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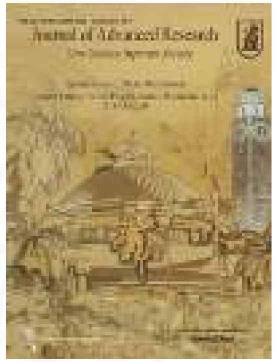

Journal of Advanced Research

Certificate of Reviewing

Awarded since July 2019 (1 review)
presented to

HAMZAH HASYIM

in recognition of the review contributed to the journal

The Editors of Journal of Advanced Research

Elsevier Reviewer RECOGNITION

hamzah fkmunsri <hamzah@fkm.unsri.ac.id>

Re: Review activity [220712-024613]

Reviewer Support (ELS) <ReviewerSupport@elsevier.com> 13 July 2022 at 23:21
Reply-To: "Reviewer Support (ELS)" <ReviewerSupport@elsevier.com>
To: hamzah@fkm.unsri.ac.id

How was our service today?

Dear Dr Hasyim,

Thank you for your prompt response.

I understand that you require some information regarding the manuscript that you reviewed last 2019.

From checking, I can confirm that you reviewed the paper JARE-D-19-00908 on July 15, 2019 with the manuscript title *"Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data".*

Please be advised that I have attached the PDF that you requested for reference. Moreover, the correspondence during the paper's review including the invitation from the Editor has also been provided below:

Reviewer Invitation (July 12, 2019)

Date: Jul 12 2019 07:20PM
To: "Hamzah Hasyim" hamzah.hasyim@stud.uni-frankfurt.de
From: "Journal of Advanced Research" eesserver@eesmail.elsevier.com
Subject: Reviewer Invitation for JARE-D-19-00908

Reply To: "Journal of Advanced Research" jarcuhala@gmail.com
Ms. Ref. No.: JARE-D-19-00908
Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling analysis of the national survey data
Journal of Advanced Research

Dear Hamzah Hasyim,

Given your expertise in this area, I would appreciate your comments on the above paper. I have included the abstract of the manuscript below to provide you with an overview.

To view the PDF of the submission, please click here:
https://ees.elsevier.com/jare/l.asp?i=207364&l=TWD7JLFM

If you accept this invitation, your comments will be due in 21 days. If you are unable to act as a reviewer at this time, I would greatly appreciate your suggestions for alternate reviewers.

To accept this invitation, please click here:

https://ees.elsevier.com/jare/l.asp?i=207366&l=ERZP5PQ2

To decline this invitation, please click here:

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Alternatively, to register your response using the Elsevier Editorial System please do the following:

1. Go to this URL: https://ees.elsevier.com/jare/

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Your username is: hamzah.hasyim@stud.uni-frankfurt.de

If you need to retrieve password details, please go to: http://ees.elsevier.com/JARE/automail_query.asp

3. Click [Reviewer Login]
This takes you to the Reviewer Main Menu.

4. Click [New Reviewer Invitations]

5. Click either [Agree to Review] or [Decline to Review]

I look forward to hearing from you in the near future.

Reviewer Instructions and Due Date (July 15, 2019)

Date:	Jul 15 2019 02:31PM
To:	"Hamzah Hasyim" hamzah.hasyim@stud.uni-frankfurt.de
From:	"Journal of Advanced Research" eesserver@eesmail.elsevier.com
Subject:	Thank you for agreeing to review

Reply To: "Journal of Advanced Research" jarcuhala@gmail.com
*** Automated email sent by the system ***

Ms. Ref. No.: JARE-D-19-00908
Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling analysis of the national survey data
Journal of Advanced Research

Dear Hamzah Hasyim,

Thank you for agreeing to review manuscript number JARE-D-19-00908 for Journal of Advanced Research.

If possible, I would appreciate receiving your review by Aug 5 2019 11:59PM.

