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Anti-VEGF intravitreal injection rates and associated factors in Portugal: A National Study

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TITLE PAGE

TITLE: ANTI-VEGF INTRAVITREAL INJECTION RATES AND ASSOCIATED FACTORS IN PORTUGAL: A NATIONAL STUDY

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ABSTRACT

Aims: The arrival of anti-vascular endothelial growth factor (anti-VEGF) therapies represented a treatment shift for several ophthalmologic disorders and led to an increasing number of patients undergoing intravitreal injections. The aims of this observational study were to assess the expansion of anti-VEGF intravitreal injections in the Portuguese National Health System (NHS) and to identify factors correlated with geographic variations in episode rates. **Methods:** Administrative database on discharge from Portuguese NHS hospitals was analysed for annual values and rates of intravitreal anti-VEGF injections at a national and regional level, between 2013 and 2018. **Results:** The number of episodes of anti-VEGF treatment and patients treated increased 16% and 9% per year, respectively, between 2013 and 2018. During the study period around 72% of patients were treated in the Metropolitan areas of Lisbon and Porto and in the Central region. Intravitreal anti-VEGF treatment rates in 2018 were 560 per 100,000 population and presented high variability between municipalities. Higher anti-VEGF treatment rates at the municipality level were associated with shorter distances between their residence and the hospital. At the hospital level, higher ratio of ophthalmologists and higher organizational level were associated with higher anti-VEGF treatment rates. **Conclusion:** The number of episodes and patients treated with anti-VEGF injections has been growing in recent years. Proximity to health care, more access to ophthalmologists, and hospitals with higher organizational levels are associated with higher anti-VEGF treatment rates. Improving access is crucial to reduce regional discrepancies and ensure optimal treatment frequency, which may improve health outcomes.

Keywords: Anti-VEGF, Intravitreal injection, Access to eye care, Neovascular age-related macular degeneration, diabetic macular oedema

Synopsis: The number of episodes of anti-VEGF injections and treated patients increased between 2013 and 2018 in Portugal. Regional variations in treatment rates were associated with proximity to health care, ophthalmologists supply, and hospitals´ organizational levels.

Article Summary:

Strengths and limitations of the study

- Nationwide information on antivascular endothelial growth factor (anti-VEGF) intravitreal injections in the Portuguese NHS between 2013 and 2018.
- Characterization of anti-VEGF intravitreal injections according to diagnostic, geographic distribution, and average number of injections per year per patient.
- Methods employed produced evidence of inequalities in treatment for diseases that can lead to irreversible loss of sight.
- ICD codes and procedures used as a proxy to identify episodes with anti-VEGF.
- Activity in the private health sector was not included in the analysis.

INTRODUCTION

The availability of anti-vascular endothelial growth factor (anti-VEGF) therapies represented a treatment shift for a range of ophthalmologic disorders, with a dramatic impact on serious conditions that were previously untreatable resulting in irreversible damages and loss of sight [1,2]. Anti-VEGF intravitreal injections act by reducing neovascular progression and were initially approved for the treatment of neovascular age-related macular degeneration (nAMD) [3,4]. Currently, anti-VEGF therapies are indicated for the treatment of a vast number of other ocular diseases such as diabetic macular oedema (DME), choroidal neovascularization (CNV), and retinal vein occlusion (RVO) [2]. Clinical trials have showed that anti-VEGF intravitreal injections prevented vision loss in the majority of patients and, in some cases, significantly improved vision [2,3,5]. The positive impact of anti-VEGF injections in visual outcomes [2,6–8] combined with the lack of previous efficient treatments, led to rapid diffusion of anti-VEGF treatments in many countries [4,6,9,10].

The main barriers for treatment with anti-VEGF are the high costs of the drugs, the need for multiple treatments, and the need for the treatments to be administered by specially trained personnel at hospitals [6,11]. Access is hindered in countries such as the United States [11] and in many Asian countries [6], where the drugs are not reimbursed by the health systems. Even in countries for which anti-VEGF treatments are reimbursed by the health system, such as England, Norway, and Portugal, studies report considerable geographic variation in treatment rates [4,10,12]. The study in Norway showed that the geographic variations in episode rates are challenges to the policy goals regarding equitable access and care, calling for further investigation [4]. The study in Portugal indicated that the number of hospital episodes related with anti-VEGF injections increased from 1,815 in 2001 to 25,106 in 2012, which is a mean annual increase of 32% [10].

In Portugal, Ranibizumab has been reimbursed by the NHS since 2008 [10], and by 2018 Bevacizumab and Aflibercept were also reimbursed [13]. Despite the equity-oriented nature of the Portuguese health system and the low co-payment values, a study covering the 2002-2012 period found unequal geographic distribution in treatment rates across the country [10]. Patients from regions without ophthalmology departments and lower population density received fewer treatments than other regions [10]. More recent estimates on the diffusion of anti-VEGF intravitreal injections are needed to understand how this treatment has expanded with the existence of additional elective pharmaceuticals.

Understanding the trends in anti-VEGF treatments in terms of number of episodes and patients is of great importance for assessing health technologies. Assessing access to and impact of health technologies is paramount in investigating the number of episodes and patients treated. Periodic investigations about access to health technologies is vital to prevent health inequalities and to learn how to proceed if different technologies arise. The aim of this study was twofold: to analyse the expansion of anti-VEGF intravitreal injections in the Portuguese NHS between 2013 and 2018 and to identify factors associated with geographic variation in treatment rates.

MATERIALS AND METHODS

Data source and inclusion/exclusion criteria

This observational study used an administrative database on hospital discharges from public hospital institutions in mainland Portugal, which includes information about sex, age, municipality of residence,

principal and secondary diagnosis and procedures, discharge hospital, and a unique patients' identifier from all inpatient and day case episodes. Use of this database was authorized for research purposes by the Portuguese Health System Central Administration (ACSS). The database is anonymized, guaranteeing the confidentiality of individuals, and it was therefore not necessary to obtain patients´ consent or approval by an ethics committee for this study.

Episodes related to intravitreal injections with anti-VEGF between 2013 and 2018 were selected according to procedures records coded with International Classification of Diseases (ICD) 9th version- Clinical Modification (ICD-9CM) and ICD 10th version (ICD-10) for episodes registered from 2017. As in previous studies, ICD-9CM procedures codes 1474, 1475, 1479, and 149 and ICD10 procedures codes 3E0C30M and 3E0C3GC were used as proxy to anti-VEGF treatments [10,12]. Note, however, that these codes might also capture intravitreal injections for other drugs such as injectable antibiotics or corticosteroids [10,12].

Subsequently, the criteria for classification and exclusion of episodes were applied to assign a diagnosis for each episode. Episodes with missing data on sex, age, diagnosis and procedures, and discharge hospitals were excluded. ICD-10 bilateral episodes were counted as two injections, while the number of patients was counted as one. The *Supplementary Material- Appendix 1* contains details on the ICD codes used and the criteria to assign a diagnosis for each episode.

Data analysis

We examined the number of episodes and patients treated by year, by diagnosis, and by region (according to patient's municipality of residence). The number of patients treated per year was estimated using the unique patients' identifier, regardless of whether they were already in treatment in the previous years or if they entered the database in that specific year. Then, using the patient as unit of observation, we computed the average number of injections per year for each diagnosis (nAMD, CNV, DME or RVO). Finally, we proceeded with the investigation of factors associated with geographic variations in anti-VEGF standardized treatment-rates.

Statistical analysis was conducted to investigate factors associated with geographic variations in anti-VEGF standardized treatment-rates. This ecological analysis was performed in two parts: the first had as unit of analysis the municipality of residence of the patient and in the second the unit of analysis was the hospital where the injection was performed. For analysis refinement, only patients aged 50 years or older were included in the analysis of associated factors, as the conditions for which anti-VEGF injections are indicated affects mostly people in this age category [2,12].

For the ecological analysis at the municipality level the rate of episodes related to intravitreal injections with anti-VEGF treatments per 100,000 population was the dependent variable. The independent variables analysed were patients' characteristics (mean age, proportion by sex, mean distance to hospital in kilometres - according to patient's municipality of residence and municipality where the hospital is located), and municipalities´ characteristics (purchasing power, number of ophthalmologists per 20,000 persons, and number of ophthalmology consultations per 1,000 persons). The characteristics of the patients were retrieved from the hospital discharge database, and the characteristics of the municipality variables obtained from Statistics Portugal [14]. For the characteristics of patients, municipalities were separated into two categories for each year: "Higher rates" category for the municipalities with episode rates higher than the median and "Lower rates" category for the municipalities with episode rates lower than the median. The Mann-Whitney test was used to compare patients' characteristics according to these two categories. For the

characteristics of the municipalities, associations were analysed according to Spearman's correlation analysis and multivariate linear regression models, with treatment rates as dependent variables and the independent variables (purchasing power, number of ophthalmologists per 20,000 persons, and number of ophthalmology consultations per 1,000 persons) added following the stepwise method.

For the ecological analysis at the hospital level, the dependent variable was the episode rates, and the independent variables were the number of ophthalmologists per 20,000 persons in the hospital's catchment area and the organizational level of the hospital's ophthalmology departments (hospitals´ ophthalmology units were divided into three groups, classified according to the general requirements established by the National Network of hospital specialties and referral for Ophthalmology [15], as shown in the *Supplementary Material- Appendix 2*). As these independent variables were not available per year, the years 2013-2018 were collapsed into a single period of analysis. The association with ophthalmologist specialists was analysed using Spearman´s correlation analysis. The Kruskal-Wallis test was used to compare the episode rate between the three groups of hospitals. Hospitals in group III have a wider range of health care activities, longer opening hours, and greater equipment availability than hospitals in group II, and the same for group II in relation to group I hospitals. Data on number of ophthalmologists and more details on organizational level of hospitals by groups can be found in the report of the National network of hospital specialty and referral for Ophthalmology [15].

A 5% significance level was adopted. Statistical analysis was performed using the IBM SPSS Statistics v26.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. The study was conducting by analysing hospitalization databases, therefore not possible to involve patients or the public.

RESULTS

Evolution, characteristics, and distribution of anti-VEGF treatments

There were 298,429 episodes of anti-VEGF treatment between 2013 and 2018, and 65,534 patients treated. As illustrated in Figure 1, the number of episodes increased from 30,542 in 2013 to 64,867 in 2018, which corresponds to a mean annual increase of 16%. The number of patients treated in 2013 was 12,951, growing to 19,627 in 2018 (mean annual increase of 9%). In 2018, the anti-VEGF standardized treatment-rate was 560 per 100,000 persons.

Figure 1. Number of hospital episodes of anti-VEGF treatments and patients treated per year, from 2013 to 2018. Portugal

The majority of patients (71%) were treated with intravitreal anti-VEGF in the Metropolitan area of Lisbon, Central region, and Metropolitan area of Porto (Table 1). The Algarve had the lowest proportion of patients treated between 2013 to 2018 (2.6%).

Table 1. Proportion of patients treated with anti-VEGF injections, between 2013 and 2018, per year, Portugal

Region	2013	2014	2015	2016	2017	2018	Total
Alentejo	6.32%	6.46%	6.74%	7.51%	6.88%	7.54%	7.53%
Algarve	2.03%	1.97%	1.99%	2.71%	3.33%	3.21%	2.58%
Metropolitan area of Lisbon	23.72%	23.03%	23.59%	23.50%	23.96%	23.64%	24.32%
Metropolitan area of Porto	24.70%	25.34%	24.41%	22.68%	27.30%	26.81%	23.44%
Central region	25.73%	24.77%	25.39%	25.39%	17.22%	18.35%	23.69%
Northern region	17.50%	18.44%	17.88%	18.20%	21.31%	20.46%	18.43%

As summarized in Table 2, the most common diagnosis was nAMD, followed by DME and RVO. These three diagnoses accounted for 70% of episodes. nAMD was the most common condition in every year analysed, except 2016, when DME was the most common.

