Author's response to reviews

Title: Descriptive epidemiology of selected birth defects, areas of Lombardy, Italy, 1999

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Author's response to reviews: see over
Re Ms.: 8780217601157934 Title: **Descriptive epidemiology of selected birth defects, areas of Lombardy, Italy, 1999**

Dear Sirs,

Thank you for your letter regarding our manuscript (above). We have extensively revised the paper in response to the reviewers' concerns and criticisms and are uploading the revised version.

We are also uploading detailed point-by-point replies to the reviewers' comments and criticisms.

Reviewer 1 (Dr. de Klerk) presented a useful critique, with specific suggestions. In response to these, we have added a table comparing the working methods of the three Birth Defect registries used for comparison with our dataset, in order to clarify why we chose their data as reference. We also explain why we chose those particular registries for comparison. We have also calculated 95% CIs for number of cases for each birth defects, and have added a paragraph about noting ethical approval. Minor spelling errors have also been corrected. We believe we have exhaustively addressed all Dr. de Klerk’s points in our new version.

At the beginning of his critique Reviewer 2 (Dr Shibuya) states, “...The descriptive analysis in this paper adds very little to our knowledge on the birth prevalence and their etiologies...” We accept that our paper was mainly a descriptive analysis. We do not accept that it adds little to our knowledge of birth prevalence: we believe it important to publish prevalence data to make them available to other researchers. It was not the aim of our paper to address the huge problem of aetiology, although we hope the data provided by our registry will contribute to aetiological studies in the future.

We have also sought to respond with major changes to the paper to the other points raised by Dr Shibuya. In particular we have added a section to Materials and Methods describing the methods used to generate birth defect cases. This provides important information about quality assurance. To further assess the quality of our registry data we performed a completeness analysis using the capture-recapture method with birth certificates.

The files are now correctly formatted as required by the instructions for authors. We hope the paper may now be acceptable for publication in Population Health Metrics.

Yours sincerely,

Giovanna Tagliaabue and Paolo Contiero
Replies to Dr de Klerk

“The authors need to describe differences in methods of collection in the different Centres.”
We now give reasons why we chose to compare our birth defect rates with those produced by Georgia, Hawaii and Finland and include a table (Table 5) that lists their main characteristics in comparison to our registry.

“In order to make some conclusions about any observed differences, some idea of how much of the difference my be due to random variability would help. One easy way would be to produce 95% confidence limits….. .”
We now present birth prevalence rates with calculated 95% confidence intervals (95% CI) for each defect. We assumed the observed number of cases followed a Poisson distribution, and a Poisson model was used to estimate the 95% CI. We have added a sentence to the Statistical methods section stating this, and have also added the 95% CIs to Tables 1 and 2.

“Given that no zero prevalences are reported by three Centres, the authors should clarify whether ‘Not reported’ actually means zero.”
“Not reported” does not mean zero. Simply, the registries chose not to present rates of certain birth defects in the annual report of the International Clearinghouse for Birth Defects (ICBD).

"There are a few minor spelling errors...”
We apologised for the errors. We have corrected “coartation” to COARCTATION; we have corrected “Prader Willy” to “Prader Willi.”

"I think that some mention of Ethics Committee approval is needed.”
We apologize for not mentioning this in the paper. After the approval of our Ethical Committee, the registry project was submitted to the Privacy Guarantee Authority (Italian Authority protecting confidentiality). See “Ethical approval” in Methods.

Replies to Dr Shibuya

“…The descriptive analysis in this paper adds very little to our knowledge on the birth prevalence and their etiologies….”

We believe our data provide a useful contribution to knowledge of the birth prevalence of birth defects. It was not our aim to present a contribution to the aetiologies of birth defects, although we believe the data produced by our registry has the potential to makes a contribution research on the aetiologies of birth defects.
We believe birth defects rates are important for research, prevention and management should be published so as to become available to other workers. Rates from other populations are of limited use because birth defect rates vary with geography. The aim of our study is to present, for the first time, the prevalence of birth defects in a geographic area in the north of Italy characterised by a well organised health system and where a malformation prevention program is in force (folic acid administration to prevent neural tube defects) but in a context where until now it has not been possible to generate data on population-based birth defect prevalence rates.
A justification for the material we provide in this paper was recently given by Meyer and Sever [Birth Defects Research, (Part A) 76:770-771(2006)] who stated that “surveillance provides information necessary for virtually all aspects of public health practice, ranging from applied research to implementation and evaluation of interventions [.....] support for basic surveillance is always a wise investment for the future.”
We have, however, sought to respond to the specific criticisms of this referee by performing a quality analysis and reintroducing a section, previously eliminated to shorten the paper, that
describes how the registry gathers and standardises its primary data, generates birth defect records and performs quality checks. We hope this new material provides the analysis requested by the reviewer.

“However, the issues related to the system, which the authors have set up to monitor the birth defects, deserve more careful investigation. Such an analysis would provide more useful implications for other regions and countries.”

As stated in our reply above, we now describe the structure of the system set up to monitor the birth defects. We also assess the quality of data produced by performing a completeness evaluation using birth certificates for comparison. We also compare our rates with those published by long established birth defect registries to provide further indications of data plausibility.

“There are several issues which the authors could explore, including the lack of standardized coding, the lack of records associated with abortions, and information on potential etiological and risk factors of birth defects.”

We note in the conclusions that the lack of data on abortions is a limitation of our study. We expect to be able to include abortion data in our registry in the future. We agree that lack of standardization is a problem with all registries. We extensively addressed this problem in our recent publications on the completeness and accuracy of cancer registration data (Tagliabue G.et al, Popul Health Metr 2006; 4:10; P Contiero et al. J biomedical Inform 2007). We are unable to provide further information without performing further extensive analyses of our data – something we hope to address in the near future. Finally, one of the aims of our birth defects registry is to provide data pertinent to the aetiology of/risk factors for birth defects. However this aspect is beyond the scope of the present paper.

“More details on manual verification [are] needed…”
We apologize for not describing the methodology of case generation, this description was eliminated at an earlier stage to shorten the paper. We have reinserted it.

“- how to reconcile differences from multiple sources…”
see new Case ascertainment, subsections Extraction and standardization of data and Data linkage. in Methods

“- how to make sure the consistency across dataset…”
see new subsection in Methods: Case generation and verification.

“- how to make sure [of] the degree of completeness and quality assurance…”
see nee section Completeness in the Results; we have also added table 5 presenting results obtained using the capture-recapture method on birth certificates and the birth defects registry sources.

"Only point estimates were shown but is preferable that they are accompanied by uncertainty ranges.”
We now give 95% confidence intervals (95% CI) for each defect, as suggested. We assumed the observed number of cases followed a Poisson distribution, and uses a Poisson model to estimate the 95% CIs. We state this in the Statistical methods section, and have added 95% CIs the tables 1 and 2.

“The authors claimed that the reduction in the reported number of the teratology of Fallot [could] be due to changes in underlying risk factors….. ”
Our comments were based on the analysis of Forrester (Paed Perinat Epidemiol, 2004; 18: 415-424), who found a decreasing time trend in the rate of tetralogy of Fallot and proposed it as possibly due to a time change in some underlying risk factors, because the practice in case ascertainment and coding in his registry were stable in time. However we have now removed our suggestion that changes in underlying risk factors might be responsible, and have cited figures from other birth defect registries which reveal considerable variation in the birth prevalence of this condition.