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Primary care doctors' attitude towards drug allergy in Portugal: a questionnaire

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KEY WORDS

Drug hypersensitivity; drug allergy; primary health care; medical education; questionnaires.

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Summary

Background. The aim of the study was to learn about perception of drug allergy by general practitioners (GP) from continental Portugal, identify difficulties and educational needs for its management. **Methods.** A total of 372 answers were obtained. A questionnaire was addressed to GPs. **Results.** The most commonly identified drugs were antibiotics for 65.3% of the GPs and skin was the most commonly affected organ for 65.8%. Drug allergy was considered as very important in clinical practice by 73.7%, but difficulties in recognizing it were stated by 70.2%. Further education in this field would be welcome by 97.8% of the doctors. The collaboration of Immunoallergology centers was considered non satisfactory by 39.8% of GPs and 45.7% of them stated that two-thirds of the suspected reactions were not investigated. **Conclusions.** These points deserve consideration in future health educational and organizational strategies.

IMPACT STATEMENT

This national survey recognized drug allergy as an important problem in clinical practice. It was evident the interest in allergology trainings and in a better Immunoallergology centers response.

Introduction

World Health Organization (WHO) defines an adverse drug reaction (ADR) as a dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans (1).

Rawlins and Thompson in 1977 and 1981 proposed a classification of ADR, which is the most commonly used classification until today (2, 3). Two groups are considered: type A reactions (predictable, dose dependent, based on pharmacological mechanism and possible in all patients if enough dose is administered) and type B (unpredictable, not dose dependent occurring in a small group of susceptible patients). Less common types of reactions were later described: type C (chronic, dose and time

dependent), type D (delayed reactions), type E (end of treatment, withdrawal reactions), and type F (unexpected failure of therapy) (4, 5). ADRs must be notified to the National Pharmacovigilance System (6).

Only 10-15% of all ADR reactions are type B being the majority type A reactions (7). Type B reactions are hypersensitivity reactions to drugs and are classified as allergic when an immunological mechanism mediated by IgE or T-cell is involved (8). An allergic drug reaction may be diagnosed by a specific allergy workup conducted by an Immunoallergology specialist in safe and controlled conditions.

ADR is an important public health problem, not only associated with significant morbidity and mortality but also to unnecessary costs. Several authors report a high number of hospital

admissions due to ADRs (9). However, in spite of the increase in ADRs reports in the last years, particularly of severe reactions (6), its prevalence is unknown, since there aren't epidemiological studies in most countries (7).

In the majority of studies, the distinction between an allergic and a non-allergic reaction to drugs isn't clear (10). The lack of differentiation between these two types of reactions is also noticed in clinical practice and may determine the exclusion of first line therapeutic drugs, leading to an unnecessary and possibly counterproductive attitude in non-allergic reactions.

The absence of allergology and clinical immunology areas in medical education and training programs contributes largely to the difficulty in the management of drug hypersensitivity. This gap is identified by the European Academy of Allergy and Clinical Immunology (EAACI) position paper about the allergy management in primary care. It emphasizes the need for homogenous and well-structured education programs in these areas (11). Further, an EAACI task force suggested a diagnosis and management approach of ADRs for primary care physicians, including the recognition of red flags and referral criteria (12). Being the first line of health care providers, General Practitioners (GPs) must cope with most ADRs and their clinical decisions have a major impact on the general management of ADRs.

A study conducted in Romania by Mihaela Leru focused on the GPs clinical practice, since they are the closest doctors to patients and the main source of drug prescription. The conclusions of this study also highlighted the need for further educational programs for GPs in drug allergies and pointed out that their knowledge of this subject, as well as their collaboration with Allergologists, wasn't standardized (13).

The aim of our study was to evaluate GPs' perception of the problem of drug allergy and identify the difficulties they encounter while managing ADRs, as well as the educational needs on this subject in different areas of Portugal.

Materials and methods

Type of study and participants

We performed a cross-sectional study based on a questionnaire addressed to all GP specialists and trainees from continental Portugal. The questionnaire was available from the 1st of June 2018 to the 31st of May 2019. According to the information provided by the Central Administration for Health System (ACSS), the total number of GP interns and specialists in May 2019 was 7,931 (2,238 and 5,693, respectively).

