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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

DOI: 10.1111/pai.13540

## Food allergic reactions during the Covid-19 pandemic lockdown in Israeli children

To the Editor,

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2, has affected Israel along with most other nations during the current global pandemic. On March 19, 2020, a national state of emergency and lockdown was declared.<sup>1</sup> These events led to an extremely unusual situation in which children stayed only at home, with their primary caregiver. Therefore, we aim to determine the incidence, risk factors for food allergic reaction (FAR) and parental willingness to seek medical treatment during the COVID-19 pandemic lockdown compared to the preceding 3 months. An online questionnaire was developed by the authors using the Google drive application. The questionnaire comprised 32 items (Appendix S1) eliciting data about the food allergy (FA) diagnosis, number and nature of FARs before

and during the lockdown period, allergy treatment availability and follow-up. The survey began on April 19, 2020 and ended on May 21, 2020. The definition of a FAR was based on the symptoms characterization of the Food Allergy and anaphylaxis Emergency Care Plan (FARE).<sup>2</sup> Notably, this document is endorsed by the Israel Association of Allergy and Clinical Immunology, and distributed to every patient. A link to the questionnaire was posted on the website of Israel Food Allergy Support Network (YAHIEL). A total of 701 questionnaires were completed. Only patients diagnosed with IgE mediated FA by an allergist were included in the study. Fifty-six questionnaires were excluded (25- not diagnosed by allergist, 23-born in 2020, 6-OIT, 1-non-IgE allergy, 1-idiopathic anaphylaxis). Thus, the study included 645 children with FA (65.3% male; age 5.9 ± 3.7 years, range 0.3-18.5 years). Of these, 395 (61.2%)

were preschoolers ( $\leq 6$  years) and 250 (38.8%) were schoolchildren (6-18.5 years).

The SPSS 25.0 software (SPSS Inc) was used for data analysis. Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test at  $p = .01$ . Categorical variables were compared using the Pearson chi-square test with Z-test for column differences. The relative odds ratios were calculated for risk estimation. Logistic regression analysis was performed to evaluate the likelihood of FAR reaction during the lockdown. Categorical risk factors for FAR during the study period were calculated separately for the preschoolers and schoolers. Lockdown mean time for our study population was  $5.9 \pm 1.3$  weeks, median 6 weeks, range 2-8 weeks. During the lockdown, parents were the primary caregivers; mothers were in 97.5% (629/645) and fathers 81.3% (525/645) of the cases. Primary caregiver of 88 out of 645 children reported on 135 FARs

during the lockdowns. In accordance with Muraro et al.'s<sup>3</sup> grading severity of anaphylaxis, there were 10 mild, 11 moderate, and no severe reactions.

Regarding caregiver management, seven went to a medical facility, six consulted their physician, and eight managed the reaction without medical consultation. In seven of the children with moderate anaphylaxis, an adrenalin auto injector was used. Table 1 summarizes the rates and number of children reacting to each specific food allergen during the lockdown. For a reasonable comparison, we calculated that during a dummy lockdown of 3 months, the number of the FARs would be 270, which is still significantly less than 365 reactions during the 3 months before the lockdown,  $p < .00001$ . Similarly, less children had FARs during the lockdown period (176 vs. 212,  $p = .02$ ). The overall rate of FARs in the different age groups during lockdown period is presented in Figure 1.

**TABLE 1** Rates (percent) of specific food allergy, number of reacting children to specific food allergen during the lockdown

Food allergen	Number of children with specific FA (%) <sup>a</sup>	Number of children with specific reaction during lockdown (%) <sup>b</sup>	Number of food reaction during lockdown (%)
Milk	279 (43.26)	22 (25)	30 (22.2)
Peanuts	228 (35.35)	7 (7.95)	10 (7.4)
Sesame	204 (31.63)	8 (9.0)	11(8.1)
Egg	151 (23.41)	15 (17.05)	18 (13.3)
Tree nuts	290 (44.96)	20 (22.73)	22 (16.3)
Fish	60 (9.3)	2 (2.27)	2 (1.5)
Lentils	26 (4.03)	1(1.14)	2 (1.5)
Soy	13 (2.02)	3 (3.41)	4 (3.0)
Other <sup>c</sup>	56 (8.68)	4 (4.55)	7 (5.2)
Unknown*		20 (22.73)	29 (21.5)
All	645 (100)	88 (100)	135 (100)

