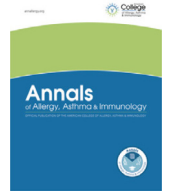




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Original Article

Home epinephrine-treated reactions in food allergy oral immunotherapy

Lessons from the coronavirus disease 2019 lockdown

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ARTICLE INFO

Article history:

Received for publication March 8, 2021.

Received in revised form April 20, 2021.

Accepted for publication May 9, 2021.

ABSTRACT

Background: Oral immunotherapy (OIT) is effective in desensitizing patients with food allergy but adverse reactions limit its use.**Objective:** To study the effect of the coronavirus disease 2019 lockdown in Israel between March 15, 2020, and April 30, 2020, on the incidence of home epinephrine-treated reactions.**Methods:** All patients who were in the up-dosing phase of OIT for greater than or equal to 1 month during the lockdown, or a respective period in years 2015 to 2019, were studied. The incidence of home-epinephrine treated reactions during the 2020 lockdown was compared with that in the respective period in 2015 to 2019 and to periods before and after the lockdown.**Results:** A total of 1163 OIT treatments were analyzed. Two epinephrine injections occurred during 2020 (0.7%) compared with 29 injections (3.28%) during 2015 to 2019 ($P = .03$). Patients treated in 2020 were older (8.1 vs 7 years, $P < .01$) and had a significantly lower single highest tolerated dose (12 vs 20 mg protein, $P < .01$). The rate of milk-OIT was lower ($P = .01$), but the total number of milk treatments was higher (99 vs 71 to 82) in 2020 compared with 2015 to 2019. On multivariate analysis, treatments during the 2020 lockdown were performed in older patients ($P = .001$), primarily for nonmilk ($P = .03$), began with a lower single highest tolerated dose ($P = .006$), and were associated with significantly less home epinephrine-treated reactions ($P = .05$) compared with those in 2015 to 2019. Patients treated in 2020 experienced more epinephrine-treated reactions in adjacent periods before ($n = 8$) and after ($n = 6$) the lockdown.**Conclusion:** The lower rate of home epinephrine-treated reactions during the coronavirus disease 2019 lockdown in Israel suggests that potentially avoidable triggers contribute significantly to the rate of adverse reactions during OIT.

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Introduction

Oral immunotherapy (OIT) is an effective treatment for desensitizing patients with food allergy.^{1–3} The recent approval of the Food and Drug Administration for a commercial peanut product for OIT may substantially expand the treatment availability.⁴ Nevertheless, the widespread application of OIT is limited by adverse reactions,⁵ which can be severe.⁶ Reactions that occur during the home treatment phase and specifically those requiring injectable epinephrine treatment represent its extreme. Although patients are guided to recognize severe reactions and to treat them promptly, such reactions still pose a risk,^{6,7} impair patient quality

of life,^{8,9} and affect treatment outcome.¹⁰ Attempts to reduce adverse reactions during OIT by starting treatment at an earlier age¹¹ or by using low doses of protein,¹² modified food proteins, or biologics¹³ either improved safety, but were less effective in achieving full desensitization, or are not as practical on a population level.^{11,13}

Certain intrinsic nonmodifiable patient characteristics (male sex, OIT to milk, asthma comorbidity, lower tolerated dose, and reactions requiring epinephrine during clinic up-dosing) have been described to be risk factors for home reactions during OIT.^{10,14–17} In addition, reactions frequently occur in the setting of various avoidable factors (exercise, fatigue, viral illnesses, etc), which may either increase the likelihood or trigger such reactions.^{7,18,19} Although patients are instructed to avoid these triggers during home dosing (eTable 1), the relative impact of

Reprints: Liat Nachshon, MD, Institute of Allergy, Immunology and Pediatric Pulmonology, Shamir Medical Center, Zerifin, 70300, Israel. E-mail: liatna2@gmail.com.**Disclosures:** The authors have no conflicts of interest to report.**Funding:** Dr Goldberg reports being funded by a Kamea grant from the Ministry of Health, Israel. The remaining authors have no funding sources to report.

intrinsic risk factors vs potentially avoidable triggers on the rate of adverse reactions during OIT is difficult to decipher.

