereas colleagues in nonacademic centers restart build-up from zero after almost 3 months, with a difference of 22 days (CI: 12.1-31.9 days, $P < .0001$) (Table E2).

In line with the above on academic settings is the finding that colleagues working in an urban setting more rapidly restart AIT from the beginning after a gap in administration during build-up as compared with colleagues working in the suburban or rural area. Urban physicians do this after a mean of 68 days after the last administered dose, whereas colleagues in suburban-rural centers restart build-up from zero after 85 days, with a difference of 17 days (95% CI: 7.0-27 days, $P < .001$) (Table E3).

III When to completely restart AIT after a gap during maintenance

During maintenance colleagues would restart completely AIT after a gap in administration of YY weeks, depending on years in practice. Here we see again a tendency to restart after a longer interval in those with more years in practice, but the difference is less than 1 week, and not significant (Table E4). Also, comparing only 2 groups, ≤ 10 years' or ≥ 11 years' experience, the difference is just over a week, and not significant.

It is interesting to note that almost a quarter of the physicians with more than 10 years' experience restart AIT after a gap in administration of 6 months or more.

Colleagues working in an academic setting more rapidly restart AIT from the beginning after a gap in administration during build-up. They do this after a mean of 14.5 weeks after the last administered dose, whereas colleagues in nonacademic centers restart build-up from zero after almost 4.5 months, with a difference of almost 3 weeks (95% CI: 1.1-4.7 weeks, $P < .005$) (Table E5). This difference is less remarkable when comparing the median values.

In line with this is the finding that colleagues working in an urban setting more rapidly restart AIT from the beginning after a gap in administration during maintenance as compared with colleagues working in the suburban or rural area. Urban physicians do this after a mean of 15 weeks after the last administered dose, whereas colleagues in suburban-rural centers restart maintenance from zero after 17.6 weeks, with a difference of 2.6 weeks (95% CI: 0.99-4.2 weeks, $P < .005$) (Table E6). This is also reflected in the difference between the median values.

When asked about when to completely restart during build-up and during maintenance treatment, 119 of 482 (24.7%) indicated the same time-lapse; for this subgroup, the time indicated when they would completely restart AIT ranged between 6 and 52 weeks.

According to years-in-practice dose adjustment is based on:

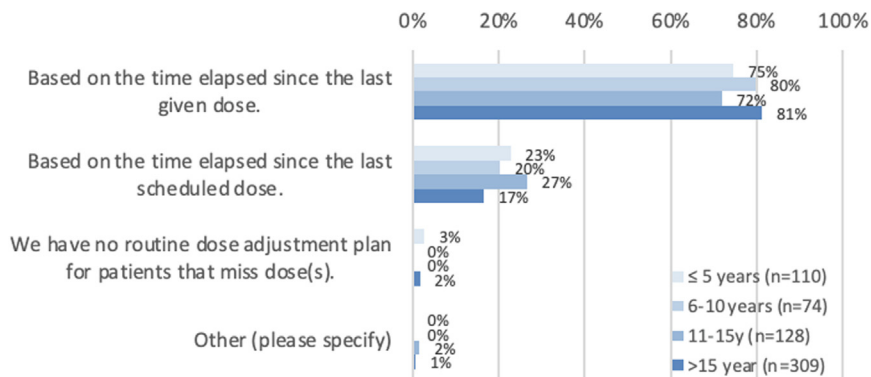


FIGURE E1. Physicians who practice allergen immunotherapy (AIT) were asked how their dose-adjustment schedule was for a patient who came in late for his AIT shot: if the decision to dose-adjust was based on the time elapsed since the last given dose, or since the last planned dose (scheduled but not given). Here the replies of the responding physicians (%) according to years in practice, ≤ 5 years (n = 110), 6 to 10 years (n = 74), 11 to 15 years (n = 128), or >15 years (n = 309).

In academic versus non-academic settings adjustment of dose is based on:

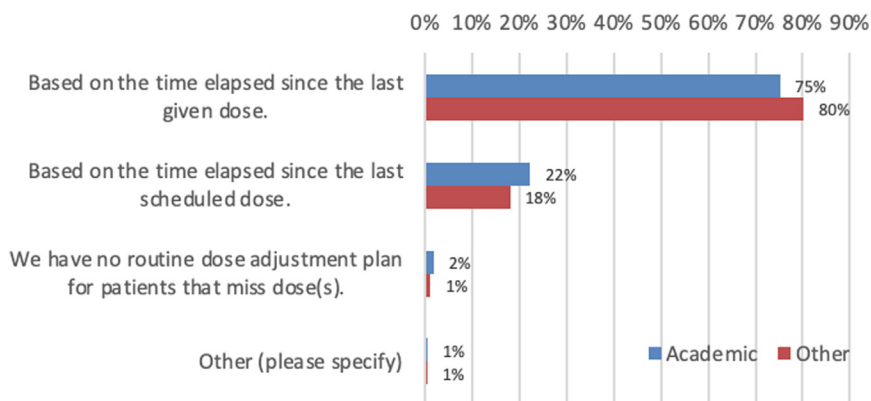


FIGURE E2. Physicians who practice allergen immunotherapy (AIT) were asked how their dose-adjustment schedule was for a patient who came in late for his AIT shot: if the decision to dose-adjust was based on the time elapsed since the last given dose, or since the last planned dose (scheduled but not given). Here the replies of the responding physicians (%) according to the settings of their practice, academic (n = 161) or nonacademic (n = 399).