To submit your review, please do the following:

1. Go to this URL: https://ees.elsevier.com/jare/

2. Enter these login details:
Your username is: hamzah.hasyim@stud.uni-frankfurt.de

If you need to retrieve password details, please go to: http://ees.elsevier.com/JARE/automail_query.asp

3. Click [Reviewer Login]
This takes you to the Reviewer Main Menu.

4. Click [Pending Assignments]

5. Click [Submit Recommendation] (in the Actions column)

6. Choose the appropriate recommendation term for the paper e.g. Accept, Revise, Reject

7. Rate the paper by clicking on the appropriate check boxes in the Manuscript Review form underneath

8. Insert your confidential comments to the author (your name will not be released to the author)

9. Enter your comments to the editor (these are not available to the author)

10. Click [Proceed]

11. Click [Edit Review] if you wish to make further changes or [Submit Review to Journal Office] to confirm

12. Click [OK] to confirm your overall recommendation.

Review Confirmation (July 15, 2019)

Date:	Jul 15 2019 03:12PM
To:	"Hamzah Hasyim" hamzah.hasyim@stud.uni-frankfurt.de
From:	Hussein Khaled eesserver@eesmail.elsevier.com
Subject:	Thank you for the review of JARE-D-19-00908

Reply To: Hussein Khaled xed.chief@els.ie
*** Automated email sent by the system ***

Ms. Ref. No.: JARE-D-19-00908
Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling analysis of the national survey data
Journal of Advanced Research

Dear Hamzah Hasyim,

This is to confirm that we have received your review for the manuscript referenced above.

We appreciate the time that you have contributed to this important component of the peer review process.
Your cooperation is greatly appreciated, and we hope that you will continue to support Journal of Advanced Research for publishing significant advancement in interdisciplinary sciences and hope also to receive your own research papers that are appropriate to our aims and scope.

You can collect your certificate, perks and rewards, including discount in Elsevier's services by visiting this link. (https://www.reviewerrecognition.elsevier.com/#/)

Reviewer Notification Letter for Decision (September 4, 2019)

Date: Sep 04 2019 11:31PM
To: "Hamzah Hasyim" hamzah.hasyim@stud.uni-frankfurt.de
From: "Journal of Advanced Research" eesserver@eesmail.elsevier.com
Subject: Reviewer Notification of Editor Decision

Reply To: "Journal of Advanced Research" jarcuhala@gmail.com
*** Sent by JAR Editorial Office on behalf of Hussein M. Khaled ***

Ref: JARE-D-19-00908R1
Title: Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data
Article Type: Original Manuscript

Dear Hamzah Hasyim,

Thank you once again for reviewing the above-referenced paper. With your help the following final decision has now been reached:

Accept

We appreciate your time and effort in reviewing this paper and greatly value your assistance as a reviewer for Journal of Advanced Research.

If you have not yet activated or completed your 30 days of access to Scopus and ScienceDirect, you can still access them via this link:

http://scopees.elsevier.com/ees_login.asp?journalacronym=JARE&username=hamzah.hasyim@stud.uni-frankfurt.de

You can use your EES password to access Scopus and ScienceDirect via the URL above. You can save your 30 days access period, but access will expire 6 months after you accepted to review.

I hope you find this information useful. If you wish to access all correspondence history in full, you may access these using your email address (hamzah.hasyim@stud.uni-frankfurt.de).

Please let me know if I can be of any further assistance.

Kind regards,

Jason Javier
Researcher Support
ELSEVIER

ELSEVIER

View in browser

Dear Hamzah,

Many thanks indeed for your review for *Journal of Advanced Research*. We are pleased to recognize you on the My Elsevier Reviews platform for this valuable input to the journal.

Your review, and details of your other reviewing activity are now available on your profile page linked below. Bookmark this page to easily return and see your updates.

To access your profile page, click here.

From your My Elsevier Reviews profile page you can collect perks and awards.

Best regards,
The Reviewer Recognition Team

From: Jason Javier
Date: Tuesday, July 12, 2022 08:36 PM GMT
[Quoted text hidden]
[Quoted text hidden]

JARE-D-19-00908_R1_reviewer.pdf
1461K

Manuscript Number: JARE-D-19-00908R1

Title: Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data

Article Type: Original Manuscript

Keywords: drinking water; sanitation; malaria; risk; children; sub-Saharan Africa