Table 2. Total episodes of anti-VEGF between 2013 and 2018, by diagnosis and year, Portugal

Diagnosis	Total			2013		2014		2015		2016		2017		2018	
	N	%	% cummulative	N	%	N	%	N	%	N	%	N	%	N	%
Neovascular age-related macular degeneration (nAMD)	100,168	33.57	33.57	11,575	37.90	13,415	36.32	16,357	33.60	16,094	28.95	20,857	33.74	21,87	33.72
Diabetic macular edema (DME)	85,997	28.82	62.38	6,578	21.54	8,044	21.78	13,371	27.47	18,181	32.70	19,769	31.98	20,054	30.92
Retinal vein occlusion (RVO)	18,716	6.27	68.65	1,451	4.75	2,104	5.70	2,841	5.84	3,500	6.30	3,956	6.40	4,864	7.50
Unspecified macular degeneration	16,042	5.38	74.03	1,750	5.73	1,862	5.04	2,712	5.57	3,979	7.16	2,724	4.41	3,015	4.65
Proliferative diabetic retinopathy	15,737	5.27	79.30	1,846	6.04	2,297	6.22	2,726	5.60	2,144	3.86	3,250	5.26	3,474	5.36
Choroidal neovascularization (CNV)	13,783	4.62	83.92	1,698	5.56	2,190	5.93	2,619	5.38	3,040	5.47	2,154	3.48	2,082	3.21
Retinal edema	12,581	4.22	88.14	1,256	4.11	1,890	5.12	1,690	3.47	1,677	3.02	2,575	4.17	3,493	5.38
Other diagnosis	35,405	11.86	100	4,388	14.37	5,129	13.89	6,361	13.07	6,979	12.55	6,533	10.57	6,015	9.27
Total	**298,429**	100		30,542	100	36,931	100	48,677	100	55,594	100	61,818	100	64,867	100

Table 3 summarizes the average increase in the number of injections per year per patient, by diagnosis. The highest number of injections per year per patient was for nAMD, which increased from 2.72 in 2013 to 3.37 in 2018. In contrast, CNV had the lowest values, reaching 2.01 injections per year per patient in 2018.

Table 3. Average number of injections per year per patient, by diagnosis, 2013 to 2018, Portugal

Diagnosis	2013	2014	2015	2016	2017	2018
nAMD	2.72	2.77	2.96	2.72	3.4	3.37
DME	2.33	2.32	2.64	2.88	2.77	2.80
CNV	1.35	1.43	1.41	1.51	2.06	2.01
RVO	1.88	2.08	2.25	2.38	2.42	2.48

Factors associated with geographic distribution of anti-VEGF injections

Table 4 shows the comparison of characteristics of patients at the municipality level. In 2016, patients treated with anti-VEGF intravitreal injections who lived in municipalities with episode rates higher than the median ("Higher rates" category) were older. In 2013, municipalities in the "Higher" category had a significantly higher proportion of females. For the distance between municipality of residence and hospital, significant differences were found for all years, with the average distance being shorter for municipalities in the "Higher" category.

Table 4. Mann-Whitney test for individual variables by municipality category

Year	Age Mean (standard deviation)				Sex (proportion of men) Mean (standard deviation)				Distance in Kilometres Mean (standard deviation)			
	Lower rates	Higher rates	U	signif.	Lower rates	Higher rates	U	signif.	Lower rates	Higher rates	U	signif.
2013	70.70 (4.64)	71.43 (2.65)	8737	0.168	**0.511 (0.214)**	**0.465 (0.130)**	**8256***	**0.036**	**88.50 (50.25)**	**46.13 (30.58)**	**4187***	**<0.001**
2014	70.90 (4.50)	71.02 (2.64)	9466	0.772	0.499 (0.198)	0.486 (0.121)	9025	0.343	**84.11 (52.25)**	**46.08 (32.22)**	**4835***	**<0.001**
2015	70.62 (4.07)	71.35 (2.92)	8553	0.098	0.519 (0.179)	0.486 (0.110)	8484	0.079	**81.04 (51.11)**	**42.62 (25.65)**	**4701***	**<0.001**
2016	**70.58 (3.71)**	**71.61 (2.62)**	**7656***	**0.004**	0.500 (0.169)	0.503 (0.099)	9218	0.576	**73.52 (49.44)**	**40.99 (28.36)**	**5098***	**<0.001**
2017	72.30 (5.37)	71.66 (2.71)	7826	0.135	0.480 (0.244)	0.511 (0.127)	7989	0.218	**69.69 (53.74)**	**41.89 (32.51)**	**6238***	**<0.001**
2018	72.26 (4.70)	72.02 (2.56)	8553	0.449	0.523 (0.233)	0.484 (0.107)	8246	0.216	**82.88 (72.94)**	**66.42 (65.37)**	**7586***	**0.002**

In the bivariate correlation analysis of the rate of anti-VEGF treatments with the independent ecological variables, a positive correlation was found for: purchasing power in the years 2016 (p-value <0.001) and 2018 (p-value <0.001); rate of ophthalmologists in 2015 (p-value = 0.042) and 2016 (p-value = 0.016); ophthalmology consultations in all hospitals in 2013 (p-value = 0.047) and 2016 (p-value = 0.018), and consultations in public hospitals in 2013 (p-value = 0.040) and in 2016 (p-value = 0.030).

Stepwise linear regression models were generated for each year. Between 2013 and 2015 the variable ophthalmology consultations was included with a positive coefficient. For 2016 to 2018, the variable that remained in the model was purchasing power, with a positive coefficient. The models had low adjusted R^2

(the highest was 0.043 in 2018) and the analysis of residues was inconclusive regarding the quality of the models.

In the ecological analysis at the hospital level, the bivariate Spearman's correlation between the rate of anti-VEGF treatments between 2013 and 2018 and the ratio of ophthalmologists had a positive correlation (ρ = 0,359; n = 40; p-value = 0.023). The Kruskal-Wallis test showed a statistically significant difference in episode rates with anti-VEGF according to the hospital's organizational level (H(2) = 7.054; p-value = 0.029). More specifically, the results indicate that hospitals in group III had a higher episode rate than hospitals in group II. These, in turn, had higher episode rates than group I hospitals.

DISCUSSION

The aim of this study was to analyse the expansion of anti-VEGF intravitreal treatments in the Portuguese NHS and to identify factors associated with geographic variations. Results indicate that access to treatment with anti-VEGF injection has been increasing in Portugal, and that they were first used to treat nAMD, followed by DME, CNV, and RVO. An increase in the number of injections per patient per year was observed for all diagnoses. More than half of the episodes with anti-VEGF were recorded in the metropolitan areas of Lisbon and Porto.

Given the positive impact of anti-VEGF injections on health outcomes for many ocular neovascular diseases, the expansion in injections performed and patients treated seems justified. The evolution of anti-VEGF treatments found from 2013 to 2018 was consistent with values reported by Marques et al. [10] from 2002 to 2012. The total number of injections per year in Portugal varied from less than 2,000 to over 60,000 in 16 years. As anti-VEGF injections are covered by the Portuguese NHS [10,13,16] and are safe and highly effective [17], there are reasons to expect that this upward tendency will continue to be observed in the coming years.

Neovascular AMD and DME diagnosis corresponded to 63% of episodes associated with anti-VEGF treatment between 2013 and 2018. An analysis of the literature revealed that AMD was the eye pathology most often addressed in scientific publications between 2013 and 2018 [18], and it was the most common condition for which anti-VEGF intravitreal injections were used in countries like England [12], Norway [4], and the United States [19].

The number of injections per year per patient for nAMD increased within the period analysed, reaching 3.37 injections per year in 2018. The on-label treatment guidelines for treatment of nAMD for both Ranibizumab and Aflibercept supported monthly injections in the first three months followed by treat and extend regimen (flexible, according to the needs of the patient) [20,21]. Therefore, in a first year of treatment, it would correspond to between 6 to 12 injections (due to loading dose), while in the second year and thereafter it would correspond to 4 to 12 injections. Although there was no information on which drug was used to treat the patients analysed, the values of the on-label standards are greater than what was observed in this study. This low frequency of injections per year was also found in Portugal before 2013 [10], England (2.7 in 2008) [12], and Norway (4.1 in 2015) [4]. On the one hand, these results may indicate difficulties to access the treatment, leaving patients undertreated [22–25]. On the other hand, some clinical studies indicate that variable frequency of anti-VEGF injections is also effective in the treatment of nAMD, and therefore this flexible regimen may have been increasingly adopted [1,26].

The geographic variations in episode rates in Portugal observed between 2002 and 2012 were associated with the availability of anti-VEGF therapies and ophthalmology services, as well as population density [10]. These results indicate that patients from distant cities or rural areas may have delayed access to treatments and were more likely to miss follow-up appointments [10]. The findings for the period from 2013 to 2018 corroborate this possibility, as the distance between municipality of residence and hospital was significantly different between municipalities with higher and lower episode rates. A systematic review of factors associated with non-adherence to anti-VEGF treatment has also identified greater distance to hospital as a potential contributing factor [27]. Lower numbers of ophthalmologist and consultations were also associated with lower episode rates.

Similar results were found in Norway [4] and England [12]. National rates of intravitreal injections in England had a 50-fold variation in age-standardized rates between regions [12]. In Norway, the age adjusted number of episodes across counties varied from 19 to 55 per 1,000 persons aged 50 years or older [4]. These studies demonstrated challenges associated with the arrival of this treatment that include frequent and long-term administration and high allocation of resources. Despite the effort to guarantee geographical equity of access afforded by the health systems in England, Norway, and Portugal, the variations in anti-VEGF rates indicate that challenges remain.

Because anti-VEGF drugs are injected directly into the vitreous body, there are requirements for use of this treatment that can include specialized training and the setting up of a location dedicated to injection [28]. These requirements might be difficult to achieve in small hospitals due to financial or technical limitations [10]. The results showed significant differences in anti-VEGF treatment rates between hospitals, according to the number of specialists and their organizational level.

The present study has found that despite the considerable expansion of anti-VEGF treatments between 2013 and 2018 in Portugal, geographic variations still remain. Although the methodology chosen did not produce robust evidence to accurately identify the reasons behind these variations, there are strong indications that barriers previously discussed by Marques et al [10] and also observed in England [12] and Norway [4] are possibly a root cause, and in any event remain a challenge.

Strengths of this study reside in the use of nationwide information and long period of analysis. The geographical and temporal analysis performed produced important results to monitor the diffusion of anti-VEGF treatments in Portugal, while raising awareness of persisting inequalities. The statistical methods employed allowed the identification of factors that should be addressed to ensure the treatment of patients with ophthalmologic needs. However, there are also limitations associated with its use that are important to mention. The procedures and ICD codes were used as a proxy to identify episodes with anti-VEGF and the associated diagnosis, since there are no further details about the intravitreal injection such as the drugs used in each episode. Thus, it is possible that in some cases anti-VEGF have not been administered, overestimating the findings reported herein. Future studies may collect more accurate information on episodes to ensure correspondence to anti-VEGF intravitreal injections.

Because the database includes activities carried out only in the public sphere in mainland Portugal, procedures carried out in private institutions and with an out-of-pocket scheme, or in the Azores and Madeira are excluded. At the time of analysis, data for 2017 and 2018 were provisional, as two hospitals had underreported information.

CONCLUSION

The development of anti-VEGF drugs has brought effective treatment for retinal diseases that can lead to severe visual impairment. This study shows that the number of episodes related to anti-VEGF treatment as well as the number of treated patients increased between 2013 and 2018. However, the distribution of treatment with anti-VEGF showed regional asymmetries. Factors such as proximity to health care, greater access to ophthalmologists and hospitals having ophthalmologic departments with more human resources, more equipment, and higher differentiation level were associated with higher rates of anti-VEGF treatment. Improving access to treatment is crucial to address the regional discrepancies found and to ensure that treatment follows patients' clinical needs and enhances better health outcomes. The increasing number of treatment episodes related to anti-VEGF, the low number of injections per patient per year, and the regional discrepancies detected impose challenges to the NHS in terms of budget and access. Given the ageing of the population and the fact that more anti-VEGF drugs have been developed and approved, both demand and supply of these treatments are likely to increase.

DECLARATIONS

Author's contribution

APM, MAS, PAL, RS conceived and designed the study. JVR, APM had full access to the data and conducted initial analysis. JVR, APM, MAS, ASA, JF conducted the analysis and interpreted the results. AFM, PAL advised on interpretation of the results. JVR, MP drafted the manuscript. AFM, ASA, JF participated in the discussions and provided the clinical feedback. MAS, RS provided critical feedback to the manuscript. All the authors revised the manuscript for important intellectual content, contributed to the data interpretation and writing, and critically reviewed the manuscript at all stages and approved the final copy.

Patient consent for publication

Obtaining informed consent was not required under national regulations because the patient data were anonymized.

Ethics approval statement

Obtaining approval by an ethics board was not required under national regulations because the patient data were anonymized.

Data sharing statement

The data of hospitalizations are the property of Central Administration of the Health System (Administração Central do Sistema de Saúde (ACSS), I.P.). However the data are available from the authors upon request and with permission of the ACSS. The data of hospitalizations are not publicly available, however the authors confirm that interested researchers can ask for access to these data by contacting ACSS directly at the following: Parque da Saúde da Lisboa, Edifício 16, Avenida do Brasil, 53 1700-063 Lisboa, Portugal (e-mail: geral@acss.min-saude.pt).

Competing interests statement

M Afonso-Silva, P A. Laires, A S. Almeida, J Fernandes, and M Pardal are employees of Novartis Farma, Produtos Farmacêuticos SA, Porto Salvo, Portugal.