As demanded by the Regional Health Administration (Administração Regional de Saúde - ARS) Ethics Committees, the questionnaire was sent by electronic mail to all Health Center Clusters (Agrupamentos de Centros de Saúde - ACES) in Continental Portugal, from where they were addressed to the Health Center coordinators, and finally forwarded to family doctors.

Questionnaire

An online questionnaire was created using Google Docs® software. The participation was voluntary, anonymous, unpaid and confidential. Data was used within the scope of this study and only available to researchers. The questionnaire included 23 questions: 2 questions focused on the professional experience and the geographical location; 17 questions on the perception of drug allergy epidemiology and how to manage ADR; and 4 questions addressed the educational needs in allergology (questionnaire included in **online supplements appendix 1**).

Ethical considerations

The study was approved by the Ethics Committee of ARS Norte, ARS Centro, ARS Lisboa e Vale do Tejo, ARS Alentejo and ARS Algarve, in compliance with the Helsinki Declaration.

Data processing and analysis

Data was collected and analyzed using an Excel® spreadsheet, protected with a password.

To calculate the study accuracy Krejcie & Morgan formula was applied (14). Chi-square statistic was used for testing relationships on variables (categorical).

For statistical analysis IBM SPSS Statistics for Windows, version 25 was used.

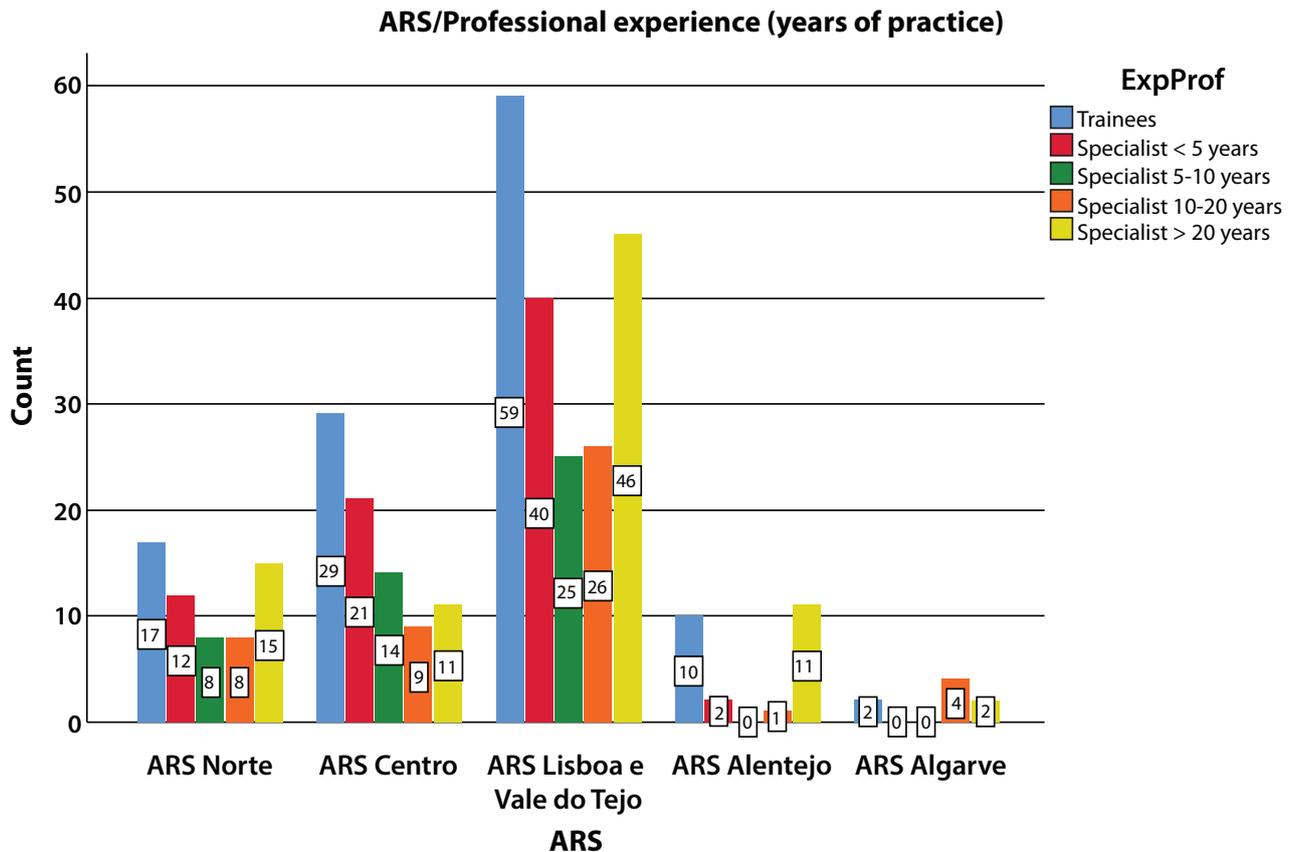
Results

Applying the Krejcie & Morgan formula to our population (7,931), the 372 completed questionnaires obtained allowed for a confidence level of 95% and 5% margin error (14). The minimum number to reach those parameters would be 363 questionnaires.

Figure 1 shows participant characterization. Out of the 372 completed questionnaires, 117 (31.5%) were filled by GP trainees and 255 (68.5%) by specialists. Sixty (16%) were received from ARS Norte, 84 (22.6%) from ARS Centro, 196 (52.7%) from ARS Lisboa e Vale do Tejo, 24 (6.5%) from ARS Alentejo and 8 (2.2%) from ARS Algarve.

Responses from all professional experience levels considered were obtained in the most represented ARS.

The GPs' perception of drug allergy is summarized in **table I**. Nearly half of the doctors described that the incidence of drug allergy is increasing. The clinicians identify antibiotics as the main cause of drug allergy (65.3%), followed by non-steroidal anti-inflammatory drugs (19%). The "patient insecurities in the future use of other medicines" and the "difficulty in finding appropriate therapies" were pointed out as the most common consequences of a drug allergy episode. Most of the clinicians were aware that drug allergies carried a risk of a fatal outcome. Regarding the impact of drug allergy in their practice (**table II**), 73.7% of GPs considered it a very important issue and 75.5% observed it monthly or twice a year. Nearly half of them estimated

