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Childhood Tuberculosis in Portugal

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Childhood Tuberculosis in Portugal - 2003 to 2012 - a descriptive analysis

Children; Tuberculosis

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Sara Martins – writing of the manuscript, epidemiology data analysis and interpretation of the study. Carla Azevedo – epidemiological data analysis. Ana Rita Gaio – epidemiological data analysis. João Vasco Santos – epidemiological data analysis and interpretation of the study. Raquel Duarte - writing of the manuscript and interpretation of the study

Abstract: In Portugal, in 2012, 73 children <15 years and 32 children <5 years developed Tuberculosis (TB). The aim of this study was to characterize TB in Portuguese children: diagnostic, clinical manifestations and factors associated with severe forms of disease. We analysed all children <6 years with TB between January/2003 and December/2012 - mandatory. Parameters in subjects with mild/severe TB were compared using Pearson's chi-square tests and gross effects analysis. 364 children were studied, mean age of 2.5±2.0 years. 330 (91%) were born in Portugal of which 161 (44.4%) in Lisbon/Oporto. 351 (96%) didn't have any comorbidity and 204 (56%) had known BCG vaccination. Median time from symptom onset until diagnosis was 83 days. TB was more frequently detected by passive (n=216, 59%) than by active (n=128, 35%) screening. 236 (65%) had pulmonary manifestations and in chest radiography, performed in 346 children, 171 (72.5%) presented non-cavitary forms. 311 (85.4%) presented mild TB and 53 (14.6%) severe TB. No predictors of severe manifestations were identified. 26% of the children had diagnostic confirmation (culture positive). TB among children is still a problem in our country particularly in the two large urban centres. We didn't identify predictors of severe forms of disease.

Introduction

An estimated 9 million individuals worldwide develop tuberculosis (TB) annually, including 1 million children under age 15 years. [1] In 2012, 2,599 individuals in Portugal were diagnosed with TB, including 73 children under age 15 years and 32 children under age 5 years. [2]

Children infected with Mycobacterium tuberculosis have a higher likelihood than adults of progression to active disease, [1, 3] with this likelihood being even higher in children under age of 5 years. The risks for progression to active disease have been reported to be 50% in children under 1 year old, 10-20% in children aged between 1 and 2 years and 5% in children aged between 2 and 5 years. [4] Most of these individuals experience disease progression during the first year after infection. Moreover, the immune system in children is not fully developed. Taken together, these findings indicate recent transmission of Mycobacterium tuberculosis in the population. [3] Furthermore, children under age 2 years and those who are immunocompromised are susceptible to more severe and potentially fatal forms of TB. [5]

Diagnostic confirmation by identification of the infectious agent is a complicated process in children. Obtaining samples is difficult, and, even if obtained, the paucibacillary nature of lesions can yield false negative laboratory results. [3] It is even more difficult in patients with extra-pulmonary disease, more prevalent in children than in adults. [3] In Europe between 2000 and 2009, only 42.3% of paediatric patients with TB underwent culture analysis, with these results being positive in 39.9%. [1] Culture confirmation rates were found to be 19.2% in Europe during 2009 [1] and 27.6% in Portugal from 2000 to 2009. [6] Currently, appropriate clinical presentation, history of recent contact with infected individuals, immunological evidence of infection

and radiological signs compatible with TB are considered indicators of TB and suggest that treatment of TB should be started. [3, 7, 8] However, the variability and low specificity of clinical and radiological findings in children indicate a need for a high level of suspicion. [3]

Thus, better methods of diagnosis can result in better disease control in individual patients, as well as providing more valid statistics, advances in clinical research and a better integration of TB into national disease control programs. [9]

This study was therefore designed to characterize TB in Portuguese children by diagnostic assessment and clinical manifestations of the disease, as well as to characterize the factors associated with more severe forms of TB.

Methods

In Portugal, all individuals with TB are diagnosed and treated for free under the National Health System, with affected individuals referred to tuberculosis outpatient centres (CDPs) in their areas of residence. These centres are responsible for the diagnosis and treatment of non-hospitalized individuals with TB, as well as for the screening of high-risk populations. All patients diagnosed with TB are reported to the National Tuberculosis Surveillance System (SVIG-TB).

In this study we included all children under 6 years old who were diagnosed with TB and reported to the SVIG-TB between January 1, 2003, and December 31, 2012. Variables analysed included age, country of origin, method of disease detection, time from symptom onset to diagnosis, immunosuppressive comorbidities, administration of bacillus Calmette-Guérin (BCG) vaccine, tuberculin test (TST) results, interferon gamma assay (IGRA) results, clinical presentation, and confirmation by microscopy and/or bacterial culture. Subjects with invalid or missing data were excluded.

Forms of TB considered mild included lymphatic extrathoracic or intrathoracic, pleural, pulmonary or pleuro-pulmonary. All other forms were defined as severe, including the involvement of more than one organ and genitourinary, meningeal, central nervous system (SNC) non-meningeal, osteoarticular non-vertebral, and vertebral and digestive/peritoneal tuberculosis.

