Reviewer's report

Title: Economic loses due to irrational use of antimalarial drugs in rural areas of eastern Pakistan: A random field study

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Reviewer: Amy Frances Wahid Mikhail

Reviewer's report:

This article addresses a subject of growing concern – the overuse of antimalarial drugs in the absence of a parasitological diagnosis of malaria. The paper would be a useful addition to the growing body of evidence concerning this problem.

Although the paper is dealing primarily with negative data (the complete absence of slide positivity or malaria vectors), the data itself and sampling methods are inadequately described. The paper could be significantly strengthened by adding the details outlined below. In addition, further minor corrections to English language usage throughout are suggested to improve the clarity of the manuscript.

Discretionary revisions:

1. Suggest removing “Economic losses due to” in the title as there isn’t adequate linkage between the data types in this study to detail or properly calculate the economic losses incurred as a result of malaria over-diagnosis. The remainder of the title is appropriate.

2. Abstract – paragraph 1: According to the manuscript, the study began in September 2008 and ended in July 2009 – just a brief query but why was the month of August excluded (part of the peak season in this area?)

3. Background – paragraph 2: Suggest that the sentence “anaemia is caused by haemolysis of red blood cells” be removed as it is superfluous to the content of the manuscript and the readership of this journal should know what it is.

4. Discussion – paragraph 1: The section of this paragraph describing the malaria transmission cycle seems superfluous to the subject matter at hand and could be removed.

Minor compulsory revisions:

5. Abstract – paragraph 3 / later in text: The results section states that there was a BER of 3.18 – suggest that this acronym be substituted for the full term as it appears later in the text (“Blood Examination Rate”). In addition, a definition of this term and brief explanation of how it was calculated, or citation of a reference describing the same, should be added to the methods section (main body of article).

6. Introduction – suggest that use of technical terms is clarified – e.g.
Background, paragraph 1 “the rate is much less than in other areas of Pakistan” be replaced with the term “incidence is much lower…” or “prevalence is much lower…” whichever phrase better encapsulates what the authors meant to communicate.

7. Background – paragraph 3: The sentence describing the predominant malaria species in Pakistan is ambiguous and the use of the term prevalence here is incorrect. Suggest rephrasing to: “P. vivax is the most common species, constituting approximately 75% of parasitologically diagnosed cases, while the remaining 25% are due to P. falciparum”. It would also be useful to add either prevalence or incidence figures for Pakistan as a whole to this sentence.

8. Background – paragraph 4: Suggest that the described side effects are divided into groups according to the specific anti-malarial drugs that cause them.

9. Methods – paragraph 1: A brief definition of the term “quacks” as it is applied locally should be given since its usage is not necessarily implicit and understanding of this term by readership from other regions may deviate from the authors intended meaning of this term. The definition should include reference to the facilities available to a quack (i.e. are they only drug sellers or do some also provide microscopy or other malaria diagnostics such as Rapid Diagnostic Tests?). Equally, a breakdown of all the health facility types mentioned with reference to the proportion that have malaria diagnostic facilities would be usefully presented in a table.

10. Methods – paragraph 4 / abstract: Clarify use of the term “living rooms” – do the authors mean “sleeping rooms”? Was insecticide treated net usage in the surveyed houses taken into account?


12. Results – paragraph 1: Change the sentence “parasite incidence in the study area was zero” to “malaria parasite incidence during the 11 month study period was zero”.

13. Results – paragraph 2: If available, the particular Culex species identified should be mentioned here as some culicines are known to predate on Anopheline larvae and may in part be responsible for the absence of anophelines in the area.

14. Results – paragraph 3: Check spelling of drug names (Fansidar, Amodiaquinne?) – also explain if the quoted prices are for a complete dosage and if so adult or child?

15. Discussion – paragraph 1: Use of the phrase “the prevalence rate of malaria…” is incorrect, because prevalence is not a rate. Suggest substituting with “malaria in Pakistan has low to moderate endemicity”. Also suggest adding a qualifier to this sentence, i.e. in which areas is malaria more prevalent in the country and why, if known.

