PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends, geographical variation, and factors associated with the use of ANTI-VEGF intravitreal injections in Portugal (2013–18): A retrospective analysis of administrative data
AUTHORS	Rocha, João Victor; Marques, Ana; Macedo, Antonio Filipe; Afonso-Silva, Marta; Laires, Pedro; Almeida, Ana Sofia; Fernandes, Julieta; Pardal, Marisa; Santana, Rui

VERSION 1 – REVIEW

REVIEWER	Solaiman , KA Zagazig University, Ophthalmology
REVIEW RETURNED	06-Nov-2021

GENERAL COMMENTS	Thank you.

REVIEWER	Yip, Wilson The Chinese University of Hong Kong, Department of Ophthalmology and Visual Sciences
REVIEW RETURNED	18-Jan-2022

GENERAL COMMENTS	The authors conducted an observational study on the anti VEGF intravitreal injection rates and associated factors in Portugal using an administrative database on hospital discharges from public hospital institutions.Congratulate on the works for ploicy makere to imporve the delivery of health care. A few points for authors to address: 1. For table 1: It will be of better reference value if the proportion of national population in each of the regions are also stated next to the region. Say 72 % intravitreal injection in metropolitan and central area is normal is 72 % of national population reside in those area.. 2.It will also be of interest to know the percentage of spectrum of diseases treated in different regions. Would it be fof higher percentage of DME in Central metropolitant area? 3.Although the authors had stated the distance in kilometres from the munucipital address to the hospital. I assumed that meant the patient address to the hospital. How and by what methods did the authors used to measure the distance should also be stated. 4. Authors should also elaborate more on the purchasing power provided by National Statistics. What and how did it be calculated. 5. Would educational level of the municipital area related? Data available from national statistics? 6. For Figure 1, The legend may better be revised to " Number" only, as the "Number of episodes/patients" could be misread as episode per patient.

	7.It will also be interest to show the rest of the ecological statistics in table.

REVIEWER	Sobaci, Gungor Hacettepe University, Ophthalmology
REVIEW RETURNED	24-Jan-2022

GENERAL COMMENTS	none

REVIEWER	Leila, Mahmoud Research Institute of Ophthalmology
REVIEW RETURNED	28-Jan-2022

GENERAL COMMENTS	I congratulate the authors for their work. They tackled an important issue and investigated thoroughly nationwide the logistics and pitfalls of delivering anti-VEGF agents to Portuguese patients. I am confident their results would help to improve the geographic distribution of anti-VEGF to patients in their country.

VERSION 1 – AUTHOR RESPONSE

First, we would like to thank the editor and reviewers for the valuable feedback provided, which has prompted us to discuss our rationale behind this study and the contribution to the current state knowledge of anti-VEGF intravitreal treatments. Below we answer the reviewers' comments and indicate the changes made to the manuscript.

Editors' comments to authors

- It is not immediately apparent how absolute data on use of anti-VEGF therapies can be used to estimate variation in use by geographical region and demographic characteristics without also having access to data on the numbers of patients who would potentially qualify for anti-VEGF therapies in each area and demographic category, in order to calculate differences in rates. Please clarify and discuss, as appropriate.

We thank the editor for this important point of discussion in our study. In Table 1 we have added information about the proportion of the population living in each region of Portugal, with results thus supporting our discussion of regional discrepancies. The proportion of the population is not the ideal information to be analyzed, however there is little information of the epidemiology (including incidence or prevalence) of these ophthalmologic diseases at a regional level in Portugal. There are studies that show the prevalence estimates at the national level for nAMD. Nevertheless not all nAMD forms are treated with Anti-VEGF; therefore these prevalence estimates would not be useful either at a regional or national level. Previous studies have shown that the prevalence of nAMD in Portugal is similar to other European countries. We are not aware of studies looking at the prevalence of retinal vein occlusions in Portugal, however, these patients tend to receive average 2 -3 injections and therefore this should not influence much our numbers. In Conclusion, the proportion of the population can be used as a proxy if we assume a homogeneous prevalence of these diseases across the country. The number of cases per 100 population (prevalence) should be similar across the country. We have added information on this matter in the results and discussion sections of the manuscript.