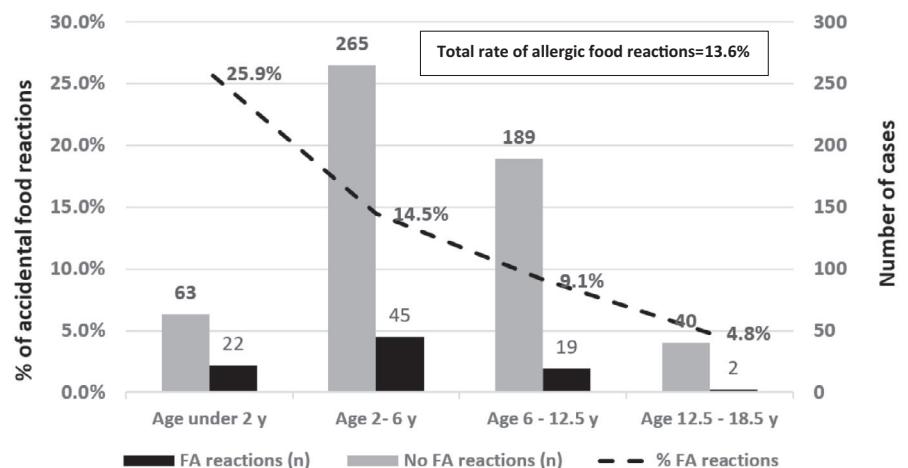
Abbreviations: FA, food allergy.

<sup>a</sup>Of the 645 children, 315 (48.8%) were allergic to only one food allergen and 330 (51.2%) were allergic to more than one (range 2-7).

<sup>b</sup>53 children (60%) had one reaction, 23 (26%) children had two reactions and 12 children (14%) had three reactions.

<sup>c</sup>Other relate to children with food allergy to pea, hummus, kiwi, avocado, peach, mustard, coconut, bean, zucchini, banana, wheat, tomato, melon, soya, curcumin and honey.

\*Unknown was defined as those with clinically allergic reaction without a clear identification of food allergen.



**FIGURE 1** Food allergic reactions in different age groups during lockdown period. FA, food allergy. The gray bars represents number of children who did not react to food allergen. The black bars represent number of children who had accidental food allergic reaction. The dashed line represents the percentage of allergic food reactions in each age group. The odds ratio of reactions among school-aged children compared to preschoolers was 0.5 (95% CI, 0.3-0.8)

The rate of reaction to a specific food allergen compared to the relative proportion of children in the study population who were allergic to a given allergen is presented in Table 2. Preschool-age children with multiple food allergies had significantly more FARs during the lockdown compared to children with allergy to only one food allergen (46/211 [21.8%] vs. 20/184 [10.9%],  $p = .005$ ), with a relative risk ratio of 2.02 (95% CI, 1.2-3.28, NNT = 9,  $p < .01$ ). Children who had a FAR in the 3 months before the lockdown were at higher risk of experiencing a FAR during the lockdown {(55/212 [25.9%] vs. 33/433 [7.6%],  $p = .0001$ ) and were 3.8 more likely to react during the lockdown period (95% CI, 2.27-5.04, NNT = 5.5,  $p < .001$ ). Children with three risk factors (previous FAR in the 3 months before the lockdown, more than one FA sensitivity and preschool age) had significantly more FARs during the lockdown compared to children with either one or two of these risk factors: 33% (30/91) versus 10.5% (58/554). Thus, these high-risk children had a relative risk ratio of 3.14 (95% CI, 2.15-4.6),  $p < .001$ , NNT = 4.4.

During the lockdown period, respondents reported that drug treatments for FARs were less available (9.5% versus 100%,  $p < .001$ ). Additionally, 124 out of 148 (84%) food challenges tests were canceled (47% by the primary caregiver). Significantly fewer children used any medical service, including ambulatory emergency services and GP clinics, compared with the rate before the lockdown period (4.9% and 58.4% respectively,  $p < .01$ ). Even in cases of a FAR, substantially fewer primary caregiver sought help from emergency rooms (10/645 vs 177/645,  $p < .0001$ ), urgent care centers (UCCs) (5/645 vs 77/645,  $p < 0.0001$ ) or their pediatrician/ family physician (14/645 vs 123/645,  $p < .0001$ ). In eight cases of AFRs, adrenaline auto injector was used. Details are presented in Table 3. Our findings show that FARs appeared at a significantly lower incidence during the lockdown period compared to the preceding 3 months. There are several possible explanations for this finding. Primary caregiver may have been more careful about what they fed their children during this period fearing that an allergic reaction would necessitate an

**TABLE 2** The rate of reaction to a specific food allergen compared to FA prevalence during the lockdown period

Food allergen	Number of children with specific food allergy <sup>a</sup>	% of specific food allergy	Number of reaction during lockdown <sup>b</sup>	% of all food allergen reactions	<i>p</i> -value <sup>c</sup>
ALL	1307	100.00	106	100.00	
Milk	279	21.35	30	28.30	.09
Peanut	<b>228</b>	<b>17.44</b>	<b>10</b>	<b>9.43</b>	<b>.03</b>
Sesame	204	15.61	11	10.38	ns
Egg	151	11.55	18	16.98	.09
Nuts	290	22.19	22	20.75	ns
Fish	60	4.59	2	1.89	ns
Lentils	26	1.99	2	1.89	ns
Soy	<b>13</b>	<b>0.99</b>	<b>4</b>	<b>3.77</b>	<b>.01</b>
Other FA	56	4.28	7	6.60	ns

Abbreviations: FA, food allergy.