Figure 1 - Participant characterization ($n = 372$) according to ARS and Professional experience.

fewer than 30 cases of drug allergy in their patient list, 59.4% considered that this condition had some clinical impact on their therapeutic decisions. Drug allergy was stated as not having been investigated in any patient with a clinical suspicion by 27.4% of clinicians and investigated in about one third of the patients by 45.7%.

Table III provides information on drug allergy recognition and management. Skin involvement and facial edema were considered the most characteristic features of drug allergy by the majority of GPs (65.8%) and almost all chose to use an alternative drug in this situation (97.3%). A severe drug reaction, the difficulty in finding an alternative therapy and pediatric patients were the most common reasons for referrals to an allergologic study. Seventy percent recognized having difficulty in distinguishing an allergic reaction from a non-allergic reaction to a drug. Considering the levels of experience this difficulty ranged from 60.0% (more than 20 years of experience) to 77.3% (less than 5 years of experience), no statistical difference was found. One hundred and eighty-five (49.7%) of the doctors have never notified the National Pharmacovigilance System.

The perceived delay in obtaining an Immunoallergy appointment was less than 6 months for most cases in Norte (73.3%), Centro (86.9%) and in Lisboa e Vale do Tejo (74.0%), whilst in Alentejo it was only 37.6% and in Algarve 50.0%. The difference between the highest and lowest value is significantly different ($\chi^2 = 22.29$, P -value < 0.01). As for global GP satisfaction levels it ranged from 72.6% in Centro to 29.2% in Alentejo (**table IV**), which was statistically different ($\chi^2 = 15.11$, P -value < 0.01). The doctor's satisfaction is related to the delay of Immunoallergy response: for a delay less than 3 months 91.2% of doctors considered it satisfactory, while for a delay longer than 3 months only 40.2% expressed satisfaction. The difference between satisfaction levels is significant ($\chi^2 = 97.1$, P -value < 0.001).

Globally, 39.8% had no drug allergy training at all and almost all (97.8%) were interested in getting further education in this area, preferably through clinical training initiatives taking place in Health Centers (**table V**).

