PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Geographical concentration of falciparum malaria treated in the United Kingdom and delay-to-treatment with artesunate in severe cases: an observational study.
AUTHORS	Broderick, Claire; Friend, Philip; Smith, Valerie; Blaze, Marie; Gothard, Philip; Whitty, Christopher

VERSION 1 - REVIEW

REVIEWER	Zeno Bisoffi, MD DTM&H (London). Head, Centre for Tropical Diseases, S. Cuore Hospital, Negrar (Verona), Italy
REVIEW RETURNED	17-Aug-2012

GENERAL COMMENTS	This was a most welcome paper with clear practical implications and lessons which go beyond the UK, as they are really useful for other countries including mine. I also think that the implications of the observed frequency of malaria cases in different regions and hospitals are more important that the "simple" delay in obtaining artesunate. If I should judge from my empirical knowledge of the situation in my country, an even more important problem is the potential delay in diagnosis (and I am referring here to simple, uncomplicated malaria) when patients are seen outside referral centres, which is, in turn, a major factor affecting the risk of developing potentially fatal complications. Therefore, the widespread availability of i.v. artesunate in the future may be part of the solution, but only if adequate training and standard of care are ensured and quality of malaria diagnosis, as well as precise time limits, are included among the criteria for accreditation of clinical centres. This, at least in my country, is hardly feasible, and I wonder if a better solution would not be to identify regional or local referral centres responding to those critera. A final comment concerns the surprisingly low number of cases seen in the North East and in Northern Ireland. On page 12 (lines 41-47) the authors seem to assume that the MRL capture rate is similar in these region if compared to the rest of the country. Once again, this is in contrast to the empirical experience in my country, where in some regions the reporting rate is certainly much lower than the average.

REVIEWER	Delane Shingadia, Great Ormond Street Hospital, UK I have no competing interests
REVIEW RETURNED	28-Aug-2012

RESULTS & CONCLUSIONS	This study is described as an observational study using national and hospital data, however there appear to be two seperate studies being combined into one. The main focus of this paper is the use of

	artesunate for severe malaria in adults based on a single centre's experience from 2002-10. The other component is the geographical distribution of all malaria cases from 2008-10 based on MRL data. There is no information on disease severity, treatment used (ie artesunate, quinine etc) and outcome as one would expect from MRL data so I find it difficult to see how this is linked with the use of artesunate for severe malaria
GENERAL COMMENTS	This study is described as an observational study using national and hospital data, however there appear to be two seperate studies being combined into one. The main focus of this paper is the use of artesunate for severe malaria in adults based on a single centre's experience from 2002-10. The other component is the geographical distribution of all malaria cases from 2008-10 based on MRL data. There is no information on disease severity, treatment used (ie artesunate, quinine etc) and outcome as one would expect from MRL data so I find it difficult to see how this is linked with the use of artesunate for severe malaria. While the single centre experience of artesunate use and delays in treatment is important, I do not think that the geographical MRL data is necessary in relation to this.

REVIEWER	Yvonne Geissbühler Global Epidemiologist Novartis Pharma AG Switzerland No competing interests with regard to this study.
REVIEW RETURNED	29-Aug-2012

THE STUDY	I find the result section of the abstract difficult to read. If the question is if limitations are mentioned in the abstract the answer would be no. The limitation section in the manuscript itself is ok.
RESULTS & CONCLUSIONS	It would be very helpful to have a flow diagram for the HTD pharmacy records. It is not clear in the section starting with: In 23 cases (68%)....why the median time is only reported for 9 out of 13 cases or 10 out of 14 cases. It would be interesting to know (if this data is available) if these malaria cases were people from the UK who traveled somewhere (and if yes where) or if it were people from malaria endemic countries.
REPORTING & ETHICS	I think overall it adheres to STROBE. It would be nice though not only in the abstract but also in the main body of the manuscript to have the objectives stated.
GENERAL COMMENTS	It would be helpful to spell out the abbreviations the first time they are used.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Zeno Bisoffi, MD, DTM&H (London). Head, Centre for Tropical Diseases, S. Cuore Hospital, Negrar (Verona), Italy

This was a most welcome paper with clear practical implications and lessons which go beyond the UK, as they are really useful for other countries including mine. I also think that the implications of the observed frequency of malaria cases in different regions and hospitals are more important that the "simple" delay in obtaining artesunate.
AU. We would like to thank the reviewer for these positive comments.