16. Discussion – paragraph 2: The sentence “The microscopic examination of blood smears and vector density in an area truly reflects the prevalence of malaria” is ambiguous and inaccurate. Suggest re-phrasing or omitting.
17. Discussion – paragraph 3: Suggest adding a comment about malaria control provisions (bednet use, spraying?) in this area given that the preceding description shows the area is favourable to mosquitoes – why the lack of anophelines?

18. Discussion – paragraph 4: See previous comments above regarding use of the term “incidence” and correct accordingly. Suggest substituting “there was no incidence of malaria in this area” with “no cases of malaria were recorded in this area during the study period”.

Major compulsory revisions:

19. Methods – general: the method used for determining sample size is not described. The blood slides collected and examined amount to only 3% of the study population, which may be inadequate given that this area was already suspected by the authors to have extremely low or no prevalence of malaria. A description of how the sample size was calculated should be added to this section and the limitations of such a small samples size should be clearly stated later in the text (i.e. that this work was not intended to determine if malaria has been eliminated from the area and that this question could only be answered with a more rigorous survey).

20. Methods – paragraph 3: the methods used for examining blood films were not adequately described. In health facilities that already collect and examine blood films, were the study blood films separate and additional or the same ones? Exactly what criteria were used to declare a slide malaria parasite negative (how many fields were read)? Were the slides single or double read and if the later was each reader blinded to the results of the other? Did expert microscopists perform the reading or did health facility staff perform the reading? A sentence on the limitations of using microscopy in this context (which is known to have limited sensitivity, particularly when performed by microscopists who work in areas of very low prevalence) should be added to the discussion.

21. Methods – paragraph 4: Additional details are needed - mention the timing and frequency of collections, describe methods used to select houses / stores / animal sheds, or if a standard WHO protocol was used for randomised selection of these sites, provide a reference for it.

22. Results – general: Precise information concerning study subjects who constituted the “passive detection” group is lacking but of strong relevance to the subject at hand. If possible, the authors should indicate:

a. Within the PCD group, what proportion underwent a parasitological exam at the health facility for malaria (microscopy or RDT performed by the health facility staff as part of routine procedure, where the results were available to the prescriber)?

b. Of those that did undergo a routine parasitological exam (microscopy or RDT) how many (if any) had malaria parasite positive results according to the health facility?

c. Within the PCD group, what proportion were given prescriptions for
anti-malarial drugs by the health facility?

d. Of those treated with anti-malarials, which anti-malarials were prescribed and what proportion of each type (the drug itself, not brand type is of interest because, for example, over-prescription of artemesinin combination therapies (ACTs) is more costly than over-prescription of chloroquine).

e. Subdivide data concerning anti-malarial treatment from (d) above into three groups, i.e.

i. No laboratory diagnosis available

ii. Laboratory diagnosis available – health facility result was malaria negative

iii. Laboratory diagnosis available – health facility result was malaria positive

The provision of this additional data would greatly enhance the value of results and would give some initial indication as to the potential cause(s) of over-diagnosis in the study region.

23. Discussion – paragraph 5: The authors note that higher numbers of male Culex were caught than females, but this result is not discussed. Why do the authors think this is – sampling bias, timing of the spray catch, etc? Is there a difference in the male/female ratio between the three types of venue where the collections took place? Could any of these factors have an impact on the complete absence of anophelines in the study catches? What is known about anopheline resistance to pyrethroids in this area? The potential limitations of using only pyrethrum spray catch need to be discussed.

24. Discussion – paragraph 6: The discussion concerning drug use should be expanded – specifically it would be useful to sub-divide drug types and quantities by health facility type (table 3 could be modified), since this would elucidate any variation in anti-malarial prescription practice between providers. As already mentioned above – linking drug use data with parasitological malaria diagnoses according to the health facilities (where available) would greatly add value to this section.

25. Conclusion: The sentence “it is concluded that in the selected areas of study there was no prevalence of malaria” is too strong a conclusion to make given the potential limitations of the sample size and sampling methods employed. Suggest changing to something like: “Even taking into account the limitations of this small study, the lack of evidence for malaria cases and the lack of malaria vectors contrasts sharply with the high usage of anti-malarial drugs reported by participating health facilities”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.