Author’s response to reviews

Title: Diversity of infectious aetiologies of acute undifferentiated febrile illnesses in South and Southeast Asia: A systematic review

Authors:

Kinley Wangdi (kinley.wangdi@anu.edu.au)
Kaushalya Kasturiratn (kaushalyak@googlemail.com)
Susana Nery (snery@kirby.unsw.edu.au)
Colleen Lau (colleen.lau@anu.edu.au)
Darren Gray (darren.gray@anu.edu.au)
Archie Clements (archie.clements@curtin.edu.au)

Version: 2 Date: 26 Feb 2019

Author’s response to reviews:

To
Editor-in-Chief
BMC Infectious Diseases

To Prof Cecilia Devoto:

Manuscript ID: INFD-D-18-01156R1

Title: Diversity of infectious aetiologies of acute undifferentiated febrile illnesses in South and Southeast Asia: A systematic review

I am pleased to submit our responses addressing the comments of the reviewers. I confirm that the map on Figure 2 was created by myself.
Editor Comments:

1. This is an interesting and thorough review of cases of AUFI in South and SE Asia region. It provides a helpful summary of studies over the last 19 years. However, I do have some major concerns with the study. Although the authors limited their search to the last 19 years as they stated that diagnostics has changed over the past few decades, they did not provide any summary of diagnostic methods used in these studies, and whether serology v. MAT v. ELISA v. PCR were used. As these vary in sensitivity and specificity, such detail is relevant. Furthermore, the broadness of the inclusion criteria means that the results could, as reviewer #3 states, be presented with more attention to the different groups (note the conclusion in the abstract does not correspond to the data presented in the results, where is the heterogeneity in the age groups mentioned?). There is valuable information in this study but addressing concerns listed here and below will add to the study.

Response: We have added a detail description of all the diagnostic tests used in the studies (Figure 3 and Appendix 3).

Page 22, line numbers 642-643: Figure 3 Summary of different diagnostic methods. (MAT- microscopic agglutination test; ELISA- enzyme-linked immunosorbent assay; PCR- polymerase chain reaction.

The conclusion has been revised to reflect the results.

Page 2, line numbers 53-55: In this study the most common causes of AUFI were viral, followed by bacterial and protozoal (malaria). Dengue was the commonest virus that caused AUFI while leptospirosis and typhoid were important bacterial infectious causes.
Reviewer reports:

Ooriapadickal Cherian Abraham (Reviewer 1): The authors of this manuscript have tried to describe the aetiology of AUFI in South and Southeast Asia by doing a systematic search of the published literature, and including studies published over a 19 year period from 1998 to 2017.

1. The inclusion of the term "systematic review" in the title is misleading. The literature search was done in a systematic fashion. The data presented in the "Results" section is only descriptive in nature. So, this manuscript is only a narrative summary of the studies on AUFI from South and Southeast Asia during this period.

Response: We don’t agree that this is a narrative summary of studies. This review was undertaken using a strict selection and exclusion criteria. Whilst the synthesis was narrative in structure, the review methods were systematic.

2. The major problem with this study is the heterogeneity due to the following factors:

1. Inclusion criteria were either not clearly defined, or not the same across all the included studies.

2. Case definitions for each disease associated with AUFI were not standardised.

3. Most studies used commercially available serological tests to confirm the aetiology of AUFI. Validated laboratory methods were not used uniformly to form the basis of standardised case definitions for each infection.

Given the above reasons, I feel that it is best to report the results as aetiology of AUFI among children, adults, out-patients, in-patients and countries as separate categories.

Response: Thanks for the suggestion of summarizing the aetiology of AUFI by age groups and patient recruitment sites. Our results are categorized as suggested by the reviewers (Tables 2, 3 and 4). In addition, we have tried to compare within the subgroups to give a clear picture of different agents causing AUFI. We agree that case definitions and diagnostic techniques are not uniform. This was part of the limitation of this study and has been highlight under the limitations of the study.

Page 13, line numbers 314-321: This review has several limitations. Interpretation of data in this study should take into consideration the heterogeneity of the reviewed studies including study design, patient sampling and diagnostic testing. In addition, many of these studies were descriptive studies. Furthermore, there is no reliable way to judge the quality of heterogeneous descriptive studies included in this review. Some articles failed to report duration of fever and definition of AUFI varied widely between the studies. Aetiologies of AUFI of less than one-week duration would likely differ from those of a minimum of three weeks. Therefore, adherence to a common case definition between studies is important to make comparisons more reliable.

Suman Kanungo (Reviewer 2): Please see attachment.

1. The study result shows that Dengue was the commonest infection in patients recruited from both IP and OPD. So it is clear that dengue cases were mostly hospitalized irrespective of the severity of the diseases. But in the discussion section it is stated the study findings are in similar with the new admission criteria of Dengue cases which states that only severe cases of dengue: DHF and dengue shock syndrome (DSS) are admitted. This is not clear.

Response: Thanks for highlighting this issue. We have amended that statement as:

Page 11, line numbers 266-267: The admission criteria were not clear in our study since most of the cases were from both OPD and IPD.
2. Seasonal variability of influenza transmission was not considered during analysis should be mentioned.