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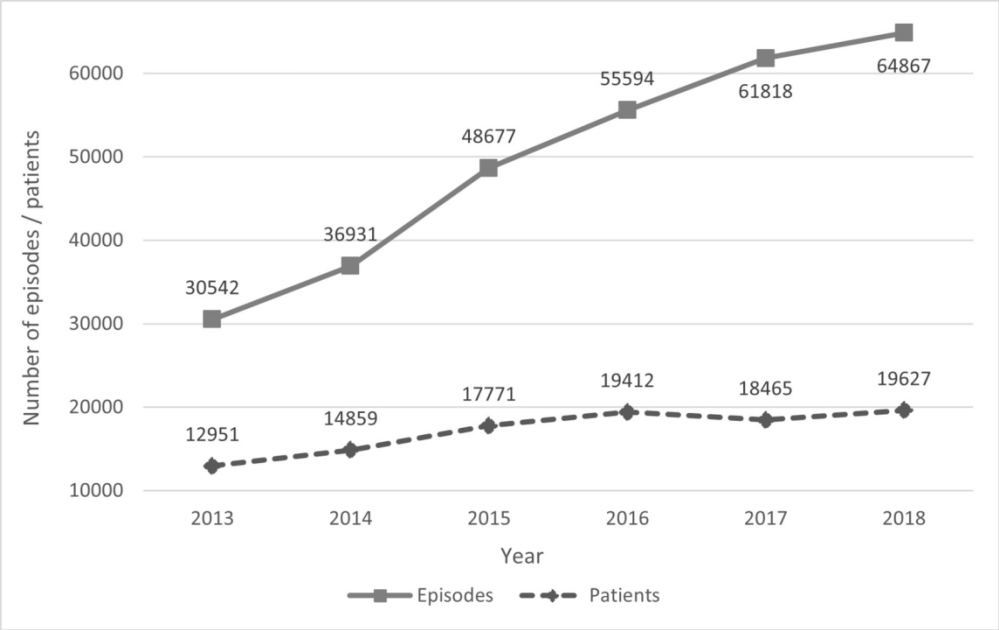

Figure 1. Number of hospital episodes of anti-VEGF treatments and patients treated per year, from 2013 to 2018. Portugal

147x92mm (300 x 300 DPI)

Appendix 1

Table 1. ICD Procedure codes used to select episodes related to intravitreal injections with anti-VEGF

ICD version	Code	Denomination
ICD-9	1474	Other mechanical vitrectomy
ICD-9	1475	Injection of vitreous substitute
ICD-9	1479	Other operations on vitreous
ICD-9	149	Other operations on retina, choroid and posterior chamber
ICD-10	3E0C30M	Introduction of monoclonal antibody into eye, percutaneous approach),
ICD-10	3E0C3GC	Introduction of other therapeutic substance into eye, percutaneous approach

IDENTIFICATION OF INTRAVITREAL ANTI-VEGF TREATMENT EVENTS FOR ICD-9

1. Main indications

Indication: DIABETIC MACULAR EDEMA (DME)

Numerator: Discharges, with either:

- A principal diagnosis code for Diabetic Macular Edema **(DIMAED)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Diabetic Macular Edema **(DIMAED)**.

Indication: RETINAL VEIN OCCLUSION (RVO)

Indication: RETINAL VEIN OCCLUSION (CENTRAL)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Central **(RVOCEN)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion- Central **(RVOCEN)**.

Indication: RETINAL VEIN OCCLUSION (BRANCH)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Branch **(RVOBRA)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion- Branch **(RVOBRA)**.

Indication: NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (nAMD)

Numerator: Discharges, with either:

- A principal diagnosis code for Exudative age-related macular degeneration **(EXARMD)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)**, or

- A principal diagnosis code for Other Conditions of the Retina and Choroid **(OCRECH)** or for Cystoid Macular Degeneration **(CYMADE)** or for Unspecified Macular Degeneration **(UNMADE)** and any secondary diagnosis codes for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)**.

Indication: CHOROIDAL NEOVASCULARIZATION (CNV)

Numerator: Discharges with either:

- A principal diagnosis code for Retinal neovascularization or Myopia **(RNVMYO)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal neovascularization or Myopia **(RNVMYO)** or
- A principal diagnosis for Other Conditions of the Retina and Choroid **(OCRECH)** and any secondary diagnosis, except if admission is for Indication neovascular age-related Macular Degeneration **(AMD)**.
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Other Conditions of the Retina and Choroid **(OCRECH)**, except if admission is for Indication neovascular age-related Macular Degeneration **(AMD)**.

2. Other indications

Indication: OTHER VASCULAR OCCLUSIONS

**This indication is not included in Retinal Vein Occlusion*

Numerator: Discharges, with either:

- A principal diagnosis code for Other Vascular Occlusions **(OTVAOC)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion **(OTVAOC)**.

Indication: ATROPHIC MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Atrophic Macular Degeneration **(ATMADE)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Atrophic Macular Degeneration **(ATMADE)**.

Indication: CYSTOID MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Cystoid Macular Degeneration **(CYMADE)** and any secondary diagnosis codes, except for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)** or for Atrophic Macular Degeneration **(ATMADE)**; and patient aged less than 50 years old.

Indication: UNSPECIFIED MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Unspecified Macular Degeneration **(UNMADE)** and any secondary diagnosis codes, except for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)** or for Atrophic Macular Degeneration **(ATMADE)**, or
- A principal diagnosis code for Cystoid Macular Degeneration **(CYMADE)** and any secondary diagnosis codes, except for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)** or for Atrophic Macular Degeneration **(ATMADE)**; and patient aged 50 years old or more.

3. Diabetes with ophthalmic manifestations not stated as uncontrolled

For episodes with principal diagnosis codes 25050 and 25052, not classified as any indication above, the following criteria applies:

If any secondary diagnosis code:	Indication
36201	Unspecified Diabetic Retinopathy
36202	Proliferative Diabetic Retinopathy
36203 to 36206	Nonproliferative Diabetic Retinopathy
Other diagnosis code	The secondary diagnosis code
No diagnosis code	25050 or 25052

4. Other relevant diagnosis to be included

For episodes with the principal diagnosis codes below, not classified as any indication above, the indication is the principal diagnosis itself:

3612	Serous retinal detachment
3619	Unspecified retinal detachment
25000	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
25052	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
25053	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
36100	Retinal detachment with retinal defect, unspecified
36101	Recent retinal detachment, partial, with single defect
36102	Recent retinal detachment, partial, with multiple defects
36103	Recent retinal detachment, partial, with giant tear
36105	Recent retinal detachment, total or subtotal
36106	Old retinal detachment, partial
36107	Old retinal detachment, total or subtotal
36181	Traction detachment of retina
36189	Other forms of retinal detachment
36210	Background retinopathy, unspecified
36212	Exudative retinopathy
36215	Retinal telangiectasia

36216	Retinal neovascularization NOS
36240	Retinal layer separation, unspecified
36242	Serous detachment of retinal pigment epithelium
36243	Hemorrhagic detachment of retinal pigment epithelium
36254	Macular cyst, hole, or pseudohole
36257	Drusen (degenerative)
36281	Retinal hemorrhage
36283	Retinal edema
36442	Rubeosis iridis
36474	Adhesions and disruptions of pupillary membranes
37060	Corneal neovascularization, unspecified
37923	Vitreous hemorrhage
37924	Other vitreous opacities
37925	Vitreous membranes and strands
37929	Other disorders of vitreous

5. Other relevant diagnosis to be excluded

For episodes with the principal diagnosis codes below, not classified as any indication above, the episode is excluded from the database:

36610	Senile cataract, unspecified
3638	Other disorders of choroid
3669	Unspecified cataract
8715	Penetration of eyeball with magnetic foreign body
36282	Retinal exudates and deposits
36289	Other retinal disorders
36504	Ocular hypertension
36563	Glaucoma associated with vascular disorders
36614	Posterior subcapsular polar senile cataract
36619	Other and combined forms of senile cataract
37922	Crystalline deposits in vitreous
99653	Mechanical complication due to ocular lens prosthesis
99679	Other complications due to other internal prosthetic device, implant, and graft

6. Other diagnosis to be excluded

For episodes with the principal diagnosis codes below, the episode is excluded from the database:

8711	Ocular laceration with prolapse or exposure of intraocular tissue
36000	Purulent endophthalmitis, unspecified
36001	Acute endophthalmitis
36615	Cortical senile cataract
36616	Senile nuclear sclerosis
36617	Total or mature cataract
36653	After-cataract, obscuring vision

37931	Aphakia
37932	Subluxation of lens
37934	Posterior dislocation of lens
99859	Other postoperative infection
99882	Cataract fragments in eye following cataract surgery
V5849	Other specified aftercare following surgery

7. Other diagnosis to be included

For all other episodes that do not meet any of the criteria above, the indication is the principal diagnosis

ICD 9 CODES

Codes for Diabetic Macular Edema (**DIMAED**):

36207	Diabetic macular edema

Codes for Retinal Vein Occlusion- Central (**RVOCEN**):

36235	Central retinal vein occlusion

Codes for Retinal Vein Occlusion- Branch (**RVOBRA**):

36236	Venous tributary (branch) occlusion

Codes for Exudative age-related macular degeneration (**EXARMD**):

36252	Exudative senile macular degeneration

Codes for Macular puckering (**MACPUC**):

36256	Macular puckering

Codes for Retinal neovascularization or Myopia (**RNVMYO**):

36021	Progressive high (degenerative) myopia
36216	Retinal neovascularization NOS
3671	Myopia

Codes for Other Conditions of the Retina and Choroid (**OCRECH**):

36241	Central serous retinopathy
36256	Macular puckering
36320	Chorioretinitis, unspecified
36343	Angioid streaks of choroid

Codes for Cystoid Macular Degeneration (**CYMADE**):

36253	Cystoid macular degeneration

Codes for Unspecified Macular Degeneration (**UNMADE**):

36250	Macular degeneration (senile), unspecified

Codes for Other Relevant Conditions (**OTRECO**):

3612	Serous retinal detachment
3619	Unspecified retinal detachment
3638	Other disorders of choroid
3669	Unspecified cataract
8715	Penetration of eyeball with magnetic foreign body
25000	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
25050	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
25051	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
25052	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
25053	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
36100	Retinal detachment with retinal defect, unspecified
36101	Recent retinal detachment, partial, with single defect
36102	Recent retinal detachment, partial, with multiple defects
36103	Recent retinal detachment, partial, with giant tear
36105	Recent retinal detachment, total or subtotal
36106	Old retinal detachment, partial
36107	Old retinal detachment, total or subtotal
36181	Traction detachment of retina
36189	Other forms of retinal detachment
36210	Background retinopathy, unspecified
36212	Exudative retinopathy
36215	Retinal telangiectasia
36216	Retinal neovascularization NOS
36240	Retinal layer separation, unspecified
36242	Serous detachment of retinal pigment epithelium
36243	Hemorrhagic detachment of retinal pigment epithelium
36254	Macular cyst, hole, or pseudohole
36257	Drusen (degenerative)
36281	Retinal hemorrhage
36282	Retinal exudates and deposits
36283	Retinal edema
36289	Other retinal disorders
36442	Rubeosis iridis
36474	Adhesions and disruptions of pupillary membranes
36504	Ocular hypertension
36563	Glaucoma associated with vascular disorders
36610	Senile cataract, unspecified
36614	Posterior subcapsular polar senile cataract
36619	Other and combined forms of senile cataract
37060	Corneal neovascularization, unspecified

37922	Crystalline deposits in vitreous
37923	Vitreous hemorrhage
37924	Other vitreous opacities
37925	Vitreous membranes and strands
37929	Other disorders of vitreous
99653	Mechanical complication due to ocular lens prosthesis
99679	Other complications due to other internal prosthetic device, implant, and graft

Codes for Other Vascular Occlusions (**OTVAOC**):

36230	Retinal vascular occlusion, unspecified
36231	Central retinal artery occlusion
36232	Retinal arterial branch occlusion

Codes for Atrophic Macular Degeneration (**ATMADE**):

36251	Nonexudative senile macular degeneration

IDENTIFICATION OF INTRAVITREAL ANTI-VEGF TREATMENT EVENTS FOR ICD-10

1. Main indications

Indication: DIABETIC MACULAR EDEMA (DME)

Numerator: Discharges, with either:

- A principal diagnosis code for Diabetic Macular Edema **(DIMAED)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or for Other Type 2 Diabetes Conditions **(ODIACO)** and any secondary diagnosis codes for Diabetic Macular Edema **(DIMAED)** or
- A principal diagnosis code for Retinal Edema **(RETEDE)** and any secondary diagnosis codes for any diabetic condition (ICD10 codes E08-E13).

Indication: RETINAL VEIN OCCLUSION (RVO)

Indication: RETINAL VEIN OCCLUSION (CENTRAL)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Central **(RVOCEN)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** and any secondary diagnosis codes for Retinal Vein Occlusion- Central **(RVOCEN)**.

Indication: RETINAL VEIN OCCLUSION (BRANCH)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Branch **(RVOBRA)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** and any secondary diagnosis codes for Retinal Vein Occlusion- Branch **(RVOBRA)**.