Parameters in subjects with mild and severe tuberculosis were compared using Pearson's chi-square tests for categorical variables and gross effects analysis for continuous variables. Analysis of the database did not require approval by the Ethics Committee, due to the retrospective nature of the study and the impossibility of linking patients' records to personal data.

Results

Survey of the SVIG-TB database identified 364 children under 6 years old, 165 (45%) females and 199 (55%) males, who were diagnosed with TB between January 1, 2003, and December 31, 2012. Mean patient age was approximately 2.5 (SD 2.0 years), and 330 (91%) were born in Portugal, of which 161 (44.4%) in the cities of Lisbon and Oporto. Of the 364 children, 351 (96%) did not have any associated comorbidity, including diabetes or infection with human immunodeficiency virus (HIV). Only 7 children (1.9%) were HIV infected at diagnosis. We found that 204 of these children (56%) had been vaccinated for BCG and 26 (7%) had not been vaccinated. No information about vaccination was available for the remaining 134 (37%) patients. The median time from symptom onset until diagnosis of TB was 83 days. TB was more frequently detected by passive (n = 216, 59%) than by active (n = 128, 35%) screening; of the latter, 126 (98%) were screened after contact with a patient with TB. The remaining 20 (5.5%) children had no information about screening.

Of the total 364 patients, 236 (65%) had pulmonary manifestations of TB; of the latter, 41 (17%) had extra-pulmonary manifestations and 194 (82%) did not. Among all children, 169 (46%) presented with extra-pulmonary forms of TB, including 49 (13.5%) with disseminated, 36 (9.9%) with lymphatic intrathoracic, and 33 (9%) with lymphatic extrathoracic forms. In addition 11 (3%) had pleural forms, four (1%) presented with CNS meningeal and two (0.5%) with non-meningeal forms, five (1.4%) with osteoarthritic vertebral, nine (2.5%) with osteoarthritic non-vertebral, three (0.8%) with genito-urinary, and one (0.3%) with digestive/peritoneal forms of TB. Thirteen patients (3.6%) had other forms of TB and four (1.1%) had unknown types.

Of the 364 children, 311 (85.4%) presented mild TB and the other 53 (14.6%) severe TB. No predictors of severe manifestations of disease could be identified, including immunosuppressive comorbidities, BCG inoculation, residence or time to diagnosis (Table 1).

Chest radiography was performed in 346 children (95%). Of the 236 children with pulmonary involvement, 171 (72.5%) presented with non-cavitary forms, 31 (13%) with cavitary forms, and 19 (8%) with no change. Results could not be determined for the other 15 (6.4%) patients.

The TST was performed in 279 children (76.6%) and the IGRA in 10 (3%).

In evaluating methods of diagnostic confirmation, we found that 172 children (47%) were not evaluated by microbacteriological methods, whether direct or cultural. Of the 192 subjects evaluated by direct methods, 69 (36%) had positive outcomes, whereas, of the 158 subjects assessed by culture, 94 (59%) had positive outcomes. Of all children, 124 (34%) had probable or confirmed diagnoses (positive on direct assays or on bacterial culture) and 26% had diagnostic confirmation (positive culture results). Of those assessed microbacteriologically, 122 (63.5%) had probable or confirmed diagnoses. Species were identified in 20% of these children.

Discussion

The mean age of the 364 Portuguese children with TB was approximately 2.5 years, similar to studies in other countries, including a recent Mexican study with a similar average age (3 years). [10] However, the last Europe-wide study showed that, in Portugal, only 42.9% of children <14 years with TB were aged 0-4 years. [11] Most of the children with TB were born in Portugal, and almost 50% resided in Lisbon and Oporto, the two largest urban centres in the country and the areas of highest incidence of TB in Portugal. [2]

Immunosuppression is an important risk factor for TB. HIV infection affects both the epidemiology and severity of TB, increasing the risk of developing and disseminating TB. [12] Nevertheless, 96% of the children surveyed had no associated immunosuppressive comorbidity, with only about 2% being HIV positive. In comparison, HIV/TB rates were reported to be 8% in Mexico and 1.5% in Peru, [13] but 12% to 37% in developing countries. [14]

The role of BCG vaccination in protecting against TB remains unclear.[10] BCG has been shown to protect against miliary and meningeal forms of TB, with a protective efficacy of approximately 60-80%. However, the efficacy of BCG vaccination against pulmonary forms of TB varies geographically. [15] Of the children in this study, 56% were vaccinated with BCG and 7% were not, with no information available about the other 37%. Studies in Mexico [10] and China [16] showed that 93% and 76%, respectively, of children with pulmonary TB were vaccinated. Vaccination coverage is higher in countries with a high prevalence of TB (e.g. China and Mexico) than in countries with intermediate or low prevalence of TB (e.g. Portugal). [15]

