

“good participants,” or that our interview guide and consent language were biased and leading are completely without merit and unnecessarily impugn our group’s research motivations and capabilities. We would presume that semistructured interviewing was discussed in the references regarding qualitative methods that were listed in the correspondence by Matthews et al² and simply refer all interested readers to seek further clarification within those references on this well-established, basic facet of conducting a qualitative research study.^{8–10}

The Aimmune employees who have authored these commentaries are entitled to their own opinions, and as scientists, we are open to thoughtful critique of our research. However, such an approach begs the question of why someone would look a gift horse of free and potentially useful information in the mouth and why they have chosen to interpret the rather generic themes as somehow being in favor of epicutaneous immunotherapy and not oral immunotherapy. Again, this was not our conclusion, and no single participant interviewed elaborated such a conclusion—Aimmune has reached this on their own accord and furthermore appears to be attempting to discredit research findings that they perceive as potentially unfavorable. It is unfortunate that the focus here has been diverted away from what is important—what the patient may value in this new and developing area of therapy. One of the purposes of qualitative research is to illuminate perspectives that are not easily gained in other ways. To reiterate, we identified that parents of children with peanut allergy had the following perspectives: (1) parents are seeking a therapy that only needs to provide minimal protection with minimal risks and (2) such protection would enhance quality of life through potentially decreasing reaction severity and enhancing life activities. Understanding parents’ perspectives should be of paramount importance to any company manufacturing a treatment for the children of these parents. Therefore, by focusing on an incorrect concern that the article may cast aspersions on their treatment and on a since-corrected typographical error, they have missed an opportunity to learn the parents’ perspectives from this rigorous qualitative study.

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References

- [1] Tilles S. Qualitative evaluation of caregiver preferences for peanut immunotherapy products: methodology and timing count. *Ann Allergy Asthma Immunology*. 2018;121:640
- [2] Matthews JG, Zawadzki R, Haselkorn T, Rosen K. Clarification of epicutaneous immunotherapy trial phase 3 results and methods for qualitative survey design. *Ann Allergy Asthma Immunology*. 2018;121:641–642
- [3] Greenhawt M, Marsh R, Gilbert H, Sicherer S, DunnGalvin A, Matlock D. Understanding caregiver goals, benefits, and acceptable risks of peanut allergy therapies [published online June 22, 2018]. *Ann Allergy Asthma Immunol*. doi.org/10.1016/j.anai.2018.06.018
- [4] DBV Technologies. https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf. Accessed April 3, 2018.
- [5] Creswell JW. *Qualitative Inquiry and Research Design: Choosing Among Five Traditions*. 2nd ed. Thousand Oaks, CA: SAGE Publications Inc; 2007.
- [6] Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15:1277–1288.
- [7] Aimmune. <http://ir.aimune.com/static-files/67220e6f-03e7-4bd6-973d-96a305aa7a6d>. Accessed April 3, 2018.
- [8] Wray N, Markovic M, Manderson L. “Researcher saturation”: the impact of data triangulation and intensive-research practices on the researcher and qualitative research process. *Qual Health Res*. 2007;17:1392–1402.
- [9] Guest G, Bunce A, Johnson L. How many interviews are enough? an experiment with data saturation and variability. *Field Methods*. 2006;18:59–82.
- [10] Fugard AJB, Potts HWW. Supporting thinking on sample sizes for thematic analyses: a quantitative tool. *Int J Social Res Method*. 2015;18:669–684.

Pressure, trigger forces, and epinephrine auto-injectors



The recent article by Dreborg et al¹ concluded that Emerade, defined as a low-pressure epinephrine auto-injector, has no risk of intraosseous injection in children and a low risk of subcutaneous injection in adolescents and adults. However, assumptions leading to these conclusions could be incorrect.

In this study and its 3 source studies,^{2–4} there is no evidence demonstrating that Emerade has a lower trigger force than other epinephrine auto-injectors. The company website and product materials do not describe Emerade as low pressure or provide any information about pressure, trigger force, or tissue compression.⁵ There also is no information on the European Medicines Agency website or in the published literature.

In addition, this study and its source studies do not describe how the ultrasonographer reliably applied force. The study of infants weighing less than 15 kg by Kim et al³ and the study of adults by Tsai et al⁴ described that minimal or an estimated maximal force of 2 to 8 lb was applied. The study of 202 children by Dreborg et al² described that minimal or 8 lb of pressure was applied. Food and Drug Administration documents for Auvi-Q indicate that trigger forces are 2 to 10 lb compared with 2 to 8 lb for EpiPen.⁶ Thus, the investigators frequently used the high-end trigger force range of these devices. Average trigger force is 6 lb for Auvi-Q (personal communication). Average trigger force for EpiPen was unavailable on request.

Force and pressure differ. Force is applied to the entire device, whereas pressure is the force per unit area over which that force is distributed. Hence, an 8-lb force applied to a rectangular ultrasound

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probe would result in different tissue compression than the same force applied to an EpiPen. A certain trigger force for an Auvi-Q device, with a larger contact surface, would produce less pressure and tissue compression at the point of needle entry than the same trigger force applied to pen-shaped devices with smaller contact surfaces.