Abstract: Current efforts for the prevention of malaria have resulted in notable reductions in global malaria burden; however, they are not enough.This work analyzed whether improved drinking water and sanitation (WS) conditions were associated with a decreased risk of malaria infection. Data were acquired through surveys published between 2006 and 2018 from the Demographic and Health Program in sub-Saharan Africa (SSA). Multiple logistic regression was used for each national survey to identify the associations between WS conditions and malaria infection diagnosed by microscopy or a malaria rapid diagnostic test (RDT) among children (0-59 months), with adjustment for age, gender, indoor residual spraying (IRS), insecticide-treated net (ITN) use, house quality, and the mother's highest educational level. Individual nationally representative survey odds ratios (ORs) were combined to obtain a summary OR using a random-effects meta-analysis. Among the 247,440 included children, 18.8% and 24.2% were positive for malaria infection based on microscopy and RDT results, respectively. Across all surveys, both unprotected water and no facility users were associated with increased malaria risks (unprotected water: aOR 1.17, 95% CI 1.07-1.27, P = 0.001; no facilities: aOR 1.35, 95% CI 1.24-1.47, P < 0.001; respectively), according to microscopy, whereas the odds of malaria infection were 48% and 49% less among piped water and flush-toilet users, respectively (piped water: aOR 0.52, 95% CI 0.45-0.59, P < 0.001; flush toilets: aOR 0.51, 95% CI 0.43-0.61, P < 0.001). The trends of individuals diagnosed by RDT were consistent with those of individuals diagnosed by microscopy. Risk associations were more pronounced among children with a "nonpoor" socioeconomic status who were unprotected water or no facility users. WS conditions are a vital risk factor for malarial infection among children (0-59 months) across SSA. Improved WS conditions should be considered a potential intervention for the prevention of malaria in the long term.

Response to Reviewers: Hussein M. Khaled
Editor-in-Chief
Journal of Advanced Research

Dear Dr. Hussein M. Khaled,

Thank you for your message of August 19, 2019 containing the decision regarding manuscript #JARE-D-19-00908. We are very pleased that the expert editor and reviewer felt that our manuscript is interesting and is well written and provides useful information to help better understand the risk of malaria in sub-Saharan Africa. We have studied each reviewer's comments carefully, and our responses to the comments are included below. We have indicated where the changes may be found in the manuscript by marking the changes in RED (change-tracked version) and noting the Additional File number, when applicable. Our response also answers all the questions that were made.

The work is truthful original research not previously published whole or in part and not under consideration for publication elsewhere. The work reported will not be submitted for publication elsewhere until a final decision has been made as to its acceptability by the Journal of Advanced Research. All authors have agreed to its content and there are no financial or other conflicts of interest.

I hope that this revised manuscript would be accepted for publication in Journal of Advanced Research.

Best regards,
Yang Liu, M.D., Ph.D.
Professor,
School of Public Health,
China Medical University,
No. 77 Puhe Road, Shenyang North New Area,
Shenyang, 110122,
P.R. China
Phone: 13386885612
Email: yangliu@cmu.edu.cn

Responses to the editor and reviewers
Editor-in-Chief Decisions to Author:
The reviewers have commented on your above paper. They indicated that it is not acceptable for publication in its present form.

However, if you feel that you can suitably address the reviewers' comments (included below), I invite you to revise and resubmit your manuscript. Please carefully address the issues raised in the comments.

If you are submitting a revised manuscript, please also: a) outline each change made (point by point) as raised in the reviewer comments AND/OR b) provide a suitable rebuttal to each reviewer comment not addressed. To submit your revision, please do the following: 1. Go to: https://ees.elsevier.com/jare/ 2. Enter your login details 3. Click [Author Login] This takes you to the Author Main Menu. 4. Click [Submissions Needing Revision].

Your revision should be submitted before Sep 9 2019 12:00AM.

Response: We would like to thank you and the reviewers for reviewing our manuscript and making very insightful comments, all of which have been followed carefully in the preparation of this revision. We have highlighted the changes to our manuscript by marking the changes in RED (change-tracked version).

Reviewers' comments:

Reviewer #1: Reviewer reports

Manuscript Number: JARE-D-19-00908
Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling analysis of the national survey data

Overall Comments:
Overall, this manuscript is well written and provides useful information to help better understand the risk of malaria in this area. However, before recommending for publication, I have a few comments that ought to be considered.

The paper revealed a connection unimproved WS (unprotected water; no facility) as a most dominant risk factor adjusted by covariate factor for age, gender, indoor residual spraying, insecticide-treated net use, house quality, and mother's highest educational level for malaria infection among children under five years old across in sub-Saharan Africa (SSA) based on the national survey data.

General Remarks:
I think the analysis is worth publishing, but serious weaknesses should be acknowledged and addressed. The author was making a connection in this finding based on aOR value. The value odds ratio is higher than one that is a positive association.