The mean time to diagnosis was approximately 83 days, similar to findings in Mexico (5 to 150 days) [10] and Vila Nova de Gaia (37 ± 47 days) [17]. TB was detected by passive screening in 59% was of our study subjects, similar to findings in Madrid (59%)[18] and in Texas (79%). [19]

We found that almost half of our study subjects (47%) were not assessed by bacteriological methods. The percentage evaluated by bacterial culture (43%) was similar to that in Europe between 2000 and 2009 (42.3%). [1] Diagnosis was confirmed by culture in 26% of the children in our study, higher than the rate in Europe in 2009 (19.2%), [1] but similar to the national percentage in Portugal between 2000 and 2009 (27.6%).[7] Moreover, 63.5% of the children evaluated microbacteriologically had a probable or confirmed diagnosis, compared with 34% in the entire sample. This finding indicates the importance of an accurate diagnosis, in particular by utilizing microbacteriological methods to assess all children with suspected TB.

The majority of children studied (85.4%) had mild forms of TB, comparable to a European study in which 53.4% of children had pulmonary TB, one form of mild TB. [1] In contrast, a study from China reported that 54% of the children studied had disseminated forms of TB with extension to organs other than the lungs, [16] compared

with the 13.5% rate of disseminated TB in this study. The study from China found statistically significant differences in several variables between patients with mild and severe forms of TB (disseminated or meningeal). Lower age, absence of BCG vaccination and shorter time to diagnosis were associated with a greater likelihood of more severe forms of TB, and residence was also associated with TB severity. [16] In contrast, we were unable to identify any factors associated with disease severity in Portuguese children.

TB in children is an indicator of disease transmission within the community. We found that these children are concentrated in large urban centres, where the incidence of TB is greater. Early detection and diagnostic confirmation of disease are necessary. We were unable to identify predictors of severe forms of disease.

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Table 1-Absolute (Abs) and relative (Rel) frequency (Freq) for each discrete variable and distinction of proportions between children with severe Tuberculosis (TB) and mild Tuberculosis

Variables	Value	Abs Freq Range	Rel Freq Range	Severe TB	Mild TB	Pearson's chi-square test (p-value)
Disease	Mild TB Severe TB	311 53	0.854 0.146	------ ------	------ ------	----- -----
Detection	Active screening Passive screening Unknown	126 216 22	0.35 0.59 0.06	16 31 6	110 185 16	0.2002
Inoculation with BCG	Does not have Have Unknown	26 204 134	0.07 0.56 0.37	4 30 19	22 174 115	0.9835
Comorbidities	No Yes	351 13	0.96 0.04	52 1	299 12	1
Cities	Another Oporto or Lisbon	203 161	0.558 0.442	26 27	177 134	0.3603
Country of origin	Other Portugal	34 330	0.09 0.91	5 48	29 282	1
TST	Unknown Does not have Have	35 50 279	0.09 0.14 0.77	3 1 49	32 49 230	0.09226
IGRA	Unknown Does not have Have	354 2 8	0.97 0.01 0.02	52 0 1	302 2 7	0.8299
Microscopy/direct study	Waits Unknown Negative Positive	1 2 120 69	0.003 0.005 0.330 0.190	0 0 23 10	1 2 97 59	0.728
Specie detection	Unknown No Yes	158 132 74	0.434 0.363 0.203	26 16 11	132 116 63	0.578
Cultural study	Waits Unknown Negative Positive	2 6 56 94	0.005 0.016 0.154 0.258	0 2 8 18	2 4 48 76	0.5686

Tuberculosis in undiagnosed children: what are the criteria to start treatment in Portugal?

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Sara Martins conceived this study and collaborated in all steps. Isabel Carvalho revised the questionnaire. João Vasco Santos provided the opportunity to use Medquest for writing the questionnaire and gave support in its creation. Raquel Duarte supervised all aspects of this work.

Dear Editor,

Worldwide, about 9 million individuals per year are newly infected with tuberculosis (TB), with 1 million of them being children under 15 years of age.[1] In Europe between 2000 and 2009, only 42.3% of patients with pediatric TB were assessed by culture, and only 39.9% of those tested were culture positive.[1] Indeed, the confirmation rate among pediatric cases was 19.2% in Europe in 2009[1] and 27.6% in Portugal from 2000 to 2009. [2] The variability and low specificity of clinical and radiological findings of TB in children indicate the need for a high level of suspicion in pediatric patients.

In Portugal, TB is managed in the 67 tuberculosis outpatient centers. These centers are responsible for the management of all cases of TB and the screening of at-risk populations. The cases that are hospitalized are orientated to these outpatient centers as soon as they are released from hospital.

All cases of TB are mandatorily notified to the National Tuberculosis Surveillance System (SVIG-TB) by the clinician.

