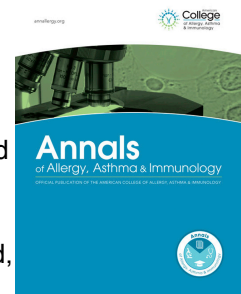


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Decades of Poor Availability of Epinephrine Auto-Injectors – Global Problems in Need of Global Solutions

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TITLE:

Decades of Poor Availability of Epinephrine Auto-Injectors – Global Problems in Need of Global Solutions

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Abbreviations:

EAI – epinephrine auto-injector(s)

EAACI POC – Patient Organisation Committee, European Academy of Allergy and Clinical Immunology

47 IFAAA – International Food Allergy & Anaphylaxis Alliance

48 IM – intramuscular

49 IPAO – International Patient Allergy Organization

50 WAO – World Allergy Organization

51

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Guidelines recommend prompt use of intramuscular epinephrine as first-line treatment for anaphylaxis¹⁻⁵. Patients at-risk of anaphylaxis are generally counselled by medical professionals to carry epinephrine in the form of an epinephrine auto-injector (EAI) to treat a severe allergic reaction. Despite its critical role as a life-saving medication, availability of EAI differs around the world. Shortages of EAI have compounded this problem.

Few studies have assessed the availability of EAI devices globally. A 2007 World Allergy Organization (WAO) survey showed that 59% (26/44) of its member countries had EAI, slightly higher than the 56% (22/39) noted in their 2003 survey⁶. With an increasing proportion of the worldwide population at-risk for life-threatening allergies⁷, we sought to learn whether EAI were readily available to those who need them and identify common barriers to access.

Representatives from the EAACI POC and IFAAA collaborated on a research study to assess the global availability of EAI, administering two online surveys between 2016 and 2017:

1) An International Patient Allergy Organization (IPAO) Survey: administered to EAACI POC and IFAAA members whose consent was implied upon participation and 2) A Consumer Survey: Consenting adults (≥ 18 years of age) with food allergy and parents/caregivers of children (< 18 years of age) with food allergy were invited to participate. Participants, recruited through allergy patient associations' members/public, were included in the study if they were diagnosed at-risk of anaphylaxis, advised by health care provider that allergy could be life-threatening or advised to carry an EAI.

Our goals were to assess country-specific availability of EAI (brands, dosages), access (prescription requirement, insurance coverage, government subsidies), and perceived challenges to use (cost, expiry dates).

Patient groups from 25 countries completed the IPAO Survey in English (Table 1). The Consumer Survey, translated into 12 languages, was completed by individuals with food allergy (or caregivers of children with food allergy) (n=7241)(Table 2 eTable 1). Eighty-five percent were diagnosed by an allergist and 91% advised to carry an EAI. Our analysis included participants from 48 countries in North America (43%) and Europe (29%), followed by South/Central America (18%), Australia/New Zealand (6%), Africa/Middle East (3%), and Asia (1%).

Two EAI dosages (0.3 mg and 0.15 mg) are available in 80% (20/25) of the IPAO countries (Table 1) vs. 59% (26/44) reported in the 2007 WAO survey. While not a direct comparison of results, findings highlight ongoing global gaps with EAI availability. The IPAO Survey reveals: EAI is not available in 20% of the countries; 12% have no formal distribution network forcing groups to import EAI from other countries; and where EAI is available (n=20), EpiPen (Fastjekt, Altellus) is the dominant product in 85% and the only device in 45% of the countries. Consumers confirm the dominance of EpiPen with 78% of respondents with this device; others have Jext (8%), Anapen (2%), Emerade (2%), and Adrenaclick (1%), or 9% other brands (Auvi-Q/Allerject).

A follow-up questionnaire with IPAO Survey participants in November 2018 reported EAI shortages in 13 countries (Canada, US, South Africa, United Kingdom, Qatar, Sweden, Italy, Chile, Germany, Spain, Japan, Australia, and France) between December 2017 and September 2018, due to EpiPen recalls, and then subsequently, Emerade shortages which saw a run on its product. Supply issues were resolved by September 2018.

Both the IPAO and Consumer Surveys reflect similar challenges with EAIs, respectively: Cost (23%, 45%), short shelf life or expiry date (39%, 39%), availability (19%, 27%), and difficulty obtaining a physician prescription (15% consumers). Seventy-six percent of consumers said a prescription was required to get an EAI. Interestingly, even when available, there was a reluctance for consumers to use an EAI when experiencing a severe allergic reaction. Only 44% used an EAI in an emergency. Overall, 55% of the individuals who had a severe reaction also had co-existent asthma, a contributing factor in fatal outcomes⁸.