Indication: NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (nAMD)

Numerator: Discharges, with either:

- A principal diagnosis code for Exudative age-related macular degeneration **(EXARMD)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** or diagnosis code for Macular Puckering **(MACPUC)** and any secondary diagnosis codes for Exudative age-related macular degeneration **(EXARMD)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** and a previous nAMD case, regardless of age.

Indication: CHOROIDAL NEOVASCULARIZATION (CNV)

Numerator: Discharges with either:

- A principal diagnosis code for Retinal neovascularization or Myopia (**RNVMYO**) or
- A principal diagnosis code for Other Relevant Conditions (**OTRECO**) or Other Diagnosis for Macular Degeneration **(ODMADE)** and any secondary diagnosis codes for Retinal neovascularization or Myopia **(RNVMYO)** or
- A principal diagnosis for Macular Puckering **(MACPUC)**, except if secondary diagnosis codes for Diabetic Macular Edema **(DIMAED)**.

2. Other indications

Indication: OTHER VASCULAR OCCLUSIONS

**This indication is not included in Retinal Vein Occlusion*

Numerator: Discharges, with either:

- A principal diagnosis code for Other Vascular Occlusions **(OTVAOC)** or
- A principal diagnosis code for Other Relevant **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion **(OTVAOC)**.

Indication: ATROPHIC MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Atrophic Macular Degeneration **(ATMADE)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Atrophic Macular Degeneration **(ATMADE)**.

3. Diabetes with Retinopathy

For episodes with the principal diagnosis codes below, without secondary diagnosis of Diabetic Macular Edema (**DIMAED**), the following criteria applies:

Principal diagnosis	Indication
E11319	Unspecified Diabetic Retinopathy
E113591, E113592, E113593	Proliferative Diabetic Retinopathy

E113291, E113292, E113491, E113551, E113552	Nonproliferative Diabetic Retinopathy

4. Other diagnosis to be excluded

For episodes with the principal diagnosis codes below, the episode is excluded from the database:

G245	Blepharospasm
H401120	Primary open-angle glaucoma, left eye, stage unspecified
H5000	Unspecified esotropia
H5005	Alternating esotropia
Z48810	Encounter for surgical aftercare following surgery on the sense organs

5. Other diagnosis to be included

For all other episodes that do not meet any of the criteria above, the indication is the principal diagnosis

ICD 10 CODES

Codes for Diabetic Macular Edema (**DIMAED**):

E10311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E103212	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E11311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E113211	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E113212	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E113213	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E11331	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E113311	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E113312	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E113313	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E113411	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E113412	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E113413	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E113419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E113511	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E113512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye

E113513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E13311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E133413	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E133511	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye

Codes for Other Type 2 Diabetes Conditions (**ODIACO**):

E113551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E113552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E1136	Type 2 diabetes mellitus with diabetic cataract

Codes for Retinal Edema (**RETEDE**):

H3581	Retinal edema

Codes for Retinal Vein Occlusion- Central (**RVOCEN**):

H348110	Central retinal vein occlusion, right eye, with macular edema
H348111	Central retinal vein occlusion, right eye, with retinal neovascularization
H348112	Central retinal vein occlusion, right eye, stable
H348120	Central retinal vein occlusion, left eye, with macular edema
H348121	Central retinal vein occlusion, left eye, with retinal neovascularization
H348122	Central retinal vein occlusion, left eye, stable
H348130	Central retinal vein occlusion, bilateral, with macular edema
H348131	Central retinal vein occlusion, bilateral, with retinal neovascularization
H348132	Central retinal vein occlusion, bilateral, stable
H348190	Central retinal vein occlusion, unspecified eye, with macular edema

Codes for Retinal Vein Occlusion- Branch (**RVOBRA**):

H348310	Tributary (branch) retinal vein occlusion, right eye, with macular edema
H348311	Tributary (branch) retinal vein occlusion, right eye, with retinal neovascularization
H348312	Tributary (branch) retinal vein occlusion, right eye, stable
H348320	Tributary (branch) retinal vein occlusion, left eye, with macular edema
H348321	Tributary (branch) retinal vein occlusion, left eye, with retinal neovascularization
H348322	Tributary (branch) retinal vein occlusion, left eye, stable
H348330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H348331	Tributary (branch) retinal vein occlusion, bilateral, with retinal neovascularization
H348332	Tributary (branch) retinal vein occlusion, bilateral, stable
H348390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema
H348391	Tributary (branch) retinal vein occlusion, unspecified eye, with retinal neovascularization
H348392	Tributary (branch) retinal vein occlusion, unspecified eye, stable

Codes for Exudative age-related macular degeneration (**EXARMD**):

H35321	Exudative age-related macular degeneration, right eye
H353210	Exudative age-related macular degeneration, right eye, stage unspecified
H353211	Exudative age-related macular degeneration, right eye, with active choroidal neovascularization
H353212	Exudative age-related macular degeneration, right eye, with inactive choroidal neovascularization
H353213	Exudative age-related macular degeneration, right eye, with inactive scar
H353220	Exudative age-related macular degeneration, left eye, stage unspecified
H353221	Exudative age-related macular degeneration, left eye, with active choroidal neovascularization
H353222	Exudative age-related macular degeneration, left eye, with inactive choroidal neovascularization
H353230	Exudative age-related macular degeneration, bilateral, stage unspecified
H353231	Exudative age-related macular degeneration, bilateral, with active choroidal neovascularization
H353232	Exudative age-related macular degeneration, bilateral, with inactive choroidal neovascularization
H353290	Exudative age-related macular degeneration, unspecified, stage unspecified
H353291	Exudative age-related macular degeneration, unspecified, with active choroidal neovascularization

Codes for Macular puckering (**MACPUC**):

H35371	Puckering of Macula, right eye
H35372	Puckering of Macula, left eye
H35379	Puckering of Macula, unspecified eye

Codes for Retinal neovascularization or Myopia (**RNVMYO**):

H35051	Retinal neovascularization, unspecified, right eye
H35052	Retinal neovascularization, unspecified, left eye
H35053	Retinal neovascularization, unspecified, bilateral
H35059	Retinal neovascularization, unspecified, unspecified eye
H3533	Angioid streaks of macula
H4421	Degenerative myopia, right eye
H4422	Degenerative myopia, left eye
H442A1	Degenerative myopia with choroidal neovascularization, right eye
H442A2	Degenerative myopia with choroidal neovascularization, left eye

Codes for Other Diagnosis for Macular Degeneration (**ODMADE**):

H3530	Unspecified macular degeneration
H35351	Cystoid macular degeneration, right eye
H35352	Cystoid macular degeneration, left eye

Codes for Other Relevant Conditions (**OTRECO**):

H2511	Age-related nuclear cataract, right eye
H2512	Age-related nuclear cataract, left eye

H25811	Combined forms of age-related cataract, right eye
H25812	Combined forms of age-related cataract, left eye
H259	Unspecified age-related cataract
H269	Unspecified cataract
H318	Other specified disorders of choroid
H33001	Unspecified retinal detachment with retinal break, right eye
H33002	Unspecified retinal detachment with retinal break, left eye
H33011	Retinal detachment with single break, right eye
H33012	Retinal detachment with single break, left eye
H33021	Retinal detachment with multiple breaks, right eye
H33022	Retinal detachment with multiple breaks, left eye
H33031	Retinal detachment with giant retinal tear, right eye
H33032	Retinal detachment with giant retinal tear, left eye
H33051	Total retinal detachment, right eye
H33052	Total retinal detachment, left eye
H3321	Serous retinal detachment, right eye
H3322	Serous retinal detachment, left eye
H3500	Unspecified background retinopathy
H35021	Exudative retinopathy, right eye
H35022	Exudative retinopathy, left eye
H35712	Central serous chorioretinopathy, left eye
H3589	Other specified retinal disorders
H4089	Other specified glaucoma
H409	Unspecified glaucoma
H4311	Vitreous hemorrhage, right eye
H4312	Vitreous hemorrhage, left eye
H59031	Cystoid macular edema following cataract surgery, right eye
H59032	Cystoid macular edema following cataract surgery, left eye

Codes for Other Vascular Occlusions (**OTVAOC**):

H3411	Central retinal artery occlusion, right eye
H3412	Central retinal artery occlusion, left eye
H349	Unspecified retinal vascular occlusion

Codes for Atrophic Macular Degeneration (**ATMADE**):

H353110	Nonexudative age-related macular degeneration, right eye, stage unspecified
H353111	Nonexudative age-related macular degeneration, right eye, early dry stage
H353112	Nonexudative age-related macular degeneration, right eye, intermediary dry stage
H353113	Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement
H353120	Nonexudative age-related macular degeneration, left eye, stage unspecified
H353121	Nonexudative age-related macular degeneration, left eye, early dry stage
H353122	Nonexudative age-related macular degeneration, left eye, intermediary dry stage

H353123	Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement
H353130	Nonexudative age-related macular degeneration, bilateral, stage unspecified
H353132	Nonexudative age-related macular degeneration, bilateral, intermediary dry stage
H353190	Nonexudative age-related macular degeneration, unspecified eye, stage unspecified

Appendix 2

Organizational level of the hospital's ophthalmology departments. Minimal requirements, as defined by the National Network of hospital specialties and referral for Ophthalmology [1]

Group I:

- Health care: refraction test and consultations (general and diabetes)
- Minimum number of inhabitants in the area of direct influence: 75,000
- Working hours: 8 am to 8 pm
- Minimum equipment required: refraction with slit lamp and keratometer, biometer, ultrasound, campimeter, optical coherence tomography (OCT), angiograph / retinograph, YAG laser, Argon laser or similar, operating microscope, phacoemulsifier
- Minimum of Ophthalmologist specialists: 5

Group II:

- Health care: all ophthalmic health care with the exception of pediatric oncology, transplantation, glaucoma and cataracts, retinopathy of prematurity, rare diseases
- Daytime medical and surgical urgency: 12h/day; 7 days/week
- Minimum of Ophthalmologist specialists: 12
- Maximum of ophthalmologists: to be defined according to the population to be served;
- Minimum equipment required: in addition to equipment required for hospitals in Group I, vitrectomy device with endolaser, specular microscope and corneal topograph.

Group III:

- Health care - responsible for all ophthalmic health care, excluding those related to Reference Centers (approved or to be approved)
- Multipurpose emergency: 2 ophthalmologists in physical presence 24h/day; 7 days/week.
- Minimum equipment required: in addition to equipment required for hospitals in Group II, Retcam and portable electrophysiology

Source: [1] Serviço Nacional de Saúde. Rede nacional de especialidade hospitalar e de referenciação de oftalmologia [Internet]. 2016. Available from: https://www.sns.gov.pt/wp-content/uploads/2016/05/Proposta-RNEHR-Oftalmologia-2016-ACSS-1_VFinal.pdf

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3,4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	5,6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends, geographical variation, and factors associated with the use of ANTI-VEGF intravitreal injections in Portugal (2013–18): A retrospective analysis of administrative data

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TITLE PAGE

TITLE: TRENDS, GEOGRAPHICAL VARIATION, AND FACTORS ASSOCIATED WITH THE USE OF ANTI-VEGF INTRAVITREAL INJECTIONS IN PORTUGAL (2013–18): A RETROSPECTIVE ANALYSIS OF ADMINISTRATIVE DATA

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ABSTRACT

Aims: The arrival of anti-vascular endothelial growth factor (anti-VEGF) therapies represented a treatment shift for several ophthalmologic disorders and led to an increasing number of patients undergoing intravitreal injections. The aims of this observational study were to assess the expansion of anti-VEGF intravitreal injections in the Portuguese National Health System (NHS) and to identify factors correlated with geographic variations in episode rates. **Methods:** Administrative database on discharge from Portuguese NHS hospitals was analysed for annual values and rates of intravitreal anti-VEGF injections at a national and regional level, between 2013 and 2018. **Results:** The number of episodes of anti-VEGF treatment and patients treated increased 16% and 9% per year, respectively, between 2013 and 2018. During the study period around 72% of patients were treated in the Metropolitan areas of Lisbon and Porto and in the Central region. Intravitreal anti-VEGF treatment rates in 2018 were 560 per 100,000 population and presented high variability between municipalities. Higher anti-VEGF treatment rates at the municipality level were associated with shorter distances between their residence and the hospital. At the hospital level, higher ratio of ophthalmologists and higher organizational level were associated with higher anti-VEGF treatment rates. **Conclusion:** The number of episodes and patients treated with anti-VEGF injections has been growing in recent years. Proximity to health care, more access to ophthalmologists, and hospitals with higher organizational levels are associated with higher anti-VEGF treatment rates. Improving access is crucial to reduce regional discrepancies and ensure optimal treatment frequency, which may improve health outcomes.

Keywords: Anti-VEGF, Intravitreal injection, Access to eye care, Neovascular age-related macular degeneration, diabetic macular oedema

Synopsis: The number of episodes of anti-VEGF injections and treated patients increased between 2013 and 2018 in Portugal. Regional variations in treatment rates were associated with proximity to health care, ophthalmologists supply, and hospitals´ organizational levels.