This study was designed to identify the criteria leading to the empirical start of antibiotic treatment in Portugal, without diagnostic confirmation, in children age <6 years.

This study was based on the implementation of a web-based survey, through Medquest®, directed to doctors at the national level with experience in TB. Professionals' experience with TB and specifically with TB in pediatric age was assessed. This survey included 30 multiple choice and simple answer questions, with all responses being anonymous.

The investigation was approved by the Ethics Committee of the EPIUnit-Institute of Public Health, University of Porto, Porto, Portugal.

The questionnaires were sent to all tuberculosis outpatient centers – two of them failed delivery. Of the 65 surveys sent, 29 (44.6%) were completed. Of the 29 responders, 20 (69%) were female. Mean age of the responders was 48.7 years, and mean clinical experience was 20 years (range, 2 to 38 years), including an average of 15.5 years of experience in TB management and 11.7 years in management of TB in children .

When asked about their criteria to start treatment in children under 6 years of age without diagnostic confirmation, 72% cited epidemiological context, 62% mentioned radiological abnormalities, and 55% cited clinical history and the results of immunological tests, including tuberculin and gamma-interferon assays.

Factors associated with epidemiological context cited as the most important in the decision to start treatment included history of exposure (n = 25, 86%), immunodeficiency (n = 17, 59%) and country of origin with a high prevalence of TB (n = 16, 55%). Radiological criteria included chest radiography, cited by 76% of responders, followed by computerized axial tomography (33%). The most valuable imaging findings were nodules and cavities (96%), adenopathies (41%), pleural effusion (41%) and "tree-in-bud" appearance (26%).

Clinical determinants associated with the decision to start treatment included sustained fever (55%), respiratory symptoms (41%) and failure to thrive (34%). The average time window considered for these symptoms was 36.5 days (range, 7 days to 3 months).

Immunological tests considered relevant to the decision to treat included tuberculin tests (41%) and interferon gamma assays (28%).

History of exposure to a patient with active disease and the presence of clinical and radiological changes associated with disease progression were considered especially valuable in determining whether to treat. Although the radiological changes perceived as more suggestive of TB are not common presentation under 6 years of age for TB,

all findings are in agreement with proposed criteria for early treatment of TB in children under 6 years of age. [3,4] One weakness of our study is that we only received 44.6% of the questionnaires sent. A more wide study should be done, including pediatricians from the hospital.

Conflict of interest: there are no conflict of interest

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Surveillance and outbreak reports: Surveillance articles should focus on epidemiological trends regarding a specific disease or a group of diseases with data from a national or international surveillance system, but they could also be an analysis of a surveillance system or a description of a new surveillance system. Longer reports on national or international outbreaks should be submitted once the outbreak has been fully investigated and focus on new or unexpected aspects and on lessons learnt. The length of these articles is up to ca. 3,500 words, with a minimum of 15 and up to around 30 references and six illustrations (figures or tables). We encourage authors to follow the STROBE guidelines that were set up for observational studies i.e. case-control, cohort and cross-sectional studies.

Review articles provide a comprehensive state-of-the-art overview of issues of major public health importance within the field of communicable disease surveillance, prevention or control. They usually are about 4,000 words in length, and contain up to 80 references and six illustrations (figures or tables). All review articles should explain the search strategy and selection criteria, justify the inclusion/exclusion of material and state the sources. For systematic reviews, we encourage authors to follow the PRISMA guidelines.

Euroroundups should provide an analysis of a specific aspect or function of communicable disease surveillance, prevention or control in at least five European countries, and present an in-depth comparison of systems and/or data. The average length of these articles is 3,500 words with a minimum of 15 and up to around 30 references and six illustrations (figures or tables).

Perspectives provide an insightful analysis of practices, policies and guidance on communicable disease prevention and control, as well as guidance on developments in the field of vaccines and immunisation. These articles have an average length of 2,000 words, and contain up to 20 references and four illustrations (figures or tables).

Other material

The following article categories are not peer reviewed. However, we may consult an expert for advice on the content of such items.

Editorials are written by experts invited to comment on articles and special topics covered by *Eurosurveillance* and usually have a maximum of two authors. Editorials are

usually 1,500 words long and contain a maximum of 20 references and four illustrations (figures or tables).

Letters to the editor comment on recent *Eurosurveillance* articles and should be submitted within four weeks after the publication of the article in question. They are intended to stimulate scientific discussion and are not a format for the publication of original data. Their average length is 600 words, with five or fewer references.

Meeting reports should focus on content and contain up to 2,000 words, 10 references (including, when possible, links to full reports of conference activities) and no illustrations. They should have no more than two authors. Before submitting a meeting report, please contact the editorial team.

News are short texts related to current public health events, either authored or commissioned by the *Eurosurveillance* editorial team. Their length is usually 400 words, with five or fewer references and no illustrations. News do not have more than one or two authors.