The rate of training in drug allergy ranged from 32.0% to 45.3% across all levels of professional experience, which wasn't significantly different.

Table I - Perception of drug allergy (*n* = 372).

	n	%
How do you describe the incidence of drug allergy in Portugal?		
Increasing	194	52.2%
Stable	161	43.3%
Decreasing	17	4.6%
What do you consider to be the class of drugs most often responsible for allergic reactions? <i>More than one possible option</i>		
Antibiotics	243	65.3%
Non-steroidal anti-inflammatory drugs	70	18.8%
Contrast media	37	9.9%
Cardiovascular medication	15	4%
Psychiatric and / or neurological medication	4	1.1%
Vaccines	2	0.5%
Vitamins	1	0.3%
Which consequences do you consider the most common after a drug allergy diagnosis? <i>More than one possible option</i>		
Patient insecurities in the future use of other medicines	309	83.1%
Difficulty in finding appropriate therapies	209	56.2%
Less therapeutic options	113	30.4%
Patient's quality of life	75	20.2%
Contraindication to some diagnostic tests	68	18.3%
Risk of death	106	28.5%
What percentage of risk of death exists because of drug allergy?		
0%	2	0.5%
≥ 1-5%	226	60.8%
> 5-10%	43	11.6%
> 10-20%	12	3.2%
> 20%	7	1.9%
I don't know	82	22%

In addition, this training showed no significant effect on the difficulty in distinguishing allergic reactions: 70.7% of non trained GPs found it difficult and 69.8% of those with training.

Discussion

Our sample allowed an acceptable accuracy level. However, we had expected a larger number of responses. The long and complicated bureaucratic process involved in the questionnaire distribution, out of our direct control, may have had a role in the low response rate. The identification of cutaneous signs as the most typical clinical manifestations of drug allergy by 65% of our responses corroborates several studies where the skin is the organ most frequently affected (15-17).

Moreover, according to our study, the drugs responsible for allergic reactions were mostly antibiotics and nonsteroidal anti-inflammatory drugs, in line with previous reports (12, 20, 21). However, the role of the latter is recognized only by 19% of GPs, being clearly underestimated by comparison with the available data (22). Allergy to antibiotics is perhaps overvalued not only in medical education, but also public opinion. Commonly, when faced with an allergic reaction, patients only remember their antibiotic intake. Similarly, to other studies (13, 23), more than a half of our study GPs perceived that drug allergy is increasing, which is understandable in the current setting of exponential medical drug consumption in Western society. In our study most of the doctors recognized drug allergy as a very important problem and revealed a good level of

Table II - Drug allergy impact in GPs clinical practice (n = 372).

	n	%
How do you evaluate the importance of drug allergy in your clinical practice? <i>Classify 1-4</i>		
1- Not Important	1	0.3%
2	27	7.3%
3	70	18.8%
4- Very important	274	73.7%
How many patients have evidence of drug allergy in your total patients list?		
< 10	97	26.1%
≥ 10-30	121	32.5%
≥ 30-50	52	14%
≥ 50-100	26	7%
≥ 100	13	3.5%
I don't know	63	16.9%
How often have you seen patients with drug allergy in the last year?		
Daily	3	0.8%
Weekly	43	11.6%
Monthly	146	39.2%
Twice a year	135	36.3%
Annually	36	9.7%
Never	9	2.4%
How many of these patients were investigated for drug allergy?		
None	102	27.4%
About 1/3	170	45.7%
About half	55	14.8%
About 2/3	21	5.6%
All	24	6.5%
In how many of these cases did this drug allergy have an impact on your therapeutic decision?		
None	11	3%
About 1/3	57	15.3%
About half	53	14.2%
About 2/3	30	8.1%
All	221	59.4%

awareness of the associated risk of fatal outcomes. A high impact in clinical practice is still reported, with 97.3% stating the need to use an alternative drug. The option not to medicate, in 6.7% of the patients, may represent a significant reduction in their quality of life, as it happens when painkillers are involved. In the case of antibiotics that option may carry a risk of a worse prognosis of infections. In fact, adverse drug reactions affect 7% of general population, which represents an important cause of death. It is the sixth leading cause in