Article Summary:

Strengths and limitations of the study

- This is an administrative database study using the universe of inpatient and day cases stays of National Health System (NHS) hospitals in Portugal between 2013 and 2018.
- For the characterization of anti-VEGF intravitreal injections, a selection of surgical codes (ICD-9-CM and ICD-10) for intravitreal procedures was used as a proxy for intravitreal anti-VEGF injections.
- Patient level data is available which, for e.g., makes it possible to analyse the real-world average number of injections per patient per year.
- This administrative database gives us the universe of the Portuguese NHS but excludes the private setting.
- Although clinical data are collected, this is not primarily a clinical database but an administrative database to inform financing of inpatient and day cases stays in NHS hospitals in Portugal.

INTRODUCTION

The availability of anti-vascular endothelial growth factor (anti-VEGF) therapies represented a treatment shift for a range of ophthalmologic disorders, with a dramatic impact on serious conditions that were previously untreatable resulting in irreversible damages and loss of sight [1,2]. Anti-VEGF intravitreal injections act by reducing neovascular progression and were initially approved for the treatment of neovascular age-related macular degeneration (nAMD) [3,4]. Currently, anti-VEGF therapies are indicated for the treatment of a vast number of other ocular diseases such as diabetic macular oedema (DME), choroidal neovascularization (CNV), and retinal vein occlusion (RVO) [2]. Clinical trials have showed that anti-VEGF intravitreal injections prevented vision loss in the majority of patients and, in some cases, significantly improved vision [2,3,5]. The positive impact of anti-VEGF injections in visual outcomes [2,6–8] combined with the lack of previous efficient treatments, led to rapid diffusion of anti-VEGF treatments in many countries [4,6,9,10].

The main barriers for treatment with anti-VEGF are the high costs of the drugs, the need for multiple treatments, and the need for the treatments to be administered by specially trained personnel at hospitals [6,11]. Access is hindered in countries such as the United States [11] and in many Asian countries [6], where the drugs are not reimbursed by the health systems. Even in countries for which anti-VEGF treatments are reimbursed by the health system, such as England, Norway, and Portugal, studies report considerable geographic variation in treatment rates [4,10,12]. The study in Norway showed that the geographic variations in episode rates are challenges to the policy goals regarding equitable access and care, calling for further investigation [4]. The study in Portugal indicated that the number of hospital episodes related with anti-VEGF injections increased from 1,815 in 2001 to 25,106 in 2012, which is a mean annual increase of 32% [10].

In Portugal, Ranibizumab has been reimbursed by the NHS since 2008 [10], and by 2018 Bevacizumab and Aflibercept were also reimbursed [13]. Despite the equity-oriented nature of the Portuguese health system and the low co-payment values, a study covering the 2002-2012 period found unequal geographic distribution in treatment rates across the country [10]. Patients from regions without ophthalmology departments and lower population density received fewer treatments than other regions [10]. More recent estimates on the diffusion of anti-VEGF intravitreal injections are needed to understand how this treatment has expanded with the existence of additional elective pharmaceuticals.

Understanding the trends in anti-VEGF treatments in terms of number of episodes and patients is of great importance for assessing health technologies. Assessing access to and impact of health technologies is paramount in investigating the number of episodes and patients treated. Periodic investigations about access to health technologies is vital to prevent health inequalities and to learn how to proceed if different technologies arise. The aim of this study was twofold: to analyse the expansion of anti-VEGF intravitreal injections in the Portuguese NHS between 2013 and 2018 and to identify factors associated with geographic variation in treatment rates.

MATERIALS AND METHODS

Data source and inclusion/exclusion criteria

This observational study used an administrative database on hospital discharges from public hospital institutions in mainland Portugal, which includes information about sex, age, municipality of residence,

principal and secondary diagnosis and procedures, discharge hospital, and a unique patients' identifier from all inpatient and day case episodes. Use of this database was authorized for research purposes by the Portuguese Health System Central Administration (ACSS). The database is anonymized, guaranteeing the confidentiality of individuals, and it was therefore not necessary to obtain patients´ consent or approval by an ethics committee for this study.

Episodes related to intravitreal injections with anti-VEGF between 2013 and 2018 were selected according to procedures records coded with International Classification of Diseases (ICD) 9th version- Clinical Modification (ICD-9CM) and ICD 10th version (ICD-10) for episodes registered from 2017. As in previous studies, ICD-9CM procedures codes 1474, 1475, 1479, and 149 and ICD10 procedures codes 3E0C30M and 3E0C3GC were used as proxy to anti-VEGF treatments [10,12]. Note, however, that these codes might also capture intravitreal injections for other drugs such as injectable antibiotics or corticosteroids [10,12].

Subsequently, the criteria for classification and exclusion of episodes were applied to assign a diagnosis for each episode. Episodes with missing data on sex, age, diagnosis and procedures, and discharge hospitals were excluded. ICD-10 bilateral episodes were counted as two injections, while the number of patients was counted as one. The *Supplementary Material- Appendix 1* contains details on the ICD codes used and the criteria to assign a diagnosis for each episode.

Data analysis

We examined the number of episodes and patients treated by year, by diagnosis, and by region (according to patient's municipality of residence). The number of patients treated per year was estimated using the unique patients' identifier, regardless of whether they were already in treatment in the previous years or if they entered the database in that specific year. Then, using the patient as unit of observation, we computed the average number of injections per year for each diagnosis (nAMD, CNV, DME or RVO). Finally, we proceeded with the investigation of factors associated with geographic variations in anti-VEGF standardized treatment-rates.

Statistical analysis was conducted to investigate factors associated with geographic variations in anti-VEGF standardized treatment-rates. This ecological analysis was performed in two parts: the first had as unit of analysis the municipality of residence of the patient and in the second the unit of analysis was the hospital where the injection was performed. For analysis refinement, only patients aged 50 years or older were included in the analysis of associated factors, as the conditions for which anti-VEGF injections are indicated affects mostly people in this age category [2,12].

For the ecological analysis at the municipality level the rate of episodes related to intravitreal injections with anti-VEGF treatments per 100,000 population was the dependent variable. The independent variables analysed were patients' characteristics (mean age, proportion by sex, mean distance to hospital in kilometres - according to patient's municipality of residence and municipality where the hospital is located), and municipalities´ characteristics (purchasing power, number of ophthalmologists per 20,000 persons, and number of ophthalmology consultations per 1,000 persons). The purchasing power variable is provided in relation to the national value, set equal to 100; and the purchasing power of the municipality can be a value above or below 100. The characteristics of the patients were retrieved from the hospital discharge database, and the characteristics of the municipality variables obtained from Statistics Portugal [14]. The mean distance to the hospital was obtained through Google Maps, as these represent the distance to be travelled by patients. For the characteristics of patients, municipalities were separated into two categories for each

year: "Higher rates" category for the municipalities with episode rates higher than the median and "Lower rates" category for the municipalities with episode rates lower than the median. The Mann-Whitney test was used to compare patients' characteristics according to these two categories. For the characteristics of the municipalities, associations were analysed according to Spearman's correlation analysis and multivariate linear regression models, with treatment rates as dependent variables and the independent variables (purchasing power, number of ophthalmologists per 20,000 persons, and number of ophthalmology consultations per 1,000 persons) added following the stepwise method.

For the ecological analysis at the hospital level, the dependent variable was the episode rates, and the independent variables were the number of ophthalmologists per 20,000 persons in the hospital's catchment area and the organizational level of the hospital's ophthalmology departments (hospitals´ ophthalmology units were divided into three groups, classified according to the general requirements established by the National Network of hospital specialties and referral for Ophthalmology [15], as shown in the *Supplementary Material- Appendix 2*). As these independent variables were not available per year, the years 2013-2018 were collapsed into a single period of analysis. The association with ophthalmologist specialists was analysed using Spearman´s correlation analysis. The Kruskal-Wallis test was used to compare the episode rate between the three groups of hospitals. Hospitals in group III have a wider range of health care activities, longer opening hours, and greater equipment availability than hospitals in group II, and the same for group II in relation to group I hospitals. Data on number of ophthalmologists and more details on organizational level of hospitals by groups can be found in the report of the National network of hospital specialty and referral for Ophthalmology [15].

A 5% significance level was adopted. Statistical analysis was performed using the IBM SPSS Statistics v26.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Evolution, characteristics, and distribution of anti-VEGF treatments

There were 298,429 episodes of anti-VEGF treatment between 2013 and 2018, and 65,534 patients treated. As illustrated in Figure 1, the number of episodes increased from 30,542 in 2013 to 64,867 in 2018, which corresponds to a mean annual increase of 16%. The number of patients treated in 2013 was 12,951, growing to 19,627 in 2018 (mean annual increase of 9%). In 2018, the anti-VEGF standardized treatment-rate was 560 per 100,000 persons.

Figure 1. Number of hospital episodes of anti-VEGF treatments and patients treated per year, from 2013 to 2018. Portugal

The majority of patients (71%) were treated with intravitreal anti-VEGF in the Metropolitan area of Lisbon, Central region, and Metropolitan area of Porto (Table 1). The Algarve had the lowest proportion of patients treated between 2013 to 2018 (2.6%). If we assume a homogeneous prevalence of these diseases across the country, the proportion of the population can be used as a proxy as those who would qualify for anti-VEGF therapy treatments in each area. There are substantial differences in the proportion of resident population

and the proportion of patients treated with anti-VEGF injections in the Metropolitan area of Porto and Algarve region. Table S1 shows the proportion of patients treated with anti-VEGF injections, from 2013 and 2018, per region and per diagnosis (*Supplementary Material- Appendix 3*).

Table 1. Proportion of patients treated with anti-VEGF injections, between 2013 and 2018, per year, Portugal

Region	2013	2014	2015	2016	2017	2018	Total	Proportion population 2018
Alentejo	6.32%	6.46%	6.74%	7.51%	6.88%	7.54%	7.53%	7.21%
Algarve	2.03%	1.97%	1.99%	2.71%	3.33%	3.21%	2.58%	4.49%
Metropolitan area of Lisbon	23.72%	23.03%	23.59%	23.50%	23.96%	23.64%	24.32%	29.10%
Metropolitan area of Porto	24.70%	25.34%	24.41%	22.68%	27.30%	26.81%	23.44%	17.61%
Central region	25.73%	24.77%	25.39%	25.39%	17.22%	18.35%	23.69%	22.66%
Northern region	17.50%	18.44%	17.88%	18.20%	21.31%	20.46%	18.43%	18.92%

As summarized in Table 2, the most common diagnosis was nAMD, followed by DME and RVO. These three diagnoses accounted for 70% of episodes. nAMD was the most common condition in every year analysed, except 2016, when DME was the most common.

Table 2. Total episodes of anti-VEGF between 2013 and 2018, by diagnosis and year, Portugal

Diagnosis	Total			2013		2014		2015		2016		2017		2018	
	N	%	% cummulative	N	%	N	%	N	%	N	%	N	%	N	%
Neovascular age-related macular degeneration (nAMD)	100,168	33.57	33.57	11,575	37.90	13,415	36.32	16,357	33.60	16,094	28.95	20,857	33.74	21,87	33.72
Diabetic macular edema (DME)	85,997	28.82	62.38	6,578	21.54	8,044	21.78	13,371	27.47	18,181	32.70	19,769	31.98	20,054	30.92
Retinal vein occlusion (RVO)	18,716	6.27	68.65	1,451	4.75	2,104	5.70	2,841	5.84	3,500	6.30	3,956	6.40	4,864	7.50
Unspecified macular degeneration	16,042	5.38	74.03	1,750	5.73	1,862	5.04	2,712	5.57	3,979	7.16	2,724	4.41	3,015	4.65
Proliferative diabetic retinopathy	15,737	5.27	79.30	1,846	6.04	2,297	6.22	2,726	5.60	2,144	3.86	3,250	5.26	3,474	5.36
Choroidal neovascularization (CNV)	13,783	4.62	83.92	1,698	5.56	2,190	5.93	2,619	5.38	3,040	5.47	2,154	3.48	2,082	3.21
Retinal edema	12,581	4.22	88.14	1,256	4.11	1,890	5.12	1,690	3.47	1,677	3.02	2,575	4.17	3,493	5.38
Other diagnosis	35,405	11.86	100	4,388	14.37	5,129	13.89	6,361	13.07	6,979	12.55	6,533	10.57	6,015	9.27
Total	**298,429**	100		30,542	100	36,931	100	48,677	100	55,594	100	61,818	100	64,867	100

Table 3 summarizes the average increase in the number of injections per year per patient, by diagnosis. The highest number of injections per year per patient was for nAMD, which increased from 2.72 in 2013 to 3.37 in 2018. In contrast, CNV had the lowest values, reaching 2.01 injections per year per patient in 2018.