In Table 1 of the article by Dreborg et al,¹ who is based in Sweden, EpiPen and Auvi-Q are described as being injected with pressure “thrust or pressed hard” and Emerade as being injected with “slight pressure.” In Sweden, EpiPen instructions use the word *stöt*, translated as “thrust.” However, in principally English-speaking countries, current EpiPen instructions state to “swing and firmly push.”⁷ Auvi-Q, not sold in Sweden, instructs to “place ... then push firmly.”⁸ Swedish instructions for Emerade state that injection occurs when “pressed lightly,” but the word *lightly* is omitted in the English version.⁹ On the Emerade website, use of the Emerade trainer causes visible tissue compression.⁵ When auto-injectors are fired into ballistic gelatin, the Emerade device appears to cause at least as much compression as other epinephrine auto-injector devices.¹⁰

Dreborg et al¹ state that they did not have trigger force data from all manufacturers. They should provide this information for Emerade, if it is available, or otherwise support their assertion that Emerade is a low-pressure device. Otherwise, it is premature to assume that Emerade has a low trigger force, because available evidence suggests otherwise. If this assumption is unsubstantiated, then the results and conclusions of this study are in question.

Authors’ response

In her letter to the editor, Brown¹ has a number of questions for us regarding the pressure required to trigger epinephrine auto-injectors (EAI) and the methodology to justify the conclusions of our study.² Her major concern is that the force required to trigger the Emerade (Medeca Pharma AB, Uppsala, Sweden) is not known so the Emerade might not inject at lower trigger forces than other EAI.

When submitting our article, we did not have all the data on the pressure required to release EAI according to the manufacturers’ specifications. Therefore, we used data published by Schwartz and Seeger³ and pressures defined by Harold Kim’s group in the 3 source studies.^{4–6} The studies by Kim’s group used low and high pressures applied to an ultrasound probe to simulate EAI that should release with low and high pressures. We used low pressure to simulate delivery of the Emerade and high pressures to simulate delivery of the other devices. High pressure was estimated at 8 lb, which we, at that time, believed would trigger the EpiPen (Mylan, Canonsburg, Pennsylvania). The pressures to be applied to the respective EAI were obtained directly from the manufacturers of the EpiPen, Emerade, and Auvi-Q (Mylan; Table 1). According to these data, there is no pronounced difference in mean pressure between some high- and low-pressure EAI. However, considering the variation, it is apparent some high-pressure EAI need much higher pressure than low-pressure EAI and the variation in pressure is not acceptable. We consider the highest pressure according to the manufacturers’ specifications most appropriate for comparison of the pressure needed for release of EAI needles (Table 1).

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References

[1] Dreborg S, Kim L, Tsai G, Kim H. Epinephrine auto-injector needle lengths: can both subcutaneous and periosteal/intraosseous injection be avoided. *Ann Allergy Asthma Immunol*. 2018;120:648–653. e1.
[2] Dreborg S, Wen X, Kim L, et al. Do epinephrine auto-injectors have an unsuitable needle length in children and adolescents at risk for anaphylaxis from food allergy. *Allergy Asthma Clin Immunol*. 2016;12:11.
[3] Kim L, Nevis IF, Tsai G, et al. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. *Allergy Asthma Clin Immunol*. 2014;10:40.
[4] Tsai G, Kim L, Nevis IF, et al. Auto-injector needle length may be inadequate to deliver epinephrine intramuscularly in women with confirmed food allergy. *Allergy Asthma Clin Immunol*. 2014;10:39.
[5] Emerade. Your adrenaline pen for emergency treatment of anaphylaxis. <http://www.emerade.com>. Accessed June 8, 2018.
[6] Zhao L, Doddapaneni S. Clinical pharmacology and biopharmaceutics review, Intelliject. United States: Food and Drug Administration Center for Drug Evaluation and Research; 2010; 201739:1–42. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000ClinPharmR.pdf. Accessed September 1, 2018.
[7] EpiPen patient information. <https://www.epipen.com/-/media/files/epipen/patient%20information.pdf>. Accessed June 8, 2018.
[8] Auvi-Q patient instructions. <https://dailymed.nlm.nih.gov/dailymed/fda/fda-DrugXsl.cfm?setid=6180fb40-7fca-4602-b3da-ce62b8cd2470&type=display#JB200>. Accessed June 8, 2018.
[9] Emerade patient instructions. https://docetp.mpa.se/LMF/Emerade%20solution%20for%20injection%20ENG%20PL_09001be6803a3ac8.pdf. Accessed June 8, 2018.
[10] Brown J. Epinephrine auto-injector compression tests. <https://www.youtube.com/watch?v=XIQYjwBo3sE>. Accessed June 8, 2018.

Table 1
Accepted Variation of Pressure Applied to Release the Needle According to Schwartz and Seeger³ and Data Obtained From the Respective Companies^a

EAI	Activation force Range	Mean	Maximum pressure applied
HPEAI			
Schwartz and Seeger ^{3,b}			
Jext	21–43	28	43
EpiPen	17–34	25	34
Manufacturers’ specifications			
Auvi-Q	8.5–53	27	53
EpiPen Jr	8.5–35	20–22 ^c	35
EpiPen	8.5–35	20–21 ^c	35
LPEAI			
Manufacturers’ specifications			
Emerade	8–25	15–17 ^c	25

Abbreviations: EAI, epinephrine auto-injector; HPEAI, high-pressure epinephrine auto-injector; LPEAI, low-pressure epinephrine auto-injector.
^aValues are expressed as Newtons (1N = 0.226 lb; 1 lb = 4.425 N).
^bEstimated from Figure 5 in Schwartz and Seeger.³
^cVariation between batches.

There are no peer-reviewed publications by manufacturers presenting the force or pressure required to trigger the different EAI. Based on data presented in Table 1, we request manufacturers to decrease the variation in pressure required for needle release. The approved wording on how to inject epinephrine was taken from the respective summaries of product characteristics (SmPCs). For example, the injection method in the English version of the Emerade SmPC⁷ reads, “The injection occurs when the triggering cylinder is gently pressed into the thigh,” and in the Swedish