Strict emergency laws of lockdown were applied in Israel between March 15, 2020, and April 30, 2020, in an attempt to prevent the outbreak of the coronavirus disease 2019 (COVID-19) pandemic. A ban was imposed on leaving the house for nonemergency purposes at a variable distance of 100 to 500 m, depending on the stage of the lockdown. The current study aimed to evaluate the effects of this lockdown and its associated drastic environmental and social changes on the rate of severe home reactions during the up-dosing phase of OIT, as determined by epinephrine treatment.

Methods

Patients

An open-label OIT treatment program was initiated in the Institute of Allergy, Immunology and Pediatric Pulmonology, at the Shamir (formerly Assaf-Harofeh) Medical Center for milk, egg, and peanuts in 2010, sesame in 2014, and tree nuts in 2016.^{20–23} A mandatory home web-based reporting system was introduced to the program in 2015, enabling documentation of home adverse events with minimal recall-bias.²⁴ All patients who underwent OIT to milk, egg, peanut, sesame, or tree nuts at our institute and were in the up-dosing phase of treatment for greater than or equal to 1 month between March 15 and April 30 of the years 2015 to 2020 were included. The 1-month minimal home treatment duration was chosen to ensure an adequate impact of the lockdown conditions on patients. Approval for the documentation and publication of all patient data were obtained from the institutional Helsinki review board committee.

Oral Immunotherapy Protocol

For inclusion in the OIT treatment program, patients had to have evidence of immunoglobulin (Ig) E-mediated allergy to the target food and to be able to tolerate a minimal dose of 5 mg protein in the case of milk and 1 mg in the case of all other foods.^{20–23} Patients with uncontrolled asthma were first stabilized for 2 to 3 weeks before OIT initiation. The treatment begins with determination of an individualized single highest tolerated dose (SHTD), defined as the highest dose given with no objective symptoms. The SHTD then serves as the starting home dose for each patient. The up-dosing phase consists of monthly dose escalations performed in an ambulatory care setting until patients reach a target maintenance dose of at least 180 mg milk protein (6 mL), 300 mg peanut (~1 peanut) or tree nuts (>1/4 walnut), 1500 mg egg (1/4 egg), and 240 mg protein of sesame (1 g of Tahini) (providing partial desensitization and protection in the case of accidental exposure) or continue to a full dose of milk (7200 mg protein), 3000 mg peanut, 3900 mg tree nuts, 12,000 mg egg, and 4000 mg sesame (providing full desensitization and enabling free consumption). After reaching partial or full desensitization, patients enter the maintenance phase, consisting of unlimited daily consumption of the treated food. The rate of home-epinephrine treated reactions during maintenance is minimal,^{21–23,25} and this phase was therefore excluded from the study.

Home Dose Instructions

Between dose escalations, patients are required to consume a daily dose at home under the supervision of an adult family member for at least 1.5 hours.^{20–23} Patients are instructed to avoid physical activity 30 minutes before and 2 hours after the dose, not to take the dose on an empty stomach or when fatigued, and, during viral illness, to pre-dose with antihistamines and give a reduced dose. Anticipatory home treatment guidance to patients and parents is given (eTable 1). No dose increase at home is permitted. Each patient is prescribed

antihistamines, bronchodilators, and 2 up-to-date epinephrine autoinjectors. An on-call staff physician is readily available 24 hours a day, 7 days a week. Patients are required to send a daily report of their home dose consumption by a web-based reporting system.²⁴ Patients are guided on the treatment of reactions and on the administration of an epinephrine autoinjector in the case of severe reactions (any reaction consisting of severe abdominal pain, shortness of breath, or lethargy, or whenever in doubt) (eTable 2). In the case of a reaction treated with injectable epinephrine, patients are advised to go to a local emergency department. During the lockdown, continuous internet and phone contact with the patients was maintained, patients were instructed to continue their home-dosing regularly, and the instructions for management of severe reactions have not changed.^{26,27} Given the COVID-19 regulations, only a limited number of patients were allowed to attend the clinic at any given moment. Still, our center was open and active during the entire lockdown period, and patient scheduling was designed to minimize changes in their treatment protocol.