- Please revise the title of your manuscript to include the research question, study design and setting. This is the preferred format of the journal. E.g, "Trends, geographical variation, and factors associated with the use of anti-VEGF intravitreal injections in Portugal (2013–18): a

retrospective analysis of administrative data" (or similar, please amend as needed for accuracy and clarity).

We have revised the title of the manuscript, and we accepted the suggestion of the Editor.

- Please revise the abstract to ensure that it is formatted according to our Instructions for Authors (http://bmjopen.bmj.com/pages/authors/#research), including all relevant subheadings and required details.

The abstract includes the relevant subheadings and the required details

- Please also ensure that any study design descriptors added in response to the above requests are used consistently in the title, abstract, and main text Methods section, as appropriate.

The study design descriptors are consistent in the manuscript

- Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The results of the study should not be summarised here. Use of full sentences would enhance the readability and clarity of the bullet points included.

We have updated the 'Strengths and limitations' section with full sentences related specifically to the methods.

- Please ensure that you have fully described the methodological limitations of the study in the 'Strengths and limitations' section and (in greater detail) in the Discussion section of the main text

We have updated the discussion section of the main text to fully describe the methodological limitations of the study.

- Please delete the sentence starting "The study was conducting by analysing" from the "Patient and Public Involvement" statement.

We deleted the sentence as suggested.

- Please change the subheading "Data sharing statement" to "Data availability statement".

We changed the subheading as requested

- Please update the COI statement to indicate the funder's interests in the topic, eg "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 XXXX" (replacing XXXX with the scientific names of the anti-VEGF therapy(ies) marketed by Novartis), in order to improve transparency on potential competing interests.

We have added the scientific names of the anti-VEGF therapies marketed by Norvartis at the COI statement.

- Please complete a thorough proofread of the text and correct any spelling and grammar errors that you identify. It may be useful to ask a native English-speaking colleague to assist you or to enlist the help of a professional copy-editing service, if possible, to ensure any English grammar issues or problems with respect to clarity of meaning are identified and addressed.

The manuscript has been proofread by a native English-speaking professor.

Reviewer: 2 (Dr. Wilson Yip, The Chinese University of Hong Kong)

- For table 1: It will be of better reference value if the proportion of national population in each of the regions are also stated next to the region. Say 72 % intravitreal injection in metropolitan and central area is normal is 72 % of national population reside in those area.

We have added a column for table 1 and added information regarding these differences in the text. The proportion of national population and the proportion of intravitreal injections are not the same, thus supporting our discussion of regional discrepancies.

- It will also be of interest to know the percentage of spectrum of diseases treated in different regions. Would it be of higher percentage of DME in Central metropolitan area?

We have added this information at a Supplementary Table, and indicated it on the text.

- Although the authors had stated the distance in kilometres from the municipal address to the hospital. I assumed that meant the patient address to the hospital. How and by what methods did the authors used to measure the distance should also be stated.

The mean distance to the hospital was obtained through Google Maps, as these represent the distance to be travelled by patients. This information was added to the manuscript.

- Authors should also elaborate more on the purchasing power provided by National Statistics. What and how did it be calculated.

We have provided more information in the "Data Analysis" section.

- Would educational level of the municipal area related? Data available from national statistics?

Educational level at the municipality level is only available for the last census, conducted in 2011. Because Portugal faced significant economic and financial transformations in the first half of 2010s, we considered the data on educational level to be too old to be considered.

- For Figure 1, The legend may better be revised to " Number" only, as the "Number of episodes/patients" could be misread as episode per patient.

We have updated the Figure as suggested

- It will also be interest to show the rest of the ecological statistics in table.

We have added these tables as Supplementary Material

We thank Reviewer 1 (Dr. KA Solaiman , Zagazig University); Reviewer 3 (Dr. Gungor Sobaci, Hacettepe University) and Reviewer 4 (Dr. Mahmoud Leila, Research Institute of Ophthalmology) for taking part in the Review Process and their positive response.