Table 3. Average number of injections per year per patient, by diagnosis, 2013 to 2018, Portugal

Diagnosis	2013	2014	2015	2016	2017	2018
nAMD	2.72	2.77	2.96	2.72	3.4	3.37
DME	2.33	2.32	2.64	2.88	2.77	2.80
CNV	1.35	1.43	1.41	1.51	2.06	2.01
RVO	1.88	2.08	2.25	2.38	2.42	2.48

Factors associated with geographic distribution of anti-VEGF injections

Table 4 shows the comparison of characteristics of patients at the municipality level. In 2016, patients treated with anti-VEGF intravitreal injections who lived in municipalities with episode rates higher than the median ("Higher rates" category) were older. In 2013, municipalities in the "Higher" category had a significantly higher proportion of females. For the distance between municipality of residence and hospital, significant differences were found for all years, with the average distance being shorter for municipalities in the "Higher" category.

Table 4. Mann-Whitney test for individual variables by municipality category

Year	Age Mean (standard deviation)				Sex (proportion of men) Mean (standard deviation)				Distance in Kilometres Mean (standard deviation)			
	Lower rates	Higher rates	U	signif.	Lower rates	Higher rates	U	signif.	Lower rates	Higher rates	U	signif.
2013	70.70 (4.64)	71.43 (2.65)	8737	0.168	**0.511 (0.214)**	**0.465 (0.130)**	**8256***	**0.036**	**88.50 (50.25)**	**46.13 (30.58)**	**4187***	**<0.001**
2014	70.90 (4.50)	71.02 (2.64)	9466	0.772	0.499 (0.198)	0.486 (0.121)	9025	0.343	**84.11 (52.25)**	**46.08 (32.22)**	**4835***	**<0.001**
2015	70.62 (4.07)	71.35 (2.92)	8553	0.098	0.519 (0.179)	0.486 (0.110)	8484	0.079	**81.04 (51.11)**	**42.62 (25.65)**	**4701***	**<0.001**
2016	**70.58 (3.71)**	**71.61 (2.62)**	**7656***	**0.004**	0.500 (0.169)	0.503 (0.099)	9218	0.576	**73.52 (49.44)**	**40.99 (28.36)**	**5098***	**<0.001**
2017	72.30 (5.37)	71.66 (2.71)	7826	0.135	0.480 (0.244)	0.511 (0.127)	7989	0.218	**69.69 (53.74)**	**41.89 (32.51)**	**6238***	**<0.001**
2018	72.26 (4.70)	72.02 (2.56)	8553	0.449	0.523 (0.233)	0.484 (0.107)	8246	0.216	**82.88 (72.94)**	**66.42 (65.37)**	**7586***	**0.002**

In the bivariate correlation analysis of the rate of anti-VEGF treatments with the independent ecological variables, a positive correlation was found for: purchasing power in the years 2016 (p-value <0.001) and 2018 (p-value <0.001); rate of ophthalmologists in 2015 (p-value = 0.042) and 2016 (p-value = 0.016); ophthalmology consultations in all hospitals in 2013 (p-value = 0.047) and 2016 (p-value = 0.018), and consultations in public hospitals in 2013 (p-value = 0.040) and in 2016 (p-value = 0.030). (Table S2. Supplementary Material- Appendix 3).

Stepwise linear regression models were generated for each year. Between 2013 and 2015 the variable ophthalmology consultations was included with a positive coefficient. For 2016 to 2018, the variable that remained in the model was purchasing power, with a positive coefficient. The models had low adjusted R^2

(the highest was 0.043 in 2018) and the analysis of residues was inconclusive regarding the quality of the models. (Table S3. Supplementary Material- Appendix 3).

In the ecological analysis at the hospital level, the bivariate Spearman's correlation between the rate of anti-VEGF treatments between 2013 and 2018 and the ratio of ophthalmologists had a positive correlation (ρ = 0,359; n = 40; p-value = 0.023). The Kruskal-Wallis test showed a statistically significant difference in episode rates with anti-VEGF according to the hospital's organizational level (H(2) = 7.054; p-value = 0.029). More specifically, the results indicate that hospitals in group III had a higher episode rate than hospitals in group II. These, in turn, had higher episode rates than group I hospitals.

DISCUSSION

The aim of this study was to analyse the expansion of anti-VEGF intravitreal treatments in the Portuguese NHS and to identify factors associated with geographic variations. Results indicate that access to treatment with anti-VEGF injection has been increasing in Portugal, and that they were first used to treat nAMD, followed by DME, CNV, and RVO. An increase in the number of injections per patient per year was observed for all diagnoses. More than half of the episodes with anti-VEGF were recorded in the metropolitan areas of Lisbon and Porto.

Given the positive impact of anti-VEGF injections on health outcomes for many ocular neovascular diseases, the expansion in injections performed and patients treated seems justified. The evolution of anti-VEGF treatments found from 2013 to 2018 was consistent with values reported by Marques et al. [10] from 2002 to 2012. The total number of injections per year in Portugal varied from less than 2,000 to over 60,000 in 16 years. As anti-VEGF injections are covered by the Portuguese NHS [10,13,16] and are safe and highly effective [17], there are reasons to expect that this upward tendency will continue to be observed in the coming years.

Neovascular AMD and DME diagnosis corresponded to 63% of episodes associated with anti-VEGF treatment between 2013 and 2018. An analysis of the literature revealed that AMD was the eye pathology most often addressed in scientific publications between 2013 and 2018 [18], and it was the most common condition for which anti-VEGF intravitreal injections were used in countries like England [12], Norway [4], and the United States [19].

The number of injections per year per patient for nAMD increased within the period analysed, reaching 3.37 injections per year in 2018. The on-label treatment guidelines for treatment of nAMD for both Ranibizumab and Aflibercept supported monthly injections in the first three months followed by treat and extend regimen (flexible, according to the needs of the patient) [20,21]. Therefore, in a first year of treatment, it would correspond to between 6 to 12 injections (due to loading dose), while in the second year and thereafter it would correspond to 4 to 12 injections. Although there was no information on which drug was used to treat the patients analysed, the values of the on-label standards are greater than what was observed in this study. This low frequency of injections per year was also found in Portugal before 2013 [10], England (2.7 in 2008) [12], and Norway (4.1 in 2015) [4]. On the one hand, these results may indicate difficulties to access the treatment, leaving patients undertreated [22–25]. On the other hand, some clinical studies indicate that variable frequency of anti-VEGF injections is also effective in the treatment of nAMD, and therefore this flexible regimen may have been increasingly adopted [1,26].

The geographic variations in episode rates in Portugal observed between 2002 and 2012 were associated with the availability of anti-VEGF therapies and ophthalmology services, as well as population density [10]. These results indicate that patients from distant cities or rural areas may have delayed access to treatments and were more likely to miss follow-up appointments [10]. The findings for the period from 2013 to 2018 corroborate this possibility, as the distance between municipality of residence and hospital was significantly different between municipalities with higher and lower episode rates. A systematic review of factors associated with non-adherence to anti-VEGF treatment has also identified greater distance to hospital as a potential contributing factor [27]. Lower numbers of ophthalmologist and consultations were also associated with lower episode rates.

Similar results were found in Norway [4] and England [12]. National rates of intravitreal injections in England had a 50-fold variation in age-standardized rates between regions [12]. In Norway, the age adjusted number of episodes across counties varied from 19 to 55 per 1,000 persons aged 50 years or older [4]. These studies demonstrated challenges associated with the arrival of this treatment that include frequent and long-term administration and high allocation of resources. Despite the effort to guarantee geographical equity of access afforded by the health systems in England, Norway, and Portugal, the variations in anti-VEGF rates indicate that challenges remain.

Because anti-VEGF drugs are injected directly into the vitreous body, there are requirements for use of this treatment that can include specialized training and the setting up of a location dedicated to injection [28]. These requirements might be difficult to achieve in small hospitals due to financial or technical limitations [10]. The results showed significant differences in anti-VEGF treatment rates between hospitals, according to the number of specialists and their organizational level.

The present study has found that despite the considerable expansion of anti-VEGF treatments between 2013 and 2018 in Portugal, geographic variations still remain. Substantial treatment coverage discrepancies may be observed among regions, if we assume that prevalence does not change across the Portuguese territory and if we compare the percentages of residents, at the same age group, and the percentages of patients treated with an anti-VEGF in each region. In a previous study [10], it was shown that people in the rural areas were receiving less treatments. It is possible to speculate that the needs for treatments are likely to be similar in urban and rural areas. Although the methodology chosen did not produce robust evidence to accurately identify the reasons behind these variations, there are strong indications that barriers previously discussed by Marques et al [10] and also observed in England [12] and Norway [4] are possibly a root cause, and in any event remain a challenge.

Strengths of this study reside in the use of nationwide information and long period of analysis. The geographical and temporal analysis performed produced important results to monitor the diffusion of anti-VEGF treatments in Portugal, while raising awareness of persisting inequalities. The statistical methods employed allowed the identification of factors that should be addressed to ensure the treatment of patients with ophthalmologic needs. However, there are also limitations associated with its use that are important to mention. The procedures and ICD codes were used as a proxy to identify episodes with anti-VEGF and the associated diagnosis, since there are no further details about the intravitreal injection such as the drugs used in each episode. Thus, it is possible that in some cases anti-VEGF have not been administered, overestimating the findings reported herein. Additionally, the administrative database used is not primarily a clinical database. Clinical data are collected to inform financing of inpatient and day cases stays in NHS hospitals in Portugal, thus procedures carried out in the autonomous regions of Azores and Madeira are

excluded. The database does not comprise episodes of intravitreal anti-VEGF injected at the private setting. There is also no available information for other relevant clinical data (e.g. smoking behaviour, cardiovascular diseases and previous cardiovascular events, blood pressure, cholesterol and medication use). Future studies may collect more accurate information on episodes to ensure correspondence to anti-VEGF intravitreal injections and clinical characteristics of patients. At the time of analysis, data for 2017 and 2018 were provisional, as two hospitals had underreported information.

CONCLUSION

The development of anti-VEGF drugs has brought effective treatment for retinal diseases that can lead to severe visual impairment. This study shows that the number of episodes related to anti-VEGF treatment as well as the number of treated patients increased between 2013 and 2018. However, the distribution of treatment with anti-VEGF showed regional asymmetries. Factors such as proximity to health care, greater access to ophthalmologists and hospitals having ophthalmologic departments with more human resources, more equipment, and higher differentiation level were associated with higher rates of anti-VEGF treatment. Improving access to treatment is crucial to address the regional discrepancies found and to ensure that treatment follows patients' clinical needs and enhances better health outcomes. The increasing number of treatment episodes related to anti-VEGF, the low number of injections per patient per year, and the regional discrepancies detected impose challenges to the NHS in terms of budget and access. Given the ageing of the population and the fact that more anti-VEGF drugs have been developed and approved, both demand and supply of these treatments are likely to increase.

DECLARATIONS

Author's contribution

APM, MAS, PAL, RS conceived and designed the study. JVR, APM had full access to the data and conducted initial analysis. JVR, APM, MAS, ASA, JF conducted the analysis and interpreted the results. AFM, PAL advised on interpretation of the results. JVR, MP drafted the manuscript. AFM, ASA, JF participated in the discussions and provided the clinical feedback. MAS, RS provided critical feedback to the manuscript. All the authors revised the manuscript for important intellectual content, contributed to the data interpretation and writing, and critically reviewed the manuscript at all stages and approved the final copy.

Patient consent for publication

Obtaining informed consent was not required under national regulations because the patient data were anonymized.

Ethics approval statement

Obtaining approval by an ethics board was not required under national regulations because the patient data were anonymized.

Data availability statement

The data of hospitalizations are the property of Central Administration of the Health System (Administração Central do Sistema de Saúde (ACSS), I.P.). However the data are available from the authors upon request and with permission of the ACSS. The data of hospitalizations are not publicly available, however the

authors confirm that interested researchers can ask for access to these data by contacting ACSS directly at the following: Parque da Saúde da Lisboa, Edifício 16, Avenida do Brasil, 53 1700-063 Lisboa, Portugal (e-mail: geral@acss.min-saude.pt).

Competing interests statement

M Afonso-Silva, P A. Laires, A S. Almeida, J Fernandes, and M Pardal are employees of Novartis Farma, Produtos Farmacêuticos SA, Porto Salvo, Portugal, the funder the study. Novartis is the manufacturer of Brolucizumab and Ranibizumab.