Data Collection

The information was collected from the documentation in patient files, and all the reports were transmitted by e-mail and reporting website. To control for potential seasonal effects²⁸ and national holidays and events, patients treated during the lockdown in 2020 were compared with patients treated during the same time period in 2015 to 2019. Patients were included in the analysis for all the years during which they were still in up-dosing, either for the same or for different treatments. In addition, the number of home epinephrine-treated reactions patients experienced during the lockdown period was compared with that of the reactions the same patients experienced during adjacent periods of equal duration, before and after the lockdown.

Statistical Analysis

Statistical analysis was done using SPSS version 20 (IBM Corporation, Armonk, New York) software. Differences between patients treated in 2020 and those treated during 2015 to 2019 were explored using χ^2 test (or Fisher's exact test) for categorical variables. For continuous variables, the Mann-Whitney test was implemented. Multi-variable logistic regression was used, presenting adjusted odds ratios with correspondence 95% confidence intervals. Significance was determined when *P* value was less than .05.

Results

A total of 1163 OIT treatments were analyzed. Median age of patients was 7.3 years (range, 4–37 years) and 58.9% were of male sex. Asthma was diagnosed in 51.8% of the patients, and 71.7% were sensitized to house dust mite, the main aeroallergen in Israel.²⁹ The foods treated were milk, 487 patients (41.9%); egg, 53 (4.6%); peanut, 261 (22.4%); sesame, 112 (9.6%); and tree nuts, 250 (21.5%). Median (interquartile range [IQR]) up-dosing duration was 8.3 (3.9–14.1) months. Reactions requiring epinephrine injection during clinic up-dosing were experienced by 212 patients (18.2%). A total of 31 home reactions treated with epinephrine were experienced by 28 patients during the study period (18 for milk, 1 for egg, 3 for peanut, 2 for sesame, and 4 for tree nuts). The organ systems involved in these reactions are found in eTable 3. Less home epinephrine-treated reactions were experienced as up-dosing progressed, and their rate was significantly lower in patients who were beyond 8 months (the median duration for up-dosing) into up-dosing than those treated for less than 8 months (*P* = .004) (Fig 1).

The characteristics of the different OIT treatments performed each year are presented in Table 1. The expansion of the OIT treatment

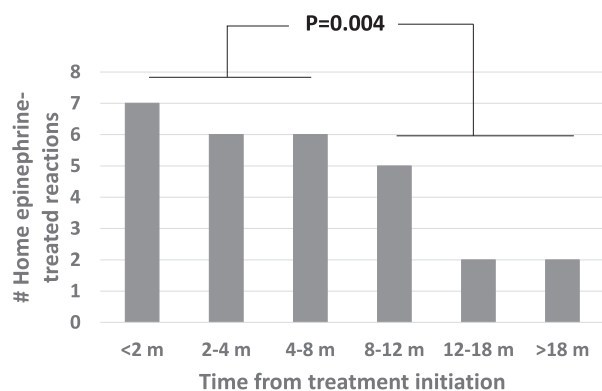


Figure 1. The number of home epinephrine-treated reactions for different treatment durations. The number of home epinephrine-treated reactions occurring in OIT between March 15 and April 30 in 2015 to 2020 for patients with different durations in treatment. Comparison was made between the rate of reactions in patients who were less than 8 months vs greater than or equal to 8 months in treatment. OIT, oral immunotherapy.

