

1 Introduction

2 Anaphylaxis, according to the World Allergy Organization (WAO), is defined as a
3 potentially fatal severe systemic hypersensitivity reaction of sudden onset after exposure to an
4 allergen [1,2]. Since it is a medical emergency, early treatment is critical.

5 Intramuscular adrenaline is the first-line treatment for this emergency, and its dosage
6 should be adjusted according to the patient weight [3,4]. Given that most episodes of anaphylaxis
7 occur in the community, i.e. outside the medical setting, the adrenaline auto-injector (AAi) should
8 be prescribed to patients at risk of anaphylaxis recurrence [5,6].

9 The European Academy of Allergy and Clinical Immunology (EAACI) published in 2014
10 the guidelines on anaphylaxis, which includes indications for the prescription of this device [7].

11 Existing data on the prevalence and incidence of anaphylaxis are inaccurate and
12 correspond to default estimates since this pathology is often underdiagnosed or underreported.
13 Based on publications between 2010 and 2015, the estimated frequency of anaphylaxis is 50-112
14 episodes per 100,000 inhabitants-year, estimated prevalence of 0.3% to 5.1% [8-12].

15 In Europe, 2 to 8 cases per 100,000 inhabitants / year have been estimated, with a
16 growing trend, inferring that approximately 0.3% of the European population is at risk of having
17 an episode of anaphylaxis at some point in their life [13]. Some population-based studies
18 estimated a rate of occurrence of anaphylaxis based on the acquisition of AAi ranging from
19 0.083% [10] to 0.95% [9], corresponding to the acquisition of 83 units of AAi and 954 units per
20 100,000 inhabitants in Israel and Canada, respectively.

21 In Portugal, based on the notified cases of anaphylaxis in the *Catálogo Português de*
22 *Alergias e Outras Reações Adversas* (CPARA), Amaral et al (2014) recorded 1209 cases of
23 anaphylaxis during a period of 10 months in a total of 20 389 records, corresponding to 6% of all
24 adverse reactions reported in this catalog. The most frequent groups of allergens inducing
25 anaphylaxis reactions were drugs (83%), foods (7%) and hymenoptera venom (3%). Of these
26 allergens, the AAi is only indicated for food and venom allergy, corresponding in this study to a
27 prevalence of patients with indications to AAi of 1.12 / 100,000 inhabitants [14].

28 The prevalence of patients at risk of anaphylaxis based on AAi acquisition and the annual
29 cost inherent to these devices acquisition in Portugal are unknown. Our aim was to evaluate the
30 frequency of AAi acquisition in Mainland Portugal during a period of 15 years (2003-2017), and
31 to calculate the economic impact in terms of cost inherent in its acquisition for the patient and
32 the National Health System (NHS). We also estimate the risk of anaphylaxis occurrence based on
33 this data.

35 **Material and methods**

36 The frequency distribution of AAi acquisition in Portugal between 2003 and 2017 was
37 analyzed through data provided by INFARMED (National Authority of Medicine and Health
38 Products I.P.) During this period, two brands of AAi were marketed with 0.15mg / 0.3mL and
39 0.3mg / 0.3mL dosages.

40 To adjust the dosage to weight and age, the studied population was divided into two
41 age groups: group A - patients aged between 5 and 9 years for the 0.15mg dose and group B –
42 patients older than 10 years [≥ 10] for the 0.3 mg dose.

43 The doses relating to body weight recommendations are based on limited
44 pharmacokinetic data in healthy volunteers. No pharmacokinetic or pharmacodynamics studies
45 involving patients with anaphylaxis have been published. They are also based on consensus and
46 standard practice. For children under 15 kg adrenaline autoinjectors are not usually recommended;
47 the recommendation for children 15-30 kg is a 0.15 mg adrenaline autoinjector device and for
48 children over 30 kg and adults an 0.3 mg adrenaline autoinjector device [2,15]. Considering that,
49 according to the growth reference values of Portuguese children, a 5 years old child has an ideal
50 weight of 18.4 kg and a 10 year old child 31.9 kg, we chose to use the range of 5-9 years and over
51 10 to define the age groups.

52 The prevalence/inhabitant calculation was performed using the National Statistics
53 Institute database for Mainland Portugal resident population during this period, based on the 2011
54 census. The devices acquisition per geographic regions (North, Center, Lisbon, Alentejo and
55 Algarve) according to the Nomenclature of Territorial Units for Statistical (NUTS 2013), was

56 also calculated. Considering the price of the devices in 2017, the inherent cost to the patient and
57 the NHS was evaluated.

58 Data analysis was performed using Microsoft® Excel 2016.

59 Data were anonymized and patient confidentiality was guaranteed. The study protocol
60 was approved by the Ethical Board of Centro Hospitalar Universitário de Lisboa Norte.

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63 Results

64 We show in Figure 1 the distribution of the frequency of AAI acquisition.

65 In 2003 and 2017, the lowest and highest numbers of AAI units were acquired for both
66 doses, respectively. There was a progressive increase in acquisition over the years for both
67 dosages. For the 0,15mg dose, there was with an average increase of 117 units per year, with the
68 largest increase from 2010 to 2011, representing an increase of 389 units acquired. The average
69 annual increase for 0.3mg dose was 349 units per year with the most significant increase occurring
70 from 2016 to 2017, representing an increase of 1,268 units acquired (Figure 1A).