If I should judge from my empirical knowledge of the situation in my country, an even more important problem is the potential delay in diagnosis (and I am referring here to simple, uncomplicated malaria) when patients are seen outside referral centres, which is, in turn, a major factor affecting the risk of developing potentially fatal complications. Therefore, the widespread availability of i.v. artesunate in the future may be part of the solution, but only if adequate training and standard of care are ensured and quality of malaria diagnosis, as well as precise time limits, are included among the criteria for accreditation of clinical centres. This, at least in my country, is hardly feasible, and I wonder if a better solution would not be to identify regional or local referral centres responding to those criteria.
AU. This is an important point. We have responded to it by changes to the discussion to reflect this more fully.

A final comment concerns the surprisingly low number of cases seen in the North East and in Northern Ireland. On page 12 (lines 41-47) the authors seem to assume that the MRL capture rate is similar in these region if compared to the rest of the country. Once again, this is in contrast to the empirical experience in my country, where in some regions the reporting rate is certainly much lower than the average.
AU. We agree this needs to be flagged up, and have highlighted it more fully in the discussion.

Reviewer: Delane Shingadia, Great Ormond Street Hospital, UK

This study is described as an observational study using national and hospital data, however there appear to be two separate studies being combined into one. The main focus of this paper is the use of artesunate for severe malaria in adults based on a single centre's experience from 2002-10. The other component is the geographical distribution of all malaria cases from 2008-10 based on MRL data. There is no information on disease severity, treatment used (ie artesunate, quinine etc) and outcome as one would expect from MRL data so I find it difficult to see how this is linked with the use of artesunate for severe malaria.
AU. We give overall data on severity. Whilst we agree that it would be good to be able to break it down by centre, there is unfortunately not reliable way to do this, and especially in centres with small numbers we are concerned it could give a misleading picture.

While the single centre experience of artesunate use and delays in treatment is important, I do not think that the geographical MRL data is necessary in relation to this.
AU. We are glad the referee is supportive on the single centre data. On the geographical data- our view remains that beyond the narrow question of deployment of artesunate (where we consider it useful, but time-bound) this is probably in the longer term the most useful output from this paper for decisions on issues ranging from targeting training to public health messages. We would therefore be reluctant to see it removed from the paper, and therefore the public domain.

Reviewer: Yvonne Geissbühler , Global Epidemiologist , Novartis Pharma AG, Switzerland

I find the result section of the abstract difficult to read. If the question is if limitations are mentioned in the abstract the answer would be no. The limitation section in the manuscript itself is ok.
AU. We are glad the referee thinks the limitations section in the MS is OK- this is for any paper, and especially an observational paper a key section, and getting an independent perspective is very useful. On putting limitations into the abstract- with the word limit it is difficult to do this justice, but we have inserted a sentence saying ‘As with all observational studies there are limitations, which are discussed’. As this is an open-access journal (one of the reasons we were keen to see it published in BMJ Open) any reader who wishes to can read this section.

It would be very helpful to have a flow diagram for the HTD pharmacy records.
AU. We understand the point which makes sense, and have tried to construct one which clarifies issues for the reader, but did not succeed, Barring the referee constructing a dummy one which we can populate we think it unlikely this will help readers.

It is not clear in the section starting with: In 23 cases (68%)....why the median time is only reported for 9 out of 13 cases or 10 out of 14 cases.
AU. Fair point- we have clarified this in the discussion.

It would be interesting to know (if this data is available) if these malaria cases were people from the UK who travelled somewhere (and if yes where) or if it were people from malaria endemic countries.
AU. We agree, and have summarised these data.

I think overall it adheres to STROBE. It would be nice though not only in the abstract but also in the main body of the manuscript to have the objectives stated.
AU. We have added the objectives laid out in the abstract into the introduction.

It would be helpful to spell out the abbreviations the first time they are used.
AU. Clearly right. We have reread and hope we have picked up all the ones which were not previously spelled out.