In urban versus rural settings adjustment of dose is based on:

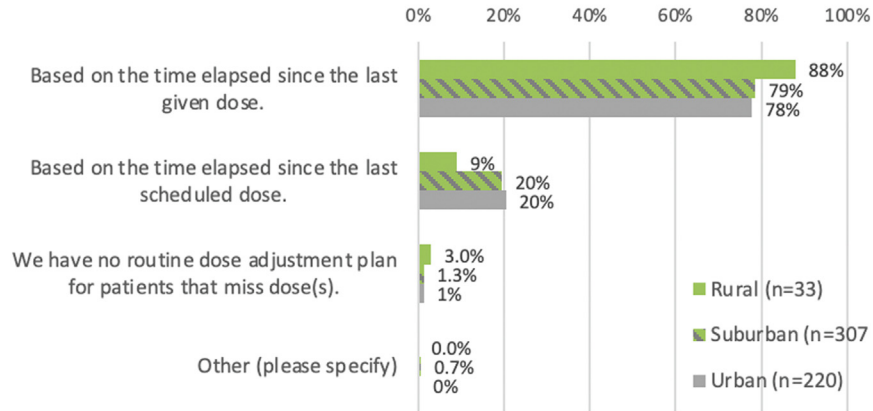


FIGURE E3. Physicians who practice allergen immunotherapy (AIT) were asked how their dose-adjustment schedule was for a patient who came in late for his AIT shot: if the decision to dose-adjust was based on the time elapsed since the last given dose, or since the last planned dose (scheduled but not given). Here the replies of the responding physicians (%) according to the site of their practice, rural (n = 33), suburban (n = 307), or urban (n = 220).

TABLE E1. Build-up: number of days after the last administration when the physician decides to restart allergen immunotherapy, according to years in practice

	<5 y	6-10 y	11-15 y	>15 y (n = 281)
Mean	67.8	68.6	87.1	82.4
SD	39.2	42.3	59.2	52.7
Median	60	60	90	60
Q1	30	30	52.5	60
Q3	90	90	95	90
IQR	60	60	42.5	30
N	87	61	51	281

IQR, Interquartile range; SD, standard deviation.

TABLE E2. Build-up: number of days after the last administration when the physician decides to restart allergen immunotherapy, according to clinical setting: academic or nonacademic

	Academic	Nonacademic
Mean	62.3	84.3
SD	44.3	51.7
Median	60	90
Q1	30	60
Q3	90	90
IQR	60	30
N	134	348

IQR, Interquartile range; SD, standard deviation.

TABLE E3. Build-up: number of days after the last administration when the physician decides to restart allergen immunotherapy, according to clinical setting: rural, suburban, or urban

	Rural	Suburban	Urban
Mean	84.9	85.0	68.0
SD	50.0	51.7	47.1
Median	90	90	60
Q1	60	60	30
Q3	90	90	90
IQR	30	30	60
N	29	267	184

IQR, Interquartile range; SD, standard deviation.

TABLE E4. Maintenance: number of weeks after the last administration when the physician decides to restart allergen immunotherapy, according to years in practice

	<5 y	6-10 y	11-15 y	>15 y
Mean	16.4	15.8	17.1	17.3
SD	19.4	7.0	7.6	9.7
Median	12	13	16	13
Q1	12	12	12	12
Q3	16	17	21	24
IQR	4	5	9	12
N	78	57	53	271

IQR, Interquartile range; SD, standard deviation.

TABLE E5. Maintenance: number of weeks after the last administration when the physician decides to restart allergen immunotherapy, according to clinical setting: academic or nonacademic

	Academic	Nonacademic
Mean	14.5	17.4
SD	6.2	9.3
Median	12	13
Q1	12	12
Q3	16	24
IQR	4	12
N	126	332

IQR, Interquartile range; SD, standard deviation.

TABLE E6. Maintenance: number of weeks after the last administration when the physician decides to restart allergen immunotherapy, according to clinical setting: rural, suburban, or urban

	Rural	Suburban	Urban
Mean	16.3	17.7	15.0
SD	7.2	9.5	7.1
Median	16	14	12
Q1	12	12	12
Q3	20.5	24	16
IQR	8.5	12	4
N	28	256	174

IQR, Interquartile range; SD, standard deviation.