71 The prevalence of acquisition per inhabitant in 2003 for the dose of 0.15 mg was 13 per
72 100,000 inhabitants, followed by a progressive increase in AAI dispensed, reaching a maximum
73 of 376 per 100,000 inhabitants in 2017, which correspond to a total average of 144 units per
74 100,000 inhabitants acquired over these 15 years. For the 0.3 mg dose, in 2003 the prevalence
75 was also the lowest, with a total of 3 units acquired per 100,000 inhabitants, and in 2017 the
76 largest (58 per 100,000 inhabitants), corresponding to a total average of 21 units per 100,000
77 inhabitants acquired for the 0.3 mg formulation. (Figure 1B).

78 According to our data, based on the adrenaline acquisition over these 15 years, it is
79 possible to predict a population-at-risk of anaphylaxis ratio of 0.165%. This corresponds to a
80 dispensing average of 165 units of AAI per 100,000 inhabitants.

81 Regarding the cumulative value of devices purchased per year and region, Lisbon was the
82 one with the most AAI devices purchased in both marketed doses: A: 40%, B: 43%, followed by

83 the North with A: 32 (%), B: 25%, the Center region with A: 21%, B: 23%, Algarve with A: 4%,
84 B: 5% and Alentejo with A: 3%, B: 4% (Figure 2).

85 In the last year of the study, in terms of acquisition prevalence per 100,000 inhabitants
86 in the different regions, Lisbon continued to be the one with the most units dispensed (8'),
87 followed by the Center region - 75, Algarve - 73, North - 71 and finally Alentejo - 33 (Table 1).

88 Also, in 2017, considering the two brands marketed in Portugal, the average cost per
89 device has A: 55.81 € and B: 54.29 €. With the NHS co-payment of 37% since 2009, cost per unit
90 per user (A / B) was € 35.16 / € 34.20 and for the NHS € 20.65 / € 20.09, which corresponds to
91 an annual cost of € 64,202.71 / € 187,447.70 for users and € 37,706.35 / € 110,1103.30 for the
92 NHS. These data are summarized in Table 2.

93

94 **Discussion**

95 According to our results, in the last 15 years there was a large increase in AAI
96 acquisition by 26 times (2508%) for the pediatric patients and by 21 times (2083%) for
97 adolescents / adults. Other published studies also showed an increase, although of a lower
98 magnitude. For example, Levy et al [10] demonstrated an increase in AAI acquisition by the
99 population of Israel between 1997 and 2004 of 59% in the pediatric formulation and 89% in that
100 of adolescents and adults. The review of pharmaceutical data in Australia between 1998 and 2002
101 by Kemp [16], demonstrated an increase in AAI dispensing to pharmacies by 300% of the
102 pediatric formulation and 193% of the adolescents and adult's formulation. In the United
103 Kingdom, the increase in AAI prescription over 13 years (1991-2004) was 1200% [17].

104 The increase can be explained by the higher reports on food and venom anaphylaxis cases
105 but also by the NHS co-payment that has been in existence since 2009, acquisition by the health
106 professionals themselves such as private clinics, dentists and immunoallergologists and better
107 knowledge through health education training within medical professionals, and due to the short
108 expiration date of the device.

109 There was a higher AAI acquisition rate per inhabitant in the younger group in relation to
110 the adolescent/adult group, which is in accordance with other studies published [9-11,18-20].

111 Simons et al [9], using a pharmaceutical database, analyzed data from all formulations of
112 epinephrine dispensed for 5 years in Manitoba (Canada), demonstrating an average dispensing
113 rate of 1.44% in patients under 17 years and 1.22% in patients over 17 years of age. Taking into
114 account the age distribution used to account for the AAI dosage and the number of people included
115 in each group, over the 15 years, our study predicts an average dispensing ratio per 100,000
116 inhabitants of 0.144% for the 5 to 9 years group, and 0.021% for the group aged 10 years or more,
117 comparatively much lower for both groups.

118 According to our data it is possible to predict a population-at-risk of recurrent anaphylaxis ratio
119 of 0.165%. This corresponds to a dispensing average of 165 units of AAI per 100,000 inhabitants.
120 This value is in the range of other studies published using the same methods [9,10]. Levy Y et al
121 predicted an incidence of anaphylaxis of 0.083% (83 per 100,000) in the Israel population between
122 1997-2004 [10]. The other study estimated the occurring anaphylaxis rate in the population of
123 Manitoba, Canada (1995-2000) at 0.95% (954 per 100,000) [9]. Our frequency is within the limits
124 published on other studies but lower than this last study, allowing us to infer that in Portugal, as
125 in many other countries, anaphylaxis is underdiagnosed and underreported. Besides that,
126 anaphylaxis seems to be undertreated, even if it is properly diagnosed, some patients are not
127 prescribed with AAI - e.g. in the emergency department, and even if it is prescribed, they often
128 do not acquire it, mostly because of the price or because they don't understand when or how to
129 use it.