United States and physicians often face the question whether a drug reaction is allergic and how it may affect patient care (24, 25). Therefore, it would be expected that a large number of patients where there is a suspicion of a drug allergy would be referred for investigation. However, we observed that almost half of our responses estimated that only one third of these patients were referred for an allergy workup. Similar or even lower rates are reported by numerous other publications (26-29). In our opin-

Table III - Drug allergy recognition and management (n = 372).

	n	%
Which sign or symptom do you consider to be the most characteristic of drug allergy? <i>More than one possible option</i>		
Skin lesions	245	65.8%
Facial edema	55	14.8%
Itching	44	11.8%
Respiratory symptoms	28	7.5%
Change in blood pressure	3	0.8%
Malaise	6	1.6%
In cases where there was an implication in the therapeutic decision, you decided to: <i>More than one possible option</i>		
Do not medicate	25	6.7%
Lower the dose of medication	4	1.1%
Alternative drug	362	97.3%
Add antiallergic drug	29	7.8%
Other (refer to specialist)	3	0.8%
Do you usually refer patients without a confirmed diagnosis to Immunoallergy? <i>More than one possible option</i>		
All patients	82	22%
No patient	16	4.3%
Children	113	30.4%
When you don't have an alternative drug	152	40.9%
Only when the reaction is caused by certain drugs	26	7%
At patient's request	86	23.1%
Patients with an history of a severe reaction	255	68.5
Other (patients with an unclear history of drug allergy)	4	1.1%
Other (patients with multiple allergies)	1	0.3%
If you have selected "only when the reaction is caused by certain drugs", specify which drugs: <i>Open question</i>		
Antibiotics	9	2.4%
Betalactam antibiotics	3	0.8%
Angiotensin converting enzyme inhibitors	1	0.3%
Non-steroidal anti-inflammatory drugs	5	0.3%
Acetylsalicylic acid	1	0.3%
Allopurinol	1	0.3%
Antihistamines	1	0.3%
Allergy to multiple drugs	1	0.3%
Unanswered	4	1.1%
Do you find it easy in your clinical practice to distinguish an allergic reaction to a drug from a non-allergic reaction?		
Yes	111	29.8%
No	261	70.2%
During the past year, did you notify the National Pharmacovigilance System for adverse drug reactions (allergic or not) in your patients? <i>Note: it does not include notification in SCLinic or other registration system used</i>		
Yes, I notified all reactions	25	6.7%
Yes, I notified the less usual and/or the most serious reactions	23	6.2%
Yes, I notified the reactions in that I considered very probable	44	11.8%
No, I never notified the National System	187	50.3%
Unanswered	93	25%

Table IV - Referral to Immunoallergology consultations (n = 372).

Currently in your clinical practice, how long does it take to have an Immunoallergology consultation requested by you to study drug allergy?										
	ARS Lisboa e Vale do Tejo		ARS Centro		ARS Norte		ARS Alentejo		ARS Algarve	
	n	%	n	%	n	%	n	%	n	%
< 1 month	5	2.6%	3	3.6%	0	0%	1	4.2%	0	0%
1-3 months	70	35.7%	41	48.8%	19	31.6%	4	16.7%	4	50%
3-6 months	70	35.7%	29	34.5%	25	41.7%	4	16.7%	0	0%
> 6 months	51	26.0%	11	13.1%	16	26.7%	15	62.4%	4	50%

Are you satisfied with the Immunoallergology specialty collaboration in your area?										
	ARS Lisboa e Vale do Tejo		ARS Centro		ARS Norte		ARS Alentejo		ARS Algarve	
	n	%	n	%	n	%	n	%	n	%
Yes	113	57.6%	61	72.6%	38	63.3%	7	29.2%	5	62.5%
No	83	42.4%	23	27.4%	22	36.7%	17	70.8%	3	37.5%

Table V - Training in drug allergy (n = 372).