program in the past 6 years is reflected in the number of treatments analyzed per year. Patients treated in 2020 were older compared with those treated during 2015 to 2019 (8.1 vs 7 years, $P < .01$) (Table 1). The rate of male sex and asthma comorbidity was comparable between the groups. The relative percentage of foods treated changed over the years, with a decrease in the rate of milk and an increase in tree nut-OIT, but the absolute number of treatments increased for most foods, including milk. Patients treated in 2020 had a significantly lower SHTD compared with those treated during 2015 to 2019 (12 vs 20 mg protein, $P < .01$). A comparable number of patients required epinephrine for reactions during in-clinic up-dosing (Table 1). A total of 29 home reactions experienced by 26 patients were treated with injectable epinephrine in 3.28% of the treatments between March 15 and April 30 during 2015 to 2019 (Fig 2). In contrast, only 2 such reactions (0.7% of the treatments) were documented in 2020 ($P = .03$). Three patients, 1 in 2016, 1 in 2017, and 1 in 2019 experienced 2 home reactions requiring epinephrine. All 3 were undergoing OIT for milk. On multivariate analysis, older age ($P = .001$), undergoing OIT to milk ($P = .03$), lower SHTD ($P = .006$), and less home epinephrine-treated reactions ($P = .05$) remained significantly different between the treatments provided during 2020 compared with 2015 to 2019 (Table 2). Treatments provided in 2020 were of longer duration compared with those in 2015 to 2019 (9.9 vs 7.7 months, respectively, $P < .001$). A higher percentage of treatments in 2020 was greater than or equal to 8 months of duration (61.3%) compared with 2015 to 2019 (48.6%; $P < .001$), but the absolute number of treatments with less than 8 months of duration in 2020 was similar to the preceding years (Fig 3).

Table 1
Comparison of Active Patients in Oral Immunotherapy During the 2020 Coronavirus Disease 2019 Home Lockdown and the Corresponding Period Each Year

Variables	2015 (n = 122)	2016 (n = 128)	2017 (n = 194)	2018 (n = 203)	2019 (n = 237)	2020 (n = 279)
Age (y)	7.0 (4.8–11.6)	7.0 (5.2–9.7)	6.5 (5.3–9.3)	6.9 (5.5–10.3)	7.5 (5.9–10.1)	8.1 ^a (6.2–11)
Male sex	70 (57.4)	76 (59.4)	110 (56.7)	120 (59.1)	150 (63.3)	159 (57.0)
Asthma	58 (47.5)	70 (54.7)	109 (56.2)	103 (50.7)	119 (50.2)	143 (51.3)
Milk OIT	78 (63.9)	80 (62.5)	77 (39.7)	71 (35.0)	82 (34.6)	99 ^a (35.5)
Egg OIT	6 (4.9)	7 (5.5)	10 (5.2)	9 (4.4)	12 (5.1)	9 (3.2)
Peanut OIT	33 (27.0)	33 (25.8)	46 (23.7)	50 (24.6)	47 (19.8)	52 (18.6)
Sesame OIT	5 (4.1)	7 (5.5)	23 (11.9)	26 (12.8)	22 (9.3)	29 (10.4)
Tree nuts OIT	0	1 (0.8)	38 (19.6)	47 (23.2)	74 (31.2)	90 (32.3)
SHTD (mg)	22 (10–60)	22 (12–90)	22 (10–60)	20 (10–60)	20 (6–43)	12 ^a (10–40)
Epinephrine-induction	18 (14.8)	21 (16.4)	33 (17.0)	42 (20.8)	46 (19.4)	52 (19.0)
Treatment duration	8.8 (4.3–12.3)	5.6 (3.8–11.1)	7.7 (3.7–13.4)	6.3 (3.5–12.4)	8.7 (3.6–14.8)	9.9 ^a (4.8–16.9)

Abbreviations: IQR, interquartile range; OIT, oral immunotherapy; SHTD, single highest tolerated dose.