Response: Thank you very much for reviewing our manuscript carefully and your appreciation to our study. We are appreciated that you have provided many expert, detailed, and valuable revisions and guidance in order to improve the quality of our manuscript.

However, we know a one-celled parasite called a Plasmodium causes malaria. When they feed on an infected person's blood, the parasite infects female mosquitoes. The mosquitoes and their ecosystems are significant spatial drivers for malaria transmission, so, based on the previous study if any, the authors need also briefly explore malaria prevalence in the same area related to the kind of Anopheles vector. Besides, distribution and 'bionomics' is used to cover both the ecology of a mosquito species (e.g. larval habitats) and its behaviour (e.g. host biting preferences).

Response: Thank you very much for your expert and detailed guidance. As you suggested, we have explored distribution and bionomics of mosquitoes in our study area. This information was included in Discussion section (Lines 386-405).

According to the study of Hasyim et al. (Ref# Hasyim et al. Does livestock protect from malaria or facilitate malaria prevalence? A cross-sectional study in endemic rural areas of Indonesia. Malar J, 2018, 17: 302.), they indicated that zoopotentiation could also occur if the physical disturbances created by animals (e.g., puddles, hoof prints, watering sites) increase the potential for larval habitats and thus adult vector density near households. Considering the range and the form of human activities is greater and more diverse, we indicated that the potential larval habitats could be constructed due to the physical disturbances created by human fetching or storing unimproved drinking water (e.g., splashing water on the ground when fetching or storing unimproved water results in shallow puddles or footprints; additionally, storing unimproved drinking water creates stagnant water sources for nearby households), further increasing mosquito breeding and adult vector densities near households.

The top three vector species of human malaria in our study area included Anopheles gambiae, An. arabiensis, and An. funestus (Additional file 6;

the data sources were derived from country profiles based on the World Health Organization (WHO) database online because the DHS and MIS did not include entomological surveys). Among these Anopheles species, An. gambiae and An. arabiensis prefer to inhabit sunlit, shallow, temporary bodies of fresh water, such as puddles, pools, ground depressions, and hoof prints. In addition, water in these larval sites is often turbid or polluted. In contrast, An. funestus inhabits permanent or semipermanent bodies of fresh water with emergent vegetation, such as swamps, ponds, and lake edges. This evidence suggests that closed systems with improved water are relatively inappropriate environments for Anopheles.

However, due to the lack of the entomological survey in DHS and MIS, we could not explore malaria prevalence in the same area related to the kind of Anopheles vector directly. We only sorted out the major types of Anopheles in our studied areas based on “Country Profiles” from WHO online database (see Additional file 6) and found that the top three vector species of human malaria in our study area mainly included An.gambiae, An.arabiensis, and An.funestus. However, in this study, it is hardly seen that malaria prevalence is associated with types of Anopheles vector due to lack of the entomological survey which can provide more detailed information on the specific density of various kinds of Anopheles.

Additional File 6. Major types of Anopheles vector in sub-Saharan Africa.

Country and Year	Major anopheles species [1]	Parasite Rate (%) for children < 5 years*	
		Microscopy	RDT
Angola 2015-2016	An.gambiae, An.funestus, An.nili	-	16.5
Angola 2011	An.gambiae, An.funestus, An.nili	9.8	12.5
Angola 2006-2007	-	-	22.2
Benin 2011-2012	An.gambiae, An.funestus, An.nili	29.9	27.1
Burkina Faso 2014	An.gambiae, An.funestus, An.arabiensis	47.6	64.5
Burkina Faso 2010	-	65	75.6
Burundi 2016-2017	An.gambiae, An.funestus, An.arabiensis	24.4	34.8
Burundi 2012	An.gambiae, An.funestus	16.2	20.5
Cameroon 2011	An.gambiae, An.funestus, An.arabiensis, An.moucheti	-	32.6
Coate D Ivoire 2011-2012	An.gambiae, An.funestus	16.1	42
DRC 2013-2014	An.gambiae, An.funestus, An.moucheti, An.nili	26.3	35.9
Gambia 2013	An.gambiae, An.funestus, An.arabiensis, An.melas, An.pharoensis, An.nili	0.5	1.8
Ghana 2016	An.gambiae, An.funestus, An.arabiensis	23	32.5
Ghana 2014	An.gambiae, An.funestus, An.arabiensis	28.8	40.8
Guinea 2012	An.gambiae, An.funestus,An.arabiensis	43.8	45.7
Kenya 2015	An.gambiae, An.arabiensis, An.funestus, An.merus	5.3	9.4
Liberia 2016	An.gambiae	-	50.3
Liberia 2011	An.gambiae	32.5	52.3
Liberia 2009	An.gambiae, An.funestus, An.hancocki, An.hargreavesi, An.pharoensis, An.nili	33.3	37.4
Madagascar 2016	An.gambiae, An.funestus, An.arabiensis	5.5	3.7
Madagascar 2013	An.gambiae, An.funestus, An.arabiensis	6.5	7.5
Madagascar 2011	An.gambiae, An.funestus, An.arabiensis	4.1	6.2
Malawi 2017	An.gambiae, An.funestus, An.arabiensis	16.9	26
Malawi 2014	An.gambiae, An.funestus, An.arabiensis	26	29.9
Malawi 2012	An.gambiae, An.funestus, An.arabiensis	24.6	37.8
Mali 2015	An.gambiae, An.funestus	35	31.5
Mali 2012-2013	An.gambiae, An.funestus	48.7	44.1
Mozambique 2015	An.gambiae, An.funestus, An.arabiensis	-	31.7
Mozambique 2011	An.gambiae, An.funestus, An.arabiensis	29.9	34