How to submit material To top

All submissions should be sent through the *Eurosurveillance* online submission system. An online author tutorial is available, if you have any difficulties during the submission process.

All submissions should contain the following information:

- the article category;
- a declaration that the material is original and has not been submitted elsewhere;
- a declaration that all authors have seen and approved the final manuscript;
- a declaration that the corresponding author, on behalf of all co-authors, has read and agreed to the terms of the *Eurosurveillance* data protection notice;
- a declaration that informed consent has been obtained from persons whose details are described in articles (or from the persons' guardians) that this information may be published;
- a statement on funding and potential competing interests of the authors;
- where appropriate, information on approval of the work by an ethics committee;
- proof of permission to use figures or tables that are adapted or reproduced from other publications.

The following material should be uploaded as separate files:

- a covering letter;
- an anonymised manuscript text in Word format (pdf files cannot be evaluated) including an abstract of appropriate length and a minimum number of eight references for rapid communications and 15 for regular articles. All author-identifiable information – authors' names, affiliations and contributions as well as any acknowledgements – should **NOT** be included in the document. No illustrations (figures or tables) should be included in this document;
- authors' names and affiliations (in the format for publication). The first name of each author should be given in full (i.e. an initial should not be given). Where a collective author is included (e.g. a working group or disease-specific network)

and if the persons comprising the group are to be included at the end of the article, please list each person in this file;
- authors' contributions: the contribution of each author to the article should be described. This information will be published at the end of the article;
- all figures in an appropriate format (see details in the section on formatting and style),
- all tables in Word format;
- a scan of the agreement with authors signed by the corresponding author on behalf of all authors.

File names of uploaded files must not contain any author-identifiable information that may lead to identification of the author.

After all files and information have been uploaded in the submission system, the corresponding author is responsible for checking and approving the pdf. Approval of the pdf is required for the article to be sent to the editorial office.

The pdf that the reviewer will receive contains only the manuscript text and any figures and tables. For rapid communications, we also give reviewers access to the source files, in case they wish to comment directly in the text. For this reason, authors of rapid communications must ensure that all personal information in the properties of the manuscript text, figures and tables is removed before submission. See instructions on how to remove personal information from Microsoft Word or Excel files.

Ensuring that the appropriate files contain no author-identifying information allows the relevant files to be sent to reviewers. If the above conditions regarding anonymity of files and file names are not met, the submission will be returned to the authors, for them to amend and resubmit.

Submissions should conform to the uniform requirements for manuscripts submitted to biomedical journals as detailed in: Uniform requirements for manuscripts submitted to biomedical journals. International Committee of Medical Journal Editors. Med Educ. 1999; 33(1):66-78 (http://www.icmje.org/index.html)

Supplementary material To top

Eurosurveillance does not publish supplementary material. All necessary information should be integrated in the article, while observing the word limit. In exceptional cases, where strong reasons preclude publication of certain information as part of the article, the authors have the option to make such material available on an independent website and to provide a link to this website in the article. Such material is not edited by *Eurosurveillance* and *Eurosurveillance* is not responsible for the content.

Formatting and style To top

Articles should be written in clear, appropriate and scientific language that is free of jargon. Avoid abbreviations when possible and define them when you first use them. Please use United Kingdom English spelling.

Titles should be interesting, informative, accurate and as short as possible. They should contain the place/country and the time period covered in the paper.

Keywords: A maximum of eight keywords suitable for indexing should be provided. Please select from the list provided and add others if needed. Separate the keywords by a semi-colon (;).

Abstracts of regular articles should stay within the limit of 150 to 200 words, those of rapid communications should not exceed 75 words. Abstracts in *Eurosurveillance* do not contain subheadings.

Main text: An introduction should put the topic into perspective using up-to-date references, and clearly state the objective of the work and its relevance. The relevant methods should be presented at an appropriate level of detail; molecular diagnostic techniques that are published or standard, for example, can be named and referenced and do not need to be described in detail. It is important to make it clear at all times which results are the work of the authors, presented as part of the article, and which are already known and given as background or for comparison. If tables and figures are provided, the text should shortly describe and summarise the content, but not unnecessarily repeat the information; the reader should be able to understand text and illustrations independently of each other. The European and international relevance should be discussed with relevant references, and where appropriate, lessons learnt and recommendations for the future should be presented.

Tables and figures

Tables and figures are inserted after the paragraph in which they are mentioned.

Any references given in them are numbered after the citations in the text, i.e. the numbering does not take into account the position of the table or figure in the text.

Figure/table titles should not contain abbreviations and be as short as possible and mention the disease, place and date as well as number of cases/samples shown, so that it can be clearly understood what is shown. Further information needed to understand the figure or table is presented in the footnote under the illustration, together with explanations of all abbreviations and information on the source of the data. Footnotes added to specific entries in the table or figure are numbered as superscript a, b, c, etc. in order of appearance. The reader should be able to understand an illustration without referring to explanations in the text.