	n	%
Do you consider that the training in drug allergy is relevant to your clinical practice? <i>Classify 1-5</i>		
1- No interest	1	0.3%
2	0	0%
3	26	7%
4	113	30.4%
5- Very interesting	232	62.4%
Have you participated in any drug allergy training? <i>More than one possible option</i>		
University	98	26.3%
Postgraduate course	28	7.5%
Congress	107	28.8%
In our health center	28	7.5%
No	148	39.8%
Other (online course, hospital fellowship as intern)	15	4%
Would you be interested in participating in training in this area?		
Yes	364	97.8%
No	8	2.2%
If so, what kind of training would you prefer?		
Online course	77	21.2%
Training actions in health centers	194	53.3%
Courses/workshops in national or regional congresses	37	10.2%
Discussion of cases with specialist regularly	54	14.8%
2 nd and 4 th options	1	0.3%
1 st and 2 nd options	1	0.3%

ion, GPs do not consider the immediate impact of using second line therapies (efficacy, adverse effects, antibiotic resistances), and more importantly do not perceive the need for long term clinical decisions.

The considerable delay in allergological evaluation, more striking in Alentejo, where the rate of Allergy specialists is the lowest in the country (0.59/100,000 inhabitants in Public Health Services according to the latest available data) (28), may be at least partially responsible for the insufficient investigations.

This delay is understandably related to physician satisfaction, according to our results, where centers reporting longer waiting times also reported higher rates of dissatisfaction. Clearly, the number of specialists is insufficient and should be increased.

In regards to GP education in drug allergy, about 40% of GPs had no specific training, the same rate was reported by Leru (13). This training is clearly insufficient, since more than two thirds of them mentioned difficulty in distinguishing allergic from non-allergic drug reactions. This same conclusion was reached by a survey undertaken by Yin Wang *et al.*, in Central China (25). Somewhat unexpected is that specific training did not improve the GPs' skills in drug allergy diagnosis, but a similar outcome was achieved by Sturmand and Temprano's survey at St. Louis University Medical Center, Missouri (USA) (24). This finding clearly calls into question the effectiveness of the training and strongly suggests that there should be an assessment of its quality by objectively measuring the results. Particularly, a more practical approach to learning should be emphasized. A positive attitude towards further training was expressed by almost all the GPs, in line with other published articles (13, 24).

Training sessions would be welcomed and locally delivered in health centers should be the chosen model. The need and interest for educational programs on drug allergy was also expressed in other European studies (12).

The use of an online questionnaire allowed us to gather information from all over the country in a practical, fast and inexpensive way, providing data that was easy to analyze and compare, while keeping the participant's anonymity. On the other hand, this methodology brought limitations to our study. Some of these limitations are those related to this type of study: the responses may not be completely truthful; there may be different interpretations of the questions, without the possibility of assuring a correct understanding; the emotional component of the answers cannot be perceived; the growing number of solicitations to respond to surveys may lead to a survey fatigue and a lower rate of response. Other limitations concerning specifically our study were the inexistence of a validated questionnaire for assessing educational needs in drug allergy and the bureaucratic difficulties faced in the distribution of questionnaires.

The results of our study suggest that GPs are generally aware of drug allergy as a problem, although sometimes fail to value

some of the impacts of not investigating it. Additionally, we can conclude that the incidence of drug is perceived as an increasing phenomenon and the main culprits that were recognized were antibiotics and non-steroidal anti-inflammatory drugs. The study also reveals that the delayed response of Immunoallergology Departments in some regions accounts to some degree for GP dissatisfaction. Finally, this study highlights the need and the interest of family doctors in further drug allergy education, but quality criteria and practical issues should be reinforced in the training.

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None.

Contributions

BKC, LS, AMM: analysis conceptualization and design, data collection, analysis performance, writing - original draft. SMF, ET: analysis conceptualization and design, analysis performance, writing - original draft. TA, CM, FI: writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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Appendix 1 - Questionnaire.

Dear colleagues,

Drug allergies are a pathology of supreme importance in the clinical practice of General Practitioners. As such, we kindly ask you to express your opinion in this area, taking into account the current clinical reality. Your answers are very important for the evaluation of this pathology in primary health care and will contribute to the identification of medical and educational training needs as well as the adequacy of the available information systems. The information obtained in this questionnaire is strictly confidential and only for scientific purposes.

Thank you for your cooperation!

I agree that collected data in this anonymous questionnaire will be processed within the scope of this study.