Nigeria 2015	An.gambiae, An.funestus, An.arabiensis, An.moucheti, An.nili, An.melas	27.3	41.3
Nigeria 2010	-	38.3	46.3
Rwanda 2017	An.gambiae, An.funestus, An.arabiensis	6.6	10.9
Rwanda 2014-2015	An.gambiae, An.funestus, An.arabiensis	2.2	7.6
Rwanda 2010	An.gambiae, An.funestus, An.arabiensis	1.2	2.4
Senegal 2017	An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas	0.6	1.6
Senegal 2016	An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas	1	1.4
Senegal 2015	An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas	0.4	1
Senegal 2014	An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas	2.8	2.9
Senegal 2012-2013	An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas	3.7	4.1
Senegal 2010-2011	An.gambiae, An.funestus, An.arabiensis, An.pharoensis	3.7	3.3
Sierra Leone 2016	An.gambiae, An.funestus, An.melas	41.9	56.3
Tanzania 2017	An.gambiae, An.funestus, An.arabiensis	-	8.4
Tanzania 2015-2016	An.gambiae, An.funestus, An.arabiensis	5.1	12.7
Tanzania 2011-2012	An.gambiae, An.funestus, An.arabiensis	4.7	10
Togo 2017	An.gambiae, An.funestus, An.arabiensis, An.melas	29.6	47.2
Togo 2013-2014	An.gambiae, An.funestus, An.arabiensis, An.melas	37.8	39.3
Uganda 2016	An.gambiae, An.funestus	-	33.2
Uganda 2014-2015	An.gambiae, An.funestus	19.9	32.6
Uganda 2009	An.gambiae, An.funestus, An.arabiensis, et al.	43.6	53.1

[1] WHO. Malaria: Country Profiles. https://www.who.int/malaria/publications/country-profiles/en/ (accessed August 22, 2019)

*The Parasite Rate was calculated by ourselves based on DHS and MIS survey.

Through the entomological survey, particularly in the unimproved drinking water sources, and unimproved sanitation facilities at this study area, to ensure and justify that the condition has the risk of malaria associations were more pronounced among in this area. It is an important confounding factor to address as distinct species may have different ecological niches, and therefore, several factors may be necessary for various places.

Response: Thank you for your expert suggestions. We definitely agree with your opinions. Unfortunately, in DHS and MIS survey, the entomological surveys were not investigated, which might be the limitations of our study (see Discussion section, Lines 506-512).

Besides, the authors should check the English grammar errors of this script like tenses, punctuation, spellings, and others and the layout of the manuscript again.

Response: Thank you for pointing this out. We have carefully double checked and revised the English writing. The paper was edited for grammar, phrasing, and punctuation. In addition, many edits were made to further improve the flow and readability of the text.

Specific Remarks:
Comments by section

Title LL 1 - 3.
The "title" and the "abstract" are the "original impressions" of a research article and must be drawn up properly, carefully, accurately, and meticulously. Therefore, you need to pick a title that captures attention, describes your manuscript's contents correctly and makes individuals want to read more. The "title" should be descriptive, accurate, direct, suitable, appealing, concise, accurate, distinctive, and not misleading.