Tables and figures that have already been published can only be accepted under specific circumstances. In such cases the authors are required to obtain permission from the copyright holder to reproduce the illustration in question. Copyright also needs to be observed, for example, for maps used as a background for entering data.

Tables should be sent in Word format. They must be uploaded as separate files.

All figures should be uploaded as separate, editable files. **Graphs** should be provided in Excel format. If that is not possible, graphs, as well as phylogenetic trees etc, have to be submitted as vector files such as .pdf, .eps, .wmf, .emf, .svg . could be given. All the

programmes used to create graphs should be able to export a file in at least one of these formats. Not all pdfs are vector files: Illustrations should be exported as a pdf directly from the programme in which they were created, rather than exporting the illustration in another format and then subsequently saving as a pdf.
Pictures of illustrations simply copied into the above formats cannot be used because they cannot be edited. We need the illustration to be linked to the original data. Bitmap files (.jpg, .bmp, .gif, etc) are not acceptable. **Maps** should be provided as vector files (.pdf, .eps, .wmf, .emf, .svg). Preferably the maps should not include bitmap elements (i.e. map as a picture in the background). Only **photographs** should be given as high-resolution bitmap files (.jpg, .tif, etc.). They should be provided as stand-alone original files, and not included in Word or PowerPoint documents.

References

Citations are numbered in the order of appearance in the text. Reference numbers are placed in square brackets [1] in the text. References cited in a table or figure legend should be numbered after the citations in the text.

Papers that are accepted for publication can be cited as forthcoming. Papers not yet accepted for publication cannot be cited. The source of such information can be indicated in parentheses in the text, either as data not shown, if the information comes from one of the authors, or as personal communication, if the information comes from someone else. Personal communications must include the name of the person and the date the communication took place.

References should be formatted according to the uniform requirements for manuscripts submitted to biomedical journals'(Vancouver style). Do not use italics, bold or underlining.
#. Author of article AA, Author of article BB, Author of article CC. Title of article. Abbreviated Title of Journal. Year;vol(issue):page number(s).

For example:
1. Geck MJ, Yoo S, Wang JC. Assessment of cervical ligamentous injury in trauma patients using MRI. J Spinal Disord. 2001;14(5):371-7.

If there are more than six authors, list the first six authors followed by et al. For example:
1. Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

More samples of reference formats can be seen at:
http://www.nlm.nih.gov/bsd/uniform_requirements.html

Authors and acknowledgements

All listed authors should have made substantive intellectual contributions to the article, be aware of its submission to *Eurosurveillance* and able to account for its content. The contribution of each author to the article must be stated: this information will be shown at the end of the published article.

We do not limit the number of authors, but for the rapid communications it may be more appropriate to list the names of people who have not contributed directly to the production of the article in the acknowledgements. You may acknowledge anyone who has helped you with any aspect of the report, but it is always the corresponding author's responsibility to obtain permission from anyone being acknowledged.

Please include complete information about each author (full name, affiliation and the name of the institution, city and country in which the work was done). Clearly identify and provide telephone number and email address for the corresponding author.

In our submission system, authors can also include an ORCID (Open Researcher and Contributor ID), if they have one. We encourage authors to use this system.

It is possible to provide a collective name as an author (working group, disease-specific network, etc.). The members of such a group can be listed at the end of the article and will appear in PubMed/MEDLINE indexation. In the online submission system, the corresponding author will be asked whether there is a collective author and for any names of members of the group or network to be listed.

A statement on funding for the work described in the manuscript should be included.

GISAID sequences

Although the database of the Global Initiative on Sharing All Influenza Data (GISAID) is publicly accessible, it is not open access, and attention should be paid to correct attribution of the data used. You should acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu™ Database on which the research is based, and to refer to the GISAID website (www.gisaid.org). In addition to an appropriate acknowledgement, we recommend including a table in the Methods section, listing all sequences with the respective background information, unless there is an unmanageable number of them. Examples of how to do this can be found here: Article 1, Article 2

Secondary publication ↑To top

Eurosurveillance allows authors to submit material that has previously been published in a language other than English, if dissemination in English would be beneficial from a scientific or public health perspective to a wider readership that cannot read the primary publication or has limited access to it. Such publication will mainly be considered for short articles on topics that have been previously covered in the bulletins of the national surveillance institutes. *Eurosurveillance* aims to add value to these publications, usually by widening the discussion to include other European countries, and including additional references. Longer articles are usually not accepted for secondary publication.

It should be clear from the submission that it is secondary publication, and permission from the editors of the primary publication must be sought and documented in advance. If published, the primary publication should be clearly acknowledged with a reference and, where possible, web link to the original material.

Prospective authors should follow the guidelines in the section III.D.3. of the International Committee of Medical Journal Editors' uniform requirements for manuscripts submitted to biomedical journals (http://www.icmje.org/publishing_4overlap.html)

Secondary publications are subject to the normal *Eurosurveillance* review process.