<sup>a</sup>In order to compare between the rate of specific food allergen and the rate of reaction to the same food allergen during the lockdown we calculate the food allergies number according to the sum of food allergic sensitizations in the study population.

<sup>b</sup>We did not include reactions to unknown food allergen resulting in 106 food reactions instead of 135.

<sup>c</sup>Bold indicates  $p \leq .05$ .

Patient number	Age (y)	Sex	Allergen	Type of reaction	Medical facility	COVID-19 influence <sup>a</sup>
1	8.2	M	Not clear	RS	UCC	
2	4.5	M	Egg	RS, skin	Phone call	Yes
3	3.3	M	Milk	Skin, GI	ER	
4	3.6	M	Milk	RS, skin, GI	ER	
5	1.4	M	Not clear	Skin	ER	
6	5.5	M	Milk	Skin, GI, CNS	None	No
7	2.5	M	Milk	Skin, GI	ER	
8	4.3	M	Tree nuts	Skin, Rhinorrhea	Phone call	Yes

Abbreviations: CNS, central nervous system; ER, emergency room; GI, gastrointestinal; M, male; RS, respiratory system; UCC, urgent care center.

<sup>a</sup>Primary caregivers were asked if their decision to seek medical attention after using adrenaline auto injector was influenced by the COVID-19 pandemic.

**TABLE 3** Children with food allergic reactions treated with adrenaline auto injector

emergency room visit. Second, they acquired less food from restaurants, which is likely to diminish unintentional FARs. Additionally, it is possible that primary caregiver are indeed the best supervisors of their children, and during the lockdown simply spent more time supervising their child's food intake. Risk factors for FARs during the lockdown were young age, previous allergic reaction, and allergy to multiple allergens in preschool children. In keeping with our findings, it has been reported that preschool-aged children may experience food-induced anaphylaxis more often than older children, but the majority of food-allergic reactions in both preschool- and school-aged children are not anaphylactic<sup>4,5</sup> and deaths are rare.<sup>6</sup> With respect to a previous allergic reaction as a risk factor, several possible explanations suggest themselves, including personal parental or child characteristics, a low threshold for reaction, or lack of understanding of how to avoid the food allergen and how to manage allergic reactions.<sup>7,8</sup> Allergy to multiple food allergens was also a risk factor for FARs. Notably, primary caregiver used medical facilities less during the lockdown period than previously. This finding aligns with worrisome reports worldwide of reduction or delays in use of medical facilities in emergency cases.<sup>9,10</sup> While COVID-19 per se does not seem to represent a significant threat to the pediatric population, the fear of contracting COVID-19 may lead to delays in access to pediatric emergency facilities even in cases of anaphylactic reaction that were treated with adrenalin. Regarding the report that drugs were less available for FAR, it is possible that some of the emergency medications were utilized early in the lockdown or expired in the lapsed time. This study has several limitations. Our use of an online questionnaire distributed via social media may have led to selection bias. Consequently, our respondents may disproportionately represent individuals who are more educated, more technologically savvy, and of higher socio-economic status compared to the general Israel food-allergic population. Moreover, because the data were de-identified and medical records were not available, we were unable to confirm diagnoses of IgE-mediated FA. Notwithstanding these limitations, this is the first study to assess the incidence of FARs among children during the COVID-19 lockdown, which were significantly lower compared to the previous period. Established risk factors of young age and multiple food allergies for a FAR were similar during the lockdown, but primary caregivers were less likely to seek medical attention even with severe FAR. Our findings support that primary caregivers should be encouraged to continue their FAR care- plan and secure an adequate sufficient quantity of anti-allergic medications at home. Despite their reluctance to visit a medical facility, they be counselled that severe FAR warrant a prompt ER visit.

#### CONFLICT OF INTEREST

All authors report no conflict of interests related to the manuscript content.

#### AUTHOR CONTRIBUTIONS

**Nadira Musallam:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (lead); Methodology (equal);

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#### PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13540>.

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**Editor:** Motohiro Ebisawa

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