NOTE. Numerical variables are non-normally distributed and are presented as n (%) or median (IQR).

^aRepresents significant differences between years 2015–2019 and the year 2020.

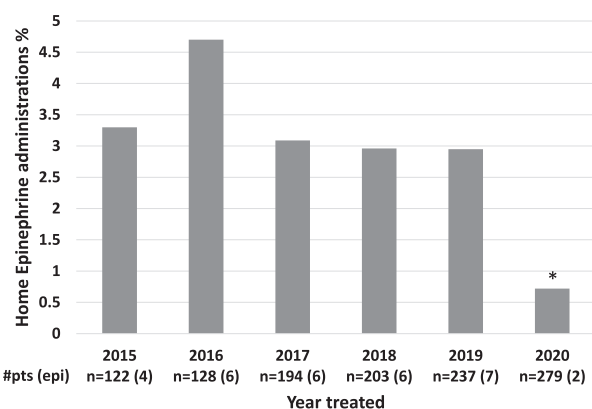


Figure 2. The rate of home epinephrine-treated reactions for each year. The rate of home epinephrine-treated reactions in patients who were in the build-up phase during the COVID-19 lockdown between March 15 and April 30, 2020, compared with the corresponding time periods in 2015 to 2019. The asterisk represents $P < .05$. COVID-19, coronavirus disease 2019. epi, epinephrine; Pts, patients.

Table 2
Multivariate Analysis for the Differences Between Year 2020 and Years 2015–2019

Variable	OR	95% CI	P value
Age (y)	1.004	1.002–1.006	.001
Male sex	1.09	0.83–1.43	.55
Milk OIT	1.35	1.02–1.8	.03
SHTD (mg)	0.997	0.995–0.999	.006
Home epinephrine	0.24	0.06–0.998	.05

Abbreviations: CI, confidence interval; OIT, oral immunotherapy; OR, odds ratio; SHTD, single highest tolerated dose.

We next compared the rate of home epinephrine-treated reactions during the 6 weeks of the COVID-19 lockdown with the 6 weeks before its initiation and the 6 weeks after its termination (when many but not all restrictions were removed). Only patients who were treated in all 3 time periods ($n = 261$) were included in this analysis. Compared with only 2 home-epinephrine treated reactions experienced during the COVID-19 lockdown, 8 such reactions were experienced in the 6 weeks before and 6 such reactions were experienced in the 6 weeks after the lockdown in the same patient-population, but the numbers were too small to meet statistical significance ($P = .11$) (Fig 4).

Discussion

This large case-control study evaluated whether reduction in environmental triggers can reduce severe home reactions, as represented by those treated with epinephrine, during the up-dosing

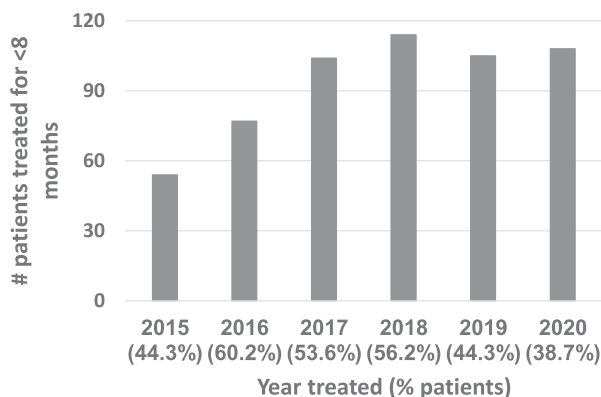


Figure 3. The number and rate of patients treated for less than 8 months for each year. The number and rate of patients whose treatment duration was less than 8 months at the time of the lockdown period in 2020 and the corresponding time periods in 2015 to 2019.