Evaluation and peer review ↑To top

Upon submission, the articles are screened by the editorial team and scheduled for discussion in the next editorial meeting. Papers received without the necessary accompanying material such as signed agreement with authors, conflict of interest declaration, manuscript text, abstract and figures in the correct length and format, etc. are not considered as submissions and will not be evaluated.

Manuscripts that pass the first evaluation will be sent for peer review to at least two (for rapid communications and e-alerts at least one) independent experts in the field. While we try to avoid delays, this part of the process relies on the availability and cooperation of the referees and can take considerable time. The reviewer is always a person working outside the team or the department of the authors, and is usually from a different institute and/or country. We follow a policy of double-blind peer review where both the authors' and the reviewers' identities are kept confidential.

In the online submission system, authors can track the status of their submission. If they wish to contact the editorial office about their manuscript at any point, this should be done by sending an ad hoc email through the submission system (via 'Action links').

Upon receipt of the reviews, the article is evaluated in detail by the editorial team taking into account the reviewers' comments and recommendations and is scheduled for the next available editorial meeting where a decision will be made whether to proceed with the manuscript or to reject it. If the reviewers' opinions are conflicting, the article may be sent for a further review.

If the decision is made to proceed with the manuscript, the reviewers' comments and suggestions are sent to the authors as guidelines for the preparation of a revised draft. On rare occasions, we may amend the reviewer's comments before they are sent to the authors, to take into account particular sensitivities or remove passages that are clearly intended as recommendations not for the authors but for the editor. When at least two reviews are obtained (for all regular articles and for some rapid communications), the anonymised comments for the authors will be shared with the other reviewer(s) of the manuscript. The editorial decision will also be passed on to the reviewers.

The invitation to submit a revised manuscript does not imply that the manuscript will eventually be accepted for publication. Together with the revised manuscript, the authors are required to return a detailed, point-by-point response to the reviewers' comments. The editorial team may decide to consult the original referees once more to judge whether their concerns have been addressed satisfactorily.

The revised manuscript is scheduled for final evaluation and editing. Our papers are rigorously edited for content and style, and the authors may need to provide further information, corrections and clarifications at this stage. Because the editing process itself can bring up points that have gone unnoticed before, we do not formally accept a manuscript before editing is complete.

Once the editor and corresponding author have agreed on the final version of the manuscript, a final copy is sent to the author for approval and the paper is published in one of the next available issues, usually within two weeks from finalisation of the text. This may be longer if the article is published as part of a special thematic issue or in the context of a particular event.

Rapid communications and e-alerts follow the same steps but are processed with priority to ensure timely dissemination of important public health information.

Some articles are processed by an editorial board member who is not working at ECDC. To avoid potential conflicts of interest, regular articles authored by our colleagues at ECDC are processed, whenever possible, by an editorial board member who is not working at ECDC, whenever possible. This includes initial evaluation, selection of peer reviewers, evaluation of the reviewers' comments and evaluation of the revisions. After that, the editorial team in Stockholm are responsible for the editing.

Corrections/errata To top

The editorial team should be informed immediately of any errata or corrections to be made. Such changes are made immediately in the original article as well as the pdf, together with an editorial note explaining the nature and date of the change.

Corrections and errata are usually published in the first issue of every month.

Contacting the editorial team To top

If you have any questions about *Eurosurveillance*, please contact our editorial team at eurosurveillance@ecdc.europa.eu

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
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
		(*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
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*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
		(*e*) Describe any sensitivity analyses
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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

*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.

Revista Portuguesa de Pneumonologia

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All manuscripts are evaluated by members of the editorial board of the journal and acceptance for publication of articles or original research, clinical reports or series of case studies which are accepted, are subject to a technical assessment by the editorial board. In this evaluation process articles may be:

a) Accepted without alteration

b) Accepted after suggested modifi cations have been agreed by the authors

c) Refused

Only manuscripts containing original material which has not yet been published, wholly or partially (including tables and fi gures), and which have not been submitted to be published elsewhere, will be considered for publication. Before submitting manuscripts, authors must obtain all necessary authorizations for the publication of the submitted material.

Presentation of manuscripts − Texts should be written in English. Manuscripts submitted to the journal should include the manuscript organized according to the guidelines presented under the Instructions to Authors. Manuscripts should be prepared in Microsoft Word processor or compatible software containing a Title Page, Abstract, Introduction, Methods, Results, Discussion, Reference List, Figure Legends, Tables numbered in Arabic numbers along with the corresponding title. Online submission is available at http://ees.elsevier. com/rpp

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Structure − The usual convention for structure should be employed, in which a new page is used for each separate section of the work, in the following order:

a) The fi rst page: Title of work and name/s or author/s with respective academic and/or professional titles, department where the study was carried out, respective contact addresses and e-mails. Where the number of authors exceeds six, this must be justifi ed.

b) The next page/s:

— An abstract in English which must not exceed 250 words for original works and 150 for case reports.