130 Regarding the distribution per geographic region, Lisbon contributed the highest
131 percentage of devices purchased for both dosages, either in terms of the cumulative average value
132 of devices purchased per year per region or per 100,000 inhabitants, while Alentejo consumed the
133 least, substantiating that the consumption is proportional to the population density.

134 In our study, in both groups, there was a progressive increase in the prevalence of AAI
135 acquisition, which also denotes an increase in the prevalence of patients at risk of anaphylaxis,
136 reaching in 2017 a consumption of 434 units per 100,000 inhabitants that represents a 0.43% rate
137 of population at risk of anaphylaxis in our country this year, closer to world values [21,22].

138 Considering that this is an analysis of acquisition, this study showed a higher number of
139 anaphylaxis cases per 100,000 inhabitants compared to another Portuguese study [14], which
140 evaluates the registry of anaphylaxis cases in the CPARA (which only represents anaphylaxis
141 reports done by an healthcare professional), implying that could have a underreport by health
142 professionals, since a large number of cases in the CPARA correspond to drug allergies in which
143 case AAi prescription is not indicated. However, our data is not a direct estimate of the number
144 of anaphylaxis cases. We use a "surrogate marker" of anaphylaxis cases to estimate the frequency
145 of its occurrence. The crude (not per patient) AAi acquisition data may have 1 or 3 devices per
146 year for the same anaphylaxis patient; that is a major difference between our data and CPARA.

147 Patients with a previous history of anaphylaxis should be studied in an
148 Immunoallergology outpatient clinic to obtain a correct diagnosis and adequate therapeutic
149 orientation in order to reduce the risk of future reactions. Although the guidelines promote the
150 AAi device prescription [7], as well as referral to specialized consultation, this is often not
151 verified. Some studies have shown that the percentage of patients observed in the emergency
152 department with suspected anaphylaxis for whom AAi is prescribed varies between 16-63% [23-
153 25] and that the percentage of referral to specialized consultation ranged from 11-33% [26-28].
154 Some factors that may contribute to these low rates are the high cost of the devices, waiting lists
155 for the specialized consultation conditioning delays in the study or withdrawal by the patients
156 themselves, and also the non-acquisition of AAi due to the expiration of the prescription.

157 In 2017 the AAi acquirement in Mainland Portugal reached the maximum of units
158 acquired implying increased costs. The annual cost for the 0.15 mg AAi dose corresponds to about
159 €65,000.00 for pediatric patients, and for the NHS about €38,000.00 with an average cost per
160 device of €35.16. Diwakar et al (2017) reports that the UK's current annual expenditure on AAi
161 for children is approximately £7,000,000.00 with an average cost per unit of £25.80 [29].

162 For the adolescent and adult population, the annual cost in 2017 was about €190,000.00
163 for the patient and €111,000.00 for the NHS, with a cost per device of €34.20. Patel et al [30]
164 estimated that the AAi device acquisition correspond to an annual average cost of \$20 million for
165 devices purchased (cost/device \$ 51).

166 The frequency of population-at-risk of anaphylaxis and its treatment, namely the
167 acquisition of AAi, impose high costs. Despite the current 37% co-payment by the NHS for these
168 devices, the cost is still high since annual renewal is necessary. Compared to the UK, an AAi is
169 less expensive in the this country where the medium monthly income is higher.

170 Some limitations of our study are that although is divided per age groups, age range <5
171 years is not included since the adrenaline dose must be adjusted for weight and at these ages is
172 rarely prescribed. The etiology of anaphylaxis for which AAi was prescribed is not known, as the
173 main cause of adult anaphylaxis is drug allergy, and in this case AAi device is not indicated. Also,
174 the fact that is an acquisition and not a prescription study and the acquisition depend on the
175 patients. Population division in urban and rural areas was not possible, which would be important
176 due to the higher prevalence of anaphylaxis to hymenoptera in rural areas. However, there was a
177 higher rate of anaphylaxis in areas with higher population density as expected.

178 There has also been a greater education for health among professionals in the most
179 diverse areas. This also allows a greater number to be aware of the need for prescribing adrenaline
180 in some patients.

181 Children are very common to carry more than one device, even if it is not mention in
182 the guidelines (e.g. one at home, one at school, one at grandparents home), this may leads to an
183 overestimation of the prevalence of patients at risk using this methodology. We estimate the rate
184 of patients at risk for anaphylaxis based on acquired AAi but not the total anaphylaxis rate in
185 Mainland Portugal .

186

187 **Conclusion**

188 In the last 15 years, there has been an increase in AAi acquisition for both the pediatric
189 age and adolescents / adults. The significant rise in the number of prescriptions per year suggests
190 an increase in the prevalence of patients at risk of anaphylaxis based on acquired AAi in Mainland
191 Portugal reaching 0.165%.

192 The authors also justify the significant increase in AAi acquisition, not only due to the
193 rise in anaphylaxis cases frequency, but also as a result of the greater knowledge through health

194 education training in the population and medical professionals, as well as the AAi device co-
195 payment by the NHS in recent year.

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Manuscript accepted for publication