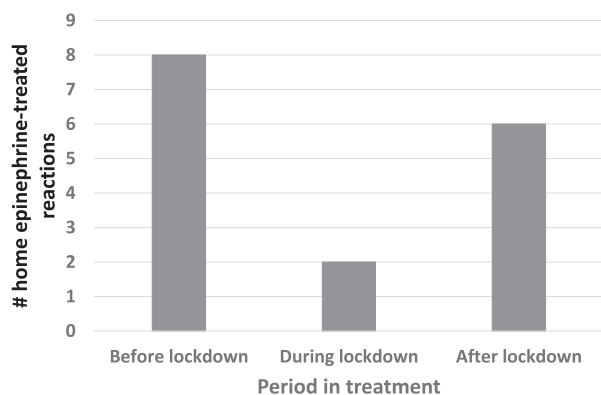


Figure 4. The number of home epinephrine-treated reactions before, during, and after the lockdown. The number of home epinephrine-treated reactions during the lockdown (March 15, 2020, to April 30, 2020) compared with comparable time periods before (February 1, 2020, to March 14, 2020) and after the lockdown (May 1, 2020, to June 16, 2020) in patients ($n = 261$) treated for greater than or equal to 1 month.

phase of OIT. The unique scenario of the COVID-19 lockdown enabled us to control for many environmental factors that are considered triggers of such reactions. We found a significant reduction in the rate of home epinephrine-treated reactions during the lockdown period compared with similar time periods in previous years and in the same year before and after the lockdown. These findings provide hope that better patient education and control of potential triggers would increase the safety of OIT even in patients with risk factors for severe reactions.

The safety of OIT is hampered by reactions to previously tolerated doses. Home reactions treated with intramuscular epinephrine represent its extreme and significantly affect treatment outcome.⁷ Certain nonmodifiable patient characteristics, including OIT to milk, asthma, lower SHTD, higher sIgE to the treated food, and epinephrine-treated reactions during clinic up-dosing, serve as risk factors for such reactions.^{10,14–16} In addition, specific factors might trigger such reactions by significantly reducing the eliciting dose in patients with food allergy, as recently revealed in the case of physical exercise and fatigue.³⁰ Therefore, OIT treatment programs typically instruct patients not to take home doses in the presence of, or in proximity to physical exercise, fatigue, and viral illnesses, which are considered potential triggers for such reactions.^{7,18,19,31} The first COVID-19 pandemic lockdown in Israel enforced reduction in many of these potential triggers. Parents and children were required to stay at home and were less exposed to outdoor triggers, such as temperature and aeroallergens.²⁸ The availability of physical activity and the burden and

fatigue associated with daily chores were probably reduced. These lifestyle changes could have contributed to the reduction observed in home epinephrine-treated reactions. Moreover, patients and parents themselves might have been more compliant with safety instructions because of their reluctance to attend the emergency department during the pandemic. In addition, patients were less exposed to viral illnesses, including COVID-19, whose prevalence in the Israeli population during the initial lockdown period was low.³² Regardless of the specific trigger, the significant reduction in the frequency of home epinephrine-treated reactions during the lockdown period provides a proof of concept that, given the proper conditions, the rate of adverse reactions during OIT could be minimized. Furthermore, this reduction occurred in patients who were at high risk for severe reactions, as evidenced by the larger number of milk-OIT treatments, lower SHTD, and older age.

The restrictions given on the number of patients who could attend the allergy clinic each day during the COVID-19 outbreak led to a delay in the up-dosing visits of some of the patients. As a result, these patients remained on the same dose for a period longer than the regular 1-month interval. It is possible that the longer duration patients remained on the same dose contributed to the reduced rate of home epinephrine-treated reactions. As was previously suggested,³³ consideration of this factor, which varies between OIT protocols, may minimize reactions during therapy. Nevertheless, the analysis revealing a high rate of epinephrine-treated reactions in the same patients treated before the beginning of the lockdown (shorter treatment duration) and after its completion (longer treatment duration) suggests that the impact of a longer interval between up-dosing rounds on the rate of severe reactions is mild.