Consider adding Logistic regression.
Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling Logistic regression analysis of the national survey data.

The title started with a catchy primary title, followed by a subtitle that provides data on the study's content and method, and this is a short, easy to understand, and conveys the essential aspects of the research.

Response: Thank you for providing the expert suggestions on how to write a catchy title. As you suggested, we have revised our title and the new title is shown as follows: Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data (Lines 1-3).

LL 27-51
Abstract
The abstract as a miniature manuscript must be smooth clear, unbiased, frank, concise, accurate, stand-alone, complete, (ideally) organised, and not misrepresented, and the abstract should answer these questions about your manuscript: What was done? Why did you do it? What did you find? Why are these findings useful and essential? Replying these queries lets readers grasp the first important points regarding your study and helps them determine whether or not they desire to examine the remainder of the paper. Make certain you observe the appropriate journal manuscript formatting tips when preparing your abstract.

Response: Thank you for providing these valuable experiences and suggestions on how to write a clear, unbiased, frank, concise, accurate, stand-alone, and complete abstract. We have revised our original abstract point by point according to your valuable suggestions below (see Abstract section, Lines 24-39).

LL 27-29
Duration of the data should be precise.
Data were acquired through surveys published starting from …. up to 18 September 2018.

Response: Thank you for pointing this out. We have revised it in Abstract (Line 30), Methods (Line 113), and Results (Line 228). The revision is shown as follows: between 2006 and 2018.

LL 34-35
The final survey-specific results were combined through meta-analysis with a random effect.

However, it is not clear the source of meta-analysis in this paper.

Meta-analysis is a method for synthesising evidence from various sources. It can be the analysis of individual data combined from two or more studies or the interpretation of summary measures obtained from two or more reports (usually from the published literature). Further, traditionally, meta-analysis strategies have been developed and used to mix data from quite a few independent scientific trials as nicely as observational studies; however, they have not been as extensively used in survey research.

You can briefly the argument using of meta-analysis based national the national survey data in background or method section

Response: Thank you for pointing this out. We definitely agree with your opinion. As you suggested, we have added why using meta-analysis based on national survey data in Method section (Lines 205-214).

The revision was shown as follows: a meta-analysis method was performed to combine data from independent scientific trials as well as observational studies. In this study, each national survey was conducted independently. Using national survey data based on a random-effects meta-analysis might eliminate many biases typically related to pooling observational data, such as publication, selection, and measurement biases and selective outcome reporting bias. In this study, to determine the overall and the stratified aORs for WS and malaria risks among all the surveys, random-effect models in the meta-analysis were used to pool logistic regression results for the surveys which were calculated among total children, “poor” children, and “nonpoor” children, respectively.

LL 29 - 30
Why the author interest directly to "WS variable" as the leading risk factor for malaria infection due to there is some covariates factor national survey at this study?

Response: Thank you for pointing this out. To briefly explain why we are interested directly to WS as the leading risk factor for malaria infection, in this study, we revised the first sentence in our original Abstract (Lines 24-27). Then, we will explain our initial thoughts on conducting the study on WS and malaria at length below.

Good hygiene is universally known as one of the most efficacious and straightforward measures to prevent disease transmission. To date, the water, sanitation, and hygiene (WASH) component of the strategy has received little attention and the potential to link efforts on WASH and malaria and many neglected tropical diseases (NTDs) has also been largely untapped. A remarkable progress has been made on the prevention of malaria and waterborne diseases in SSA. However, both diarrhea (DALYs [000s] 44,483) and malaria (DALYs [000s] 35,615) remain on the 20 top diseases with the highest DALYs globally. Diarrhea and malaria also rank as third and fourth in the region of Africa according to the WHO, respectively. If we add up the DALYs of the above two diseases, then their sum would rank them first. These two main diseases have threaten children’s lives seriously. At first, we hypothesized whether improving WS might provide double efforts to prevent malaria and diarrhea.

Additionally, many studies indicated that unimproved WS users may indirectly increase the likelihood of P.falciparum risk through increasing the risk of other waterborne parasitic diseases such as soil transmitted diseases. The latter kind of disease is more frequently found in unimproved WS users. To crucially test our idea about the association between WS and malaria, we first summarized the latest WHO statistics and obtained the proportion of