— Key words (3 to 10), which provide the index for the article, according to the terminology of the Medical Index "*Medical Subject Headings".*

c) The text, in the case or original articles, will generally be: Introduction, Material and Methods, Results, Discussion and Conclusions.

d) Acknowledgements

e) References

f) Tables and Figures

Authorship − According to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", authorship implies a substantial contribution to the manuscript. It is

therefore necessary in the covering letter to specify the contribution made by each author to the work.
Example: *António Costa conceived this study and supervised all aspects of its implementation. José Costa collaborated in the inception of the study and carried out the analysis of the data. Manuel Costa collected the data and collaborated in the analysis. All the authors contributed to the interpretation of the results and the proof reading of the manuscript.*
Presentation of work − The whole manuscript, including references, tables and fi gures, should be formatted in double-spacing, 12 point letter size, and justifi ed on the left. All pages must be numbered, including the title page. Margins in the whole manuscript must be 2.5 cm margins. Page breaks must be inserted between each section. In manuscripts signed by more than 6 authors (3 authors in the case of letters to the editor), there has to be an explicit explanation for such an extensive authorship.

TYPES OF ARTICLES

Articles on original research: The text must not exceed 2000 words, excluding references and tables, and be organized into introduction, methods, results and discussion, with a maximum of 4 tables and/or fi gures. In the materials and methods there must be a complete and appropriate reference to the statistical methods used and the results should be quite suffi ciently explicit.
Review articles: The *Portuguese Journal of Pulmonology* publishes primarily review articles which have been requested by the editors. However, unsolicited articles submitted will be considered, particularly systematic reviews (meta-analysis). The text must not exceed 5000 words, excluding references and tables, with a maximum of 5 tables and/or fi gures in total. The reviews must be organized systematically in introduction, methods, results and discussion.
Short publications: Preliminary results or new fi ndings could lead to short publications. The text should not exceed 1000 words, excluding references and tables, and be organized into introduction, methods, results and discussion, with a maximum of 2 tables and/or fi gures in total and up to 10 references. The short publications should be submitted with formal abstracts in Portuguese and English, of not more than 250 words each.
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Special articles: Where appropriate the editorial board may invite one or various authors to write an article on a subject of particular formative interest in achieving the priorities of the journal and where the subject matter is not being addressed by other areas of study (for example postgraduate study).
Clinical case studies (case reports): The text should not exceed 1200 words, excluding references and tables, with a maximum of 2 tables and/or fi gures in total. Clinical case studies should be submitted with formal abstracts in Portuguese and English, of not more than 120 words each. Depending on their interest and originality the clinical case studies may include a commentary/discussion by one of the editors or by an invited reviewer. **(Clinical case study with discussion)**
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Correspondence refers to a succinct commentaries on

articles published in the *Portuguese Journal of Pulmonology,* preferably within the previous 6 months. In this case, the text should not exceed 500 words, excluding references and tables, and can include a maximum of one table or fi gure and up to 5 references.
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Bibliography − Bibliographical references must be numbered in consecutive order from the fi rst citation in the text. The text must be identifi ed by Arabic numerals. The references must contain, in the case of reviews, the name of the fi rst author (surname and given name), followed by the other authors, the title of the article, the name of the publication and the identifi cation (year, volume and page).
A detailed description of the format of different types of references may be found in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", of which the following is an example.
Tables and fi gures – Tables and fi gures must be presented on separate pages, of high quality, suitable for reproduction, in the order they are discussed in the text. They should be accompanied by their respective titles in a way that they can be understood and interpreted without recourse to the written text. All graphs must be presented in the form of photographs of the respective original. Original photographs should not be sent nor should illustrations or other materials like X-ray fi lms.
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The costs of publication of pictures in colour will be covered by the authors. When manuscripts are accepted pictures will be requested in the most appropriate format for publication in the journal.
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Ethical considerations and informed consent − The authors must ensure that all research involving human beings has been approved by the ethical commissions within the institutions where the research was carried out, conforming to the Helsinki Declaration of the Association of World Medicine (www.wma.net). In the methods section of the manuscript this approval must be included as well whether, where applicable, informed consent has been obtained. In the submission of clinical reports it is obligatory to include the consent of the patients.
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SUBMISSION OF MANUSCRIPTS

Manuscripts submitted to the *Portuguese Journal of Pulmonology* must conform to the recommendations indicated above and must be accompanied by a covering letter. The Editorial Board will acknowledge receipt of manuscripts, supplying information as to the orientation category given to the relevant article. Whenever there are editorial recommendations to changes to the manuscripts sent, the authors should supply a new version with an explanation of changes made. Correspondence between the authors and the journal should be conducted electronically, by the Elsevier Editorial System (http://ees. elsevier.com/rpp).