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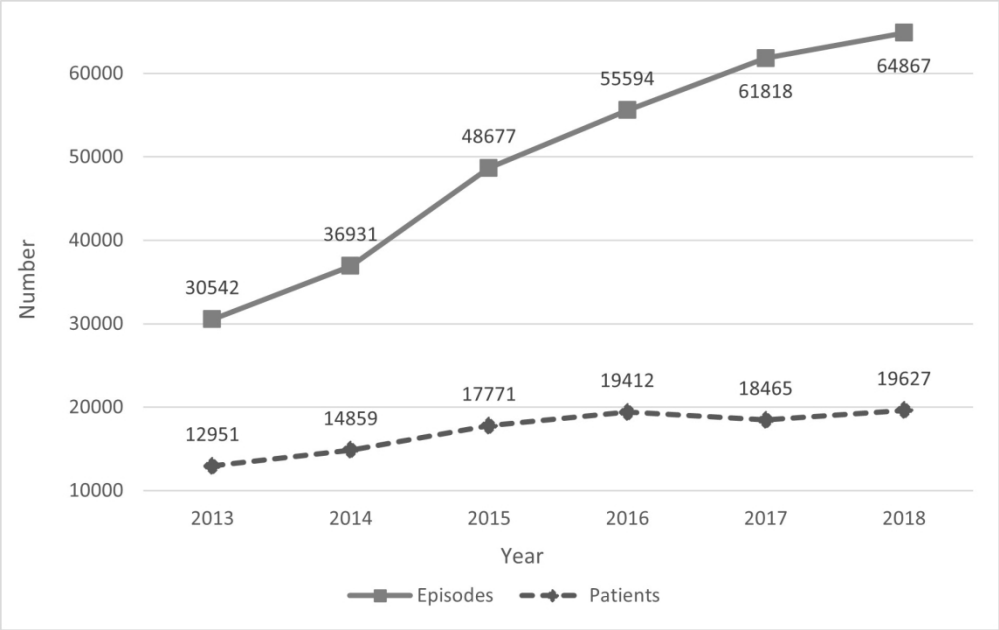
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48677
55594
61818
64867
12951
14859
17771
19412
18465
19627
2013
2014
2015
2016
2017
2018
Year
Episodes
Patients

Appendix 1

Table 1. ICD Procedure codes used to select episodes related to intravitreal injections with anti-VEGF

ICD version	Code	Denomination
ICD-9	1474	Other mechanical vitrectomy
ICD-9	1475	Injection of vitreous substitute
ICD-9	1479	Other operations on vitreous
ICD-9	149	Other operations on retina, choroid and posterior chamber
ICD-10	3E0C30M	Introduction of monoclonal antibody into eye, percutaneous approach),
ICD-10	3E0C3GC	Introduction of other therapeutic substance into eye, percutaneous approach

IDENTIFICATION OF INTRAVITREAL ANTI-VEGF TREATMENT EVENTS FOR ICD-9

1. Main indications

Indication: DIABETIC MACULAR EDEMA (DME)

Numerator: Discharges, with either:

- A principal diagnosis code for Diabetic Macular Edema **(DIMAED)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Diabetic Macular Edema **(DIMAED)**.

Indication: RETINAL VEIN OCCLUSION (RVO)

Indication: RETINAL VEIN OCCLUSION (CENTRAL)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Central **(RVOCEN)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion- Central **(RVOCEN)**.

Indication: RETINAL VEIN OCCLUSION (BRANCH)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Branch **(RVOBRA)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion- Branch **(RVOBRA)**.

Indication: NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (nAMD)

Numerator: Discharges, with either:

- A principal diagnosis code for Exudative age-related macular degeneration **(EXARMD)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)**, or

- A principal diagnosis code for Other Conditions of the Retina and Choroid **(OCRECH)** or for Cystoid Macular Degeneration **(CYMADE)** or for Unspecified Macular Degeneration **(UNMADE)** and any secondary diagnosis codes for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)**.

Indication: CHOROIDAL NEOVASCULARIZATION (CNV)

Numerator: Discharges with either:

- A principal diagnosis code for Retinal neovascularization or Myopia **(RNVMYO)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal neovascularization or Myopia **(RNVMYO)** or
- A principal diagnosis for Other Conditions of the Retina and Choroid **(OCRECH)** and any secondary diagnosis, except if admission is for Indication neovascular age-related Macular Degeneration **(AMD)**.
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Other Conditions of the Retina and Choroid **(OCRECH)**, except if admission is for Indication neovascular age-related Macular Degeneration **(AMD)**.

2. Other indications

Indication: OTHER VASCULAR OCCLUSIONS

**This indication is not included in Retinal Vein Occlusion*

Numerator: Discharges, with either:

- A principal diagnosis code for Other Vascular Occlusions **(OTVAOC)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion **(OTVAOC)**.

Indication: ATROPHIC MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Atrophic Macular Degeneration **(ATMADE)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Atrophic Macular Degeneration **(ATMADE)**.

Indication: CYSTOID MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Cystoid Macular Degeneration **(CYMADE)** and any secondary diagnosis codes, except for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)** or for Atrophic Macular Degeneration **(ATMADE)**; and patient aged less than 50 years old.

Indication: UNSPECIFIED MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Unspecified Macular Degeneration **(UNMADE)** and any secondary diagnosis codes, except for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)** or for Atrophic Macular Degeneration **(ATMADE)**, or
- A principal diagnosis code for Cystoid Macular Degeneration **(CYMADE)** and any secondary diagnosis codes, except for Exudative age-related macular degeneration **(EXARMD)** or for Macular puckering **(MACPUC)** or for Atrophic Macular Degeneration **(ATMADE)**; and patient aged 50 years old or more.

3. Diabetes with ophthalmic manifestations not stated as uncontrolled

For episodes with principal diagnosis codes 25050 and 25052, not classified as any indication above, the following criteria applies:

If any secondary diagnosis code:	Indication
36201	Unspecified Diabetic Retinopathy
36202	Proliferative Diabetic Retinopathy
36203 to 36206	Nonproliferative Diabetic Retinopathy
Other diagnosis code	The secondary diagnosis code
No diagnosis code	25050 or 25052

4. Other relevant diagnosis to be included

For episodes with the principal diagnosis codes below, not classified as any indication above, the indication is the principal diagnosis itself:

3612	Serous retinal detachment
3619	Unspecified retinal detachment
25000	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
25052	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
25053	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
36100	Retinal detachment with retinal defect, unspecified
36101	Recent retinal detachment, partial, with single defect
36102	Recent retinal detachment, partial, with multiple defects
36103	Recent retinal detachment, partial, with giant tear
36105	Recent retinal detachment, total or subtotal
36106	Old retinal detachment, partial
36107	Old retinal detachment, total or subtotal
36181	Traction detachment of retina
36189	Other forms of retinal detachment
36210	Background retinopathy, unspecified
36212	Exudative retinopathy
36215	Retinal telangiectasia

36216	Retinal neovascularization NOS
36240	Retinal layer separation, unspecified
36242	Serous detachment of retinal pigment epithelium
36243	Hemorrhagic detachment of retinal pigment epithelium
36254	Macular cyst, hole, or pseudohole
36257	Drusen (degenerative)
36281	Retinal hemorrhage
36283	Retinal edema
36442	Rubeosis iridis
36474	Adhesions and disruptions of pupillary membranes
37060	Corneal neovascularization, unspecified
37923	Vitreous hemorrhage
37924	Other vitreous opacities
37925	Vitreous membranes and strands
37929	Other disorders of vitreous

5. Other relevant diagnosis to be excluded

For episodes with the principal diagnosis codes below, not classified as any indication above, the episode is excluded from the database:

36610	Senile cataract, unspecified
3638	Other disorders of choroid
3669	Unspecified cataract
8715	Penetration of eyeball with magnetic foreign body
36282	Retinal exudates and deposits
36289	Other retinal disorders
36504	Ocular hypertension
36563	Glaucoma associated with vascular disorders
36614	Posterior subcapsular polar senile cataract
36619	Other and combined forms of senile cataract
37922	Crystalline deposits in vitreous
99653	Mechanical complication due to ocular lens prosthesis
99679	Other complications due to other internal prosthetic device, implant, and graft

6. Other diagnosis to be excluded

For episodes with the principal diagnosis codes below, the episode is excluded from the database:

8711	Ocular laceration with prolapse or exposure of intraocular tissue
36000	Purulent endophthalmitis, unspecified
36001	Acute endophthalmitis
36615	Cortical senile cataract
36616	Senile nuclear sclerosis
36617	Total or mature cataract
36653	After-cataract, obscuring vision

37931	Aphakia
37932	Subluxation of lens
37934	Posterior dislocation of lens
99859	Other postoperative infection
99882	Cataract fragments in eye following cataract surgery
V5849	Other specified aftercare following surgery

7. Other diagnosis to be included

For all other episodes that do not meet any of the criteria above, the indication is the principal diagnosis

ICD 9 CODES

Codes for Diabetic Macular Edema (**DIMAED**):

36207	Diabetic macular edema

Codes for Retinal Vein Occlusion- Central (**RVOCEN**):

36235	Central retinal vein occlusion

Codes for Retinal Vein Occlusion- Branch (**RVOBRA**):

36236	Venous tributary (branch) occlusion

Codes for Exudative age-related macular degeneration (**EXARMD**):

36252	Exudative senile macular degeneration

Codes for Macular puckering (**MACPUC**):

36256	Macular puckering

Codes for Retinal neovascularization or Myopia (**RNVMYO**):

36021	Progressive high (degenerative) myopia
36216	Retinal neovascularization NOS
3671	Myopia

Codes for Other Conditions of the Retina and Choroid (**OCRECH**):

36241	Central serous retinopathy
36256	Macular puckering
36320	Chorioretinitis, unspecified
36343	Angioid streaks of choroid

Codes for Cystoid Macular Degeneration (**CYMADE**):

36253	Cystoid macular degeneration

Codes for Unspecified Macular Degeneration (**UNMADE**):

36250	Macular degeneration (senile), unspecified

Codes for Other Relevant Conditions (**OTRECO**):

3612	Serous retinal detachment
3619	Unspecified retinal detachment
3638	Other disorders of choroid
3669	Unspecified cataract
8715	Penetration of eyeball with magnetic foreign body
25000	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
25050	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
25051	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
25052	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
25053	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
36100	Retinal detachment with retinal defect, unspecified
36101	Recent retinal detachment, partial, with single defect
36102	Recent retinal detachment, partial, with multiple defects
36103	Recent retinal detachment, partial, with giant tear
36105	Recent retinal detachment, total or subtotal
36106	Old retinal detachment, partial
36107	Old retinal detachment, total or subtotal
36181	Traction detachment of retina
36189	Other forms of retinal detachment
36210	Background retinopathy, unspecified
36212	Exudative retinopathy
36215	Retinal telangiectasia
36216	Retinal neovascularization NOS
36240	Retinal layer separation, unspecified
36242	Serous detachment of retinal pigment epithelium
36243	Hemorrhagic detachment of retinal pigment epithelium
36254	Macular cyst, hole, or pseudohole
36257	Drusen (degenerative)
36281	Retinal hemorrhage
36282	Retinal exudates and deposits
36283	Retinal edema
36289	Other retinal disorders
36442	Rubeosis iridis
36474	Adhesions and disruptions of pupillary membranes
36504	Ocular hypertension
36563	Glaucoma associated with vascular disorders
36610	Senile cataract, unspecified
36614	Posterior subcapsular polar senile cataract
36619	Other and combined forms of senile cataract
37060	Corneal neovascularization, unspecified

37922	Crystalline deposits in vitreous
37923	Vitreous hemorrhage
37924	Other vitreous opacities
37925	Vitreous membranes and strands
37929	Other disorders of vitreous
99653	Mechanical complication due to ocular lens prosthesis
99679	Other complications due to other internal prosthetic device, implant, and graft

Codes for Other Vascular Occlusions (**OTVAOC**):

36230	Retinal vascular occlusion, unspecified
36231	Central retinal artery occlusion
36232	Retinal arterial branch occlusion

Codes for Atrophic Macular Degeneration (**ATMADE**):

36251	Nonexudative senile macular degeneration

IDENTIFICATION OF INTRAVITREAL ANTI-VEGF TREATMENT EVENTS FOR ICD-10

1. Main indications

Indication: DIABETIC MACULAR EDEMA (DME)

Numerator: Discharges, with either:

- A principal diagnosis code for Diabetic Macular Edema **(DIMAED)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or for Other Type 2 Diabetes Conditions **(ODIACO)** and any secondary diagnosis codes for Diabetic Macular Edema **(DIMAED)** or
- A principal diagnosis code for Retinal Edema **(RETEDE)** and any secondary diagnosis codes for any diabetic condition (ICD10 codes E08-E13).

Indication: RETINAL VEIN OCCLUSION (RVO)

Indication: RETINAL VEIN OCCLUSION (CENTRAL)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Central **(RVOCEN)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** and any secondary diagnosis codes for Retinal Vein Occlusion- Central **(RVOCEN)**.

Indication: RETINAL VEIN OCCLUSION (BRANCH)

Numerator: Discharges, with either:

- A principal diagnosis code for Retinal Vein Occlusion- Branch **(RVOBRA)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** and any secondary diagnosis codes for Retinal Vein Occlusion- Branch **(RVOBRA)**.

Indication: NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (nAMD)

Numerator: Discharges, with either:

- A principal diagnosis code for Exudative age-related macular degeneration **(EXARMD)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** or diagnosis code for Macular Puckering **(MACPUC)** and any secondary diagnosis codes for Exudative age-related macular degeneration **(EXARMD)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** or Other Diagnosis for Macular Degeneration **(ODMADE)** and a previous nAMD case, regardless of age.