Several confounding factors must be considered in this study. First, some patient characteristics gradually changed over the years, leading to differences between 2020 and previous years. Nevertheless, most of these changes (older patients' age, a lower SHTD) were expected to increase the risk of severe reactions. Second, the introduction of OIT to tree nuts in 2016 led to a relative reduction in milk-OIT (a significant risk factor for home epinephrine-treated reactions).¹⁰ Nevertheless, the absolute number of milk OIT treatments actually increased in 2020 in comparison to previous years. Furthermore, the difference between 2020 and 2015 to 2019 in the rate of home epinephrine-treated reactions remained significant after controlling for differences in milk OIT on multivariate analysis. Lastly, the use of epinephrine might not necessarily reflect all or exclusively the most severe reactions patients experience. Nevertheless, the use of epinephrine treatment represents an objective indication of patients' perception of a severe anaphylactic reaction.¹⁰ Moreover, the association found between these reactions and worse treatment outcomes further supports their use as an outcome measure.¹⁰

In summary, the current study reveals a significant reduction in the rate of home epinephrine-treated reactions during the COVID-19 lockdown in Israel. Naturally, lockdown restrictions are not only not practical in normal daily life but also not desirable for growing children. Nevertheless, this study suggests that increased awareness of potential triggers for severe reactions is essential, particularly in patients with intrinsic risk factors for such reactions. These patients might need to take more precautions on the daily dose, at least for the first several months of OIT, to improve treatment safety and achieve a protective dose. Efforts should be invested in identifying all potential triggers and in educating patients on efficient avoidance measures, to improve OIT safety.

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Supplementary Data

eTable 1
Instructions for Safe Home Dosing

Instruction	Condition
Precautions in home dosing	Avoid physical exertion 30 min before and 2 h after dosing Avoid taking the dose while fatigued
Premedicate with antihistamine	Avoid taking the dose on an “empty stomach” Mild symptoms of concurrent illness (a “cold”)
Premedicate with antihistamine and reduce dose (1/2 to 2/3 the regular dose)	Moderate symptoms of concurrent illness (fever, cough, emesis)
Do not dose without medical staff consult	Asthma exacerbation or wheezing Missing treatment on 2 adjacent d or more

eTable 2
Action Plan for Home Reactions

Grade of reaction	Symptoms	Treatment
Mild	Rash, periorbital swelling, runny nose, sneezing, mild abdominal pain or vomiting	Antihistamines
Moderate	Cough	Antihistamines and inhaled bronchodilator
Severe	Dyspnea or shortness of breath, severe abdominal pain, lethargy, or whenever in doubt	Intramuscular epinephrine and examination at an emergency department

eTable 3
Reported Organ System Involvement in Home Epinephrine-Treated Reactions

Year	Systems involved Patient number	Skin	Gastrointestinal	Respiratory	Cardiovascular
Total n (%)	—	24 (77.4)	13 (41.9)	23 (74.2)	1 (3.2)
2015	1	0	1	0	0
	2	1	0	1	1
	3	1	1	1	0
	4	1	1	0	0
2016	5	1	0	1	0
	6	1	0	1	0
	7	1	0	1	0
	8	0	1	0	0
	9	1	0	1	0
	10	1	0	1	0
2017	11	1	1	1	0
	12	1	0	1	0
	13	1	0	1	0
	14	1	0	1	0
	15	1	0	1	0
	16	1	0	1	0
2018	17	1	1	0	0
	18	1	1	1	0
	19	1	1	1	0
	20	0	0	0	0
	21	1	1	1	0
	22	0	1	0	0
2019	23	1	0	0	0
	24	1	0	0	0
	25	1	1	1	0
	26	0	1	1	0
	27	0	0	1	0
	28	1	0	1	0
	29	1	0	1	0
2020	30	0	1	1	0
	32	1	0	1	0