Fields marked with (*) are required:

» **Professional experience***

- Specialist with less than 5 years practice
- Specialist between 5 to 10 years practice
- Specialist with 10 to 20 years of practice
- Specialist with > 20 years of practice
- Trainees

» **Of which ARS do you belong to?***

- ARS Norte
- ARS Centro
- ARS Lisboa e Vale do Tejo
- ARS Alentejo
- ARS Algarve

» **How do you describe the incidence of drug allergy in Portugal?***

- Stable
- Increasing
- Decreasing

» **What do you consider to be the class of drugs most often responsible for allergic reactions? (More than one possible option)***

- Antibiotics
- Non-steroidal anti-inflammatory drugs
- Cardiovascular medication
- Anti-inflammatory
- Vaccines
- Vitamins
- Psychiatric and/or neurological medication
- Contrast

» **Which consequences do you consider the most common after a diagnosis of drug allergy? (More than one possible option)***

- Patient insecurities in the future use of other medicines
- Risk of death
- Less therapeutic options
- Difficulty in finding appropriate therapies
- Contraindication to some diagnostic tests
- Other: _____

» **What percentage of risk of death exists because of drug allergy?***

- 0%
- > 1-5%
- > 5-10%
- > 10-20%
- > 20%
- I don't know

» **How do you evaluate the importance of drug allergy in your clinical practice?***

- 1- No important 2 3 4 5-Very important

» **How many patients have evidence of drug allergy in your total patients list?***

- < 10
- ≥ 10-30
- ≥ 30-50
- ≥ 50-100
- ≥ 100
- I don't know

» **How often have you seen patients with drug allergy in the last year?***

- Daily
- Weekly
- Monthly
- Twice a year
- Annually
- Never

» **How many of these patients were investigated for drug allergy?***

- None
- About 1/3
- About half
- About 2/3
- All

- » **In how many of these cases did this drug allergy have an impact on your therapeutic decision? ***
- None
 - About 1/3
 - About half
 - About 2/3
 - All
- » **Which sign or symptom do you consider to be the most characteristic of drug allergy? (More than one possible option) ***
- Skin lesions
 - Facial edema
 - Itching
 - Respiratory symptoms
 - Change in blood pressure
 - Indisposition
 - Other: _____
- » **In cases where there was an implication in the therapeutic decision, you decided to: (More than one possible option) ***
- Do not medicate
 - Lower the dose of medication
 - Alternative drug
 - Add antiallergic drug
 - Other: _____
- » **Do you usually refer patients without a confirmed diagnosis to Immunoallergology? (More than one possible option) ***
- All patients
 - No patient
 - Children
 - When you don't have an alternative drug
 - Only when the reaction is caused by certain drugs
 - At patient's request
 - Other: _____
- » **If you have selected the option "only when the reaction is caused by certain drugs", specify which: _____**
- » **Do you find it easy in your clinical practice to distinguish an allergic reaction to a drug from a non-allergic reaction? ***
- Yes
 - No
- » **During the past year, did you notify the National Pharmacovigilance System for adverse drug reactions (allergic or not) in your patients? Note: Does not include notification in SClinic or other registration system used. ***
- Yes, I notified all reactions
 - Yes, I notified less usual and/or the most serious reactions
 - Yes, I notified the reactions in that I considered very probable
 - No, I never notified the National System
- » **Currently in your clinical practice, how long does it take to have an Immunoallergology consultation requested by you to study drug allergy? ***
- < 1 month
 - 1-3 months
 - 3-6 months
 - > 6 months
- » **Are you satisfied with the Immunoallergology specialty collaboration in your area? ***
- Yes
 - No
- » **Do you consider that the training in drug allergy is relevant to your clinical practice? ***
- 1- No important 2 3 4 5-Very important
- » **Have you participated in any drug allergy training? (More than one possible option) ***
- University
 - Postgraduate course
 - Congress
 - In our health center
 - No
 - Other: _____
- » **Would you be interested in participating in training in this area? ***
- Yes
 - No
- » **If so, what kind of training would you prefer? ***
- Online course
 - Training actions in health centers
 - Courses/ workshops in national or regional congresses
 - Discussion of cases with specialist regularly
 - 2nd and 4th options
 - 1st and 2nd options