Indication: CHOROIDAL NEOVASCULARIZATION (CNV)

Numerator: Discharges with either:

- A principal diagnosis code for Retinal neovascularization or Myopia (**RNVMYO**) or
- A principal diagnosis code for Other Relevant Conditions (**OTRECO**) or Other Diagnosis for Macular Degeneration **(ODMADE)** and any secondary diagnosis codes for Retinal neovascularization or Myopia **(RNVMYO)** or
- A principal diagnosis for Macular Puckering **(MACPUC)**, except if secondary diagnosis codes for Diabetic Macular Edema **(DIMAED)**.

2. Other indications

Indication: OTHER VASCULAR OCCLUSIONS

**This indication is not included in Retinal Vein Occlusion*

Numerator: Discharges, with either:

- A principal diagnosis code for Other Vascular Occlusions **(OTVAOC)** or
- A principal diagnosis code for Other Relevant **(OTRECO)** and any secondary diagnosis codes for Retinal Vein Occlusion **(OTVAOC)**.

Indication: ATROPHIC MACULAR DEGENERATION

** This indication is not included in Neovascular Age-Related Macular Degeneration*

Numerator: Discharges, with either:

- A principal diagnosis code for Atrophic Macular Degeneration **(ATMADE)** or
- A principal diagnosis code for Other Relevant Conditions **(OTRECO)** and any secondary diagnosis codes for Atrophic Macular Degeneration **(ATMADE)**.

3. Diabetes with Retinopathy

For episodes with the principal diagnosis codes below, without secondary diagnosis of Diabetic Macular Edema (**DIMAED**), the following criteria applies:

Principal diagnosis	Indication
E11319	Unspecified Diabetic Retinopathy
E113591, E113592, E113593	Proliferative Diabetic Retinopathy

E113291, E113292, E113491, E113551, E113552	Nonproliferative Diabetic Retinopathy

4. Other diagnosis to be excluded

For episodes with the principal diagnosis codes below, the episode is excluded from the database:

G245	Blepharospasm
H401120	Primary open-angle glaucoma, left eye, stage unspecified
H5000	Unspecified esotropia
H5005	Alternating esotropia
Z48810	Encounter for surgical aftercare following surgery on the sense organs

5. Other diagnosis to be included

For all other episodes that do not meet any of the criteria above, the indication is the principal diagnosis

ICD 10 CODES

Codes for Diabetic Macular Edema (**DIMAED**):

E10311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E103212	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E11311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E113211	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E113212	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E113213	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E11331	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E113311	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E113312	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E113313	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E113411	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E113412	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E113413	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E113419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E113511	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E113512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye

E113513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E13311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E133413	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E133511	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye

Codes for Other Type 2 Diabetes Conditions (**ODIACO**):

E113551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E113552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E1136	Type 2 diabetes mellitus with diabetic cataract

Codes for Retinal Edema (**RETEDE**):

H3581	Retinal edema

Codes for Retinal Vein Occlusion- Central (**RVOCEN**):

H348110	Central retinal vein occlusion, right eye, with macular edema
H348111	Central retinal vein occlusion, right eye, with retinal neovascularization
H348112	Central retinal vein occlusion, right eye, stable
H348120	Central retinal vein occlusion, left eye, with macular edema
H348121	Central retinal vein occlusion, left eye, with retinal neovascularization
H348122	Central retinal vein occlusion, left eye, stable
H348130	Central retinal vein occlusion, bilateral, with macular edema
H348131	Central retinal vein occlusion, bilateral, with retinal neovascularization
H348132	Central retinal vein occlusion, bilateral, stable
H348190	Central retinal vein occlusion, unspecified eye, with macular edema

Codes for Retinal Vein Occlusion- Branch (**RVOBRA**):

H348310	Tributary (branch) retinal vein occlusion, right eye, with macular edema
H348311	Tributary (branch) retinal vein occlusion, right eye, with retinal neovascularization
H348312	Tributary (branch) retinal vein occlusion, right eye, stable
H348320	Tributary (branch) retinal vein occlusion, left eye, with macular edema
H348321	Tributary (branch) retinal vein occlusion, left eye, with retinal neovascularization
H348322	Tributary (branch) retinal vein occlusion, left eye, stable
H348330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H348331	Tributary (branch) retinal vein occlusion, bilateral, with retinal neovascularization
H348332	Tributary (branch) retinal vein occlusion, bilateral, stable
H348390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema
H348391	Tributary (branch) retinal vein occlusion, unspecified eye, with retinal neovascularization
H348392	Tributary (branch) retinal vein occlusion, unspecified eye, stable

Codes for Exudative age-related macular degeneration (**EXARMD**):

H35321	Exudative age-related macular degeneration, right eye
H353210	Exudative age-related macular degeneration, right eye, stage unspecified
H353211	Exudative age-related macular degeneration, right eye, with active choroidal neovascularization
H353212	Exudative age-related macular degeneration, right eye, with inactive choroidal neovascularization
H353213	Exudative age-related macular degeneration, right eye, with inactive scar
H353220	Exudative age-related macular degeneration, left eye, stage unspecified
H353221	Exudative age-related macular degeneration, left eye, with active choroidal neovascularization
H353222	Exudative age-related macular degeneration, left eye, with inactive choroidal neovascularization
H353230	Exudative age-related macular degeneration, bilateral, stage unspecified
H353231	Exudative age-related macular degeneration, bilateral, with active choroidal neovascularization
H353232	Exudative age-related macular degeneration, bilateral, with inactive choroidal neovascularization
H353290	Exudative age-related macular degeneration, unspecified, stage unspecified
H353291	Exudative age-related macular degeneration, unspecified, with active choroidal neovascularization

Codes for Macular puckering (**MACPUC**):

H35371	Puckering of Macula, right eye
H35372	Puckering of Macula, left eye
H35379	Puckering of Macula, unspecified eye

Codes for Retinal neovascularization or Myopia (**RNVMYO**):

H35051	Retinal neovascularization, unspecified, right eye
H35052	Retinal neovascularization, unspecified, left eye
H35053	Retinal neovascularization, unspecified, bilateral
H35059	Retinal neovascularization, unspecified, unspecified eye
H3533	Angioid streaks of macula
H4421	Degenerative myopia, right eye
H4422	Degenerative myopia, left eye
H442A1	Degenerative myopia with choroidal neovascularization, right eye
H442A2	Degenerative myopia with choroidal neovascularization, left eye

Codes for Other Diagnosis for Macular Degeneration (**ODMADE**):

H3530	Unspecified macular degeneration
H35351	Cystoid macular degeneration, right eye
H35352	Cystoid macular degeneration, left eye

Codes for Other Relevant Conditions (**OTRECO**):

H2511	Age-related nuclear cataract, right eye
H2512	Age-related nuclear cataract, left eye

H25811	Combined forms of age-related cataract, right eye
H25812	Combined forms of age-related cataract, left eye
H259	Unspecified age-related cataract
H269	Unspecified cataract
H318	Other specified disorders of choroid
H33001	Unspecified retinal detachment with retinal break, right eye
H33002	Unspecified retinal detachment with retinal break, left eye
H33011	Retinal detachment with single break, right eye
H33012	Retinal detachment with single break, left eye
H33021	Retinal detachment with multiple breaks, right eye
H33022	Retinal detachment with multiple breaks, left eye
H33031	Retinal detachment with giant retinal tear, right eye
H33032	Retinal detachment with giant retinal tear, left eye
H33051	Total retinal detachment, right eye
H33052	Total retinal detachment, left eye
H3321	Serous retinal detachment, right eye
H3322	Serous retinal detachment, left eye
H3500	Unspecified background retinopathy
H35021	Exudative retinopathy, right eye
H35022	Exudative retinopathy, left eye
H35712	Central serous chorioretinopathy, left eye
H3589	Other specified retinal disorders
H4089	Other specified glaucoma
H409	Unspecified glaucoma
H4311	Vitreous hemorrhage, right eye
H4312	Vitreous hemorrhage, left eye
H59031	Cystoid macular edema following cataract surgery, right eye
H59032	Cystoid macular edema following cataract surgery, left eye

Codes for Other Vascular Occlusions (**OTVAOC**):

H3411	Central retinal artery occlusion, right eye
H3412	Central retinal artery occlusion, left eye
H349	Unspecified retinal vascular occlusion

Codes for Atrophic Macular Degeneration (**ATMADE**):

H353110	Nonexudative age-related macular degeneration, right eye, stage unspecified
H353111	Nonexudative age-related macular degeneration, right eye, early dry stage
H353112	Nonexudative age-related macular degeneration, right eye, intermediary dry stage
H353113	Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement
H353120	Nonexudative age-related macular degeneration, left eye, stage unspecified
H353121	Nonexudative age-related macular degeneration, left eye, early dry stage
H353122	Nonexudative age-related macular degeneration, left eye, intermediary dry stage

H353123	Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement
H353130	Nonexudative age-related macular degeneration, bilateral, stage unspecified
H353132	Nonexudative age-related macular degeneration, bilateral, intermediary dry stage
H353190	Nonexudative age-related macular degeneration, unspecified eye, stage unspecified

Appendix 2

Organizational level of the hospital's ophthalmology departments. Minimal requirements, as defined by the National Network of hospital specialties and referral for Ophthalmology [1]

Group I:

- Health care: refraction test and consultations (general and diabetes)
- Minimum number of inhabitants in the area of direct influence: 75,000
- Working hours: 8 am to 8 pm
- Minimum equipment required: refraction with slit lamp and keratometer, biometer, ultrasound, campimeter, optical coherence tomography (OCT), angiograph / retinograph, YAG laser, Argon laser or similar, operating microscope, phacoemulsifier
- Minimum of Ophthalmologist specialists: 5

Group II:

- Health care: all ophthalmic health care with the exception of pediatric oncology, transplantation, glaucoma and cataracts, retinopathy of prematurity, rare diseases
- Daytime medical and surgical urgency: 12h/day; 7 days/week
- Minimum of Ophthalmologist specialists: 12
- Maximum of ophthalmologists: to be defined according to the population to be served;
- Minimum equipment required: in addition to equipment required for hospitals in Group I, vitrectomy device with endolaser, specular microscope and corneal topograph.

Group III:

- Health care - responsible for all ophthalmic health care, excluding those related to Reference Centers (approved or to be approved)
- Multipurpose emergency: 2 ophthalmologists in physical presence 24h/day; 7 days/week.
- Minimum equipment required: in addition to equipment required for hospitals in Group II, Retcam and portable electrophysiology

Source: [1] Serviço Nacional de Saúde. Rede nacional de especialidade hospitalar e de referenciação de oftalmologia [Internet]. 2016. Available from: https://www.sns.gov.pt/wp-content/uploads/2016/05/Proposta-RNEHR-Oftalmologia-2016-ACSS-1_VFinal.pdf

Appendix 3

Table S1. Proportion of patients treated with anti-VEGF injections, 2013 and 2018, per region and per diagnosis, Portugal

Region	nAMD	DME	CNV	RVO
Alentejo	4,57%	7,40%	5,22%	7,06%
Algarve	1,61%	4,04%	1,83%	1,20%
Metropolitan area of Lisbon	25,53%	21,90%	24,28%	25,45%
Metropolitan area of Porto	27,12%	24,97%	26,82%	26,08%
Central region	28,56%	19,04%	25,26%	28,57%
Northern region	12,61%	22,65%	16,58%	11,64%

Table S2. Spearman's correlation between rate of anti-VEGF treatments and ecological variables (N=278 municipalities).

Year	Purchasing power	Rate of ophthalmologists	Ophthalmology consultations in all hospitals	Ophthalmology consultations in public hospitals
2013	0.048	0.085	**0.131***	**0.124***
2014	0.041	0.109	0.102	0.106
2015	0.101	**0.122***	0.105	0.103
2016	**0.206***	**0.144***	**0.156***	**0.130***
2017	**0.152***	0.085	0.083	0.104
2018	**0.215***	0.106	0.097	0.11

**P-value < 0.05; correlation statistically significant*

Table S3. Stepwise linear regression models, rate of anti-VEGF treatments as dependent variable (N=278 municipalities).

Year	Variable	β adjusted coefficient	Significance	Adjusted R^2
2013	Constant		0	0.026
	Ophthalmology consultations in all hospitals	0.174	0.008	
2014	Constant		0.000	0.021
	Ophthalmology consultations in all hospitals	0.158	0.016	
2015	Constant		0.000	0.020
	Ophthalmology consultations in all hospitals	0.156	0.018	
2016	Constant		0.000	0.039
	Purchasing power	0.207	0.002	
2017	Constant		0.033	0.033
	Purchasing power	0.192	0.004	
2018	Constant		0.085	0.043
	Purchasing power	0.217	0.001	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3,4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	5,6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.