While EAIs are available in 80% of the 25 IPAO Survey countries, and costs are often subsidized through third party payors such as private insurance or government (69%), the actual cost to consumers can be a burden. Forty-three percent of Consumer Survey respondents report they bear the cost of EAIs, while 28% are covered by private insurers, and 15% by government. Consumer reported the price per EAI ranges from \$46 USD (Qatar) to \$294 USD (Argentina), higher than the \$54 USD to \$169 USD price range noted in the 2007 WAO survey. In the US, EAIs are only sold in units of two, at a cost \$600 USD⁹. While the requirement for an EAI prescription is lower in IPAO Survey countries at 62% vs. 81% reported in the WAO 2007

survey⁶, long wait-times to obtain a prescription from a physician can create delays in getting this medication.

Self-injectable epinephrine should be accessible to all at-risk of anaphylaxis from food and other causes, wherever they live. Although our findings show EAI availability in many countries, several countries continue to have limited access, with EAIs imported directly from other countries, and in many lower- and middle-income countries, there are no EAIs at all. Access in countries with EAIs has been compromised with shortages and a reliance on one brand, highlighting the importance for countries to have multiple brands. Manufacturers and government regulators need to be transparent and timely when product issues arise, and to work with the medical community and patient advocacy groups, to ensure that consumers stay informed. IPAOs suggest that generic EAIs could offer an alternative to brand name EAIs, however, it is uncertain whether they would be globally available and accessible at affordable prices.

Our study is unique in that it involved patient groups and allergists/researchers from 20 countries and reflects the views of those who are most impacted by EAI accessibility: consumers. Previous studies about EAI availability represent the perspective of healthcare professionals.

Our findings may not apply to the general population as information was gathered through consumers associated with allergy groups affiliated with the EAACI POC/IFAAA. There could be a skewing of more affluent/educated consumers with individuals who belong to patient groups¹⁰. In addition, the data about food allergy is self-reported and responses about allergic

reactions are based on respondent recall. However, 85% respondents were diagnosed by an allergist, decreasing potential patient bias.

Our study presents a springboard for discussion with key stakeholders, such as patient organizations, healthcare professionals, government regulators, insurance companies, manufacturers and others. Patient groups have a pivotal role to play, engaging in meaningful dialogue to better understand barriers to EAI availability such as recognition of anaphylaxis as a public health concern and the role of epinephrine as first-line treatment. We cannot let another decade go by without collectively addressing issues with the availability of EAIs.

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Table 1: EAI Availability by International Patient Allergy Organization (IPAO) country

IPAO Country	EAI BRANDS AVAILABLE
Albania	• No EAI's available
Argentina*	• EpiPen
Australia	• EpiPen
Brazil	• Anapen, EpiPen, Jext
Bulgaria	• No EAI's available
Canada*	• EpiPen
Chile	• EpiPen
France	• Anapen, EpiPen, Jext
Germany	• Emerage, Fastjekt (EpiPen), Jext
Hong Kong*	• Jext
India	• No EAI's available
Israel	• EpiPen
Italy	• Fastjekt (EpiPen), Jext
Japan	• EpiPen
Mexico	• No EAI's available
New Zealand*	• EpiPen
Qatar	• EpiPen
Republic of Korea	• Jext
Serbia	• No EAI's available
South Africa	• EpiPen
Spain	• Altellus, Jext
Sweden	• Emerade, EpiPen
The Netherlands	• Emerade, EpiPen, Jext
United Kingdom	• Emerade, EpiPen
United States	• Auvi-Q, Epi-Pen

*Prescription not required

Table 2: eTable 1: Consumer Responses by Country (N=7241)

Country	N
Argentina	25
Australia	350
Austria	1
Belgium	5
Brazil	820
Canada	1687
Chile	391
Costa Rica	1
Denmark	4
Dominican Republic	1
Ecuador	1
El Salvador	1
Egypt	1
France	97
Germany	271
Greece	1
Hong Kong	4
Hungary	1
India	2
Iraq	1
Ireland	33
Israel	160
Italy	209
Japan	62
Jordan	1
Kuwait	1
Malaysia	3
Mexico	49
Namibia	1
Netherlands	221
New Zealand	116
Paraguay	2
Philippines	1
Portugal	5
Qatar	8
Scotland	28

Singapore	1
South Africa	18
Spain	569
Sweden	223
Switzerland	10
Trinidad	1
UAE	7
UK	400
Uruguay	2
USA	1443
Venezuela	1
Vietnam	1

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