Response: Reviewer’s comment has been added as a limitation of the study.

Page 13, line numbers 322-324S: Seasonal variation of diseases particularly influenza, changes in disease patterns due to economic development, urbanization, environmental changes and changes in population densities during the last 15 years could have affected observed aetiologies and disease patterns.

3. Reconstruction of sentences and some spelling mistakes need to be corrected.

Response: Reviewer’s comment has been considered and a thorough review of the spelling and sentence structure has been undertaken.

Champica Kasmari Bodinayake, MBBS MD MRCP (Reviewer 3):

The systematic review on Diversity of infectious aetiologies of acute undifferentiated febrile illness in south and south east Asia, the authors had a successful attempt to address a very topical issue.

The methodologies used in this review are standard and has included publications from the last 19 years.

1. The following errors are noted in the methods section. In line 44 of the key words used in the literature search are aetiology OR aetiology where both words have the same spelling. As combining two identical words does not widen a boolean search, I doubt whether authors meant the word "etiology" instead of two similar words as "aetiology".

Response: The correct word “etiology” has been updated.
2.   in line 49 and 54, Singapore is included twice, which needs correction.

   Response: Correction has been made in the revised manuscript.

3.   In the results section there is inadequate description on laboratory confirmatory methods used in the studies overall. What pathogens were tested? What additional confirmatory tests were performed for pathogen identification? How many studies used blood cultures to confirm bacterial pathogens? Was HIV testing included in the studies?

   Response: The following details about the laboratory confirmatory methods and pathogen tested have been added. HIV testing was done as it was one of the causes of AUFI in the included studies.

   Page 7-8, line numbers 181-188: In all studies (n=35), diagnoses were made according to interpretation of antibody titres. Pathogen-specific IgM titres were determined by using IgM-capture enzyme-linked immunosorbent assay (ELISA) kits, which are commercially available. Molecular testing (using polymerase chain reaction [PCR] was carried out in 12 studies [23-26, 28, 30, 40, 41, 43, 45, 46, 48]. Serological diagnoses were confirmed by blood cultures in 15 studies out of 35 [2, 19-21, 23, 25, 32, 34, 35, 37, 42-45, 48]. Microscopy was used for the diagnosis of malaria parasites in 14 studies [19-21, 23, 25, 31, 33, 34, 36, 37, 42-44, 48]. Nucleotide sequencing was done in one study [28] (Figure 3 and Appendix 3).

4.   As diagnostics play a major role in the aetiology identification, inclusion of a summary of laboratory diagnostics performed in the studies need inclusion.

   Response: We have included a summary of different laboratory diagnosis methods that were carried in the reviewed studies. (refer to response to the editor).

   Page 22, Line 642-643: Figure 3 Summary of different diagnostic methods. (MAT- microscopic agglutination test; ELISA- enzyme-linked immunosorbent assay; PCR- polymerase chain reaction.)
5. In the discussion part there is inadequate emphasis to the fact that nearly two thirds of the acute undifferentiated fevers remain still unconfirmed. The underlying reasons for the above such as timing the blood sampling, lack of convalescent sample, lack of validated cost effective point of care testing etc are not discussed.

Response: the reasons for unconfirmed cases of undifferentiated fever have been described in Page 12-13, line number 301-308 (highlighted in the manuscript):

A lack of an established diagnosis could be partly due to the fact that laboratory confirmations were not done in many studies of acute self-limiting viral infections. In addition, commercial serological rapid diagnostic tests used are semi-quantitative ELISAs that detect antibodies and are not conclusive of the present or past infection [81, 82]. On the other hand, definitive diagnosis requires demonstration of a serial rise in antibody titres against a causative agent over a specific time period. Noncompliance of patients to report for repeat serological tests following improvement of the illness remains a major drawback in serology-based diagnostics [10, 83].

6. The discussion does not include any statement how the results in Asia and South Asia differ from the global point of view.

Response: The cause of fever in Asia and South Asia in relation to the global view has been added in the revised manuscript:

Page 10, line numbers 244-248: Consistent with our findings, the decline in malaria cases in Asia and Africa has resulted in a relative increase in non-malarial AUFIs in these continents [49]. Non-malarial fever was responsible for 20-50% of all fevers in Asia and Africa in children over 5 years of age and adults [50]. While dengue was mostly frequently reported febrile illness in Latin America [51].
7. The conclusions drawn from the systematic review needs major revision. There is inadequate synthesis of main messages drawn from the results and discussion to draw plausible conclusions. This section needs to be revised and strengthened.

Response: The conclusion has been revised to reflect the main finding of this study.

Page 14, Line numbers 342-349: In this study the most common causes of AUFI were viruses, followed by bacteria and malaria. Dengue fever was the commonest virus that caused AUFI while leptospirosis and typhoid were important bacterial causes. The challenges of unidentified causes of AUFI can be easily overcome by roll-out of affordable serological tests. It is imperative that data on pathogen presence collected incidentally in various studies and data collected by surveillance mechanisms of various diseases be analysed systematically and mapped to provide information on the distribution and prevalence of infectious aetiologies of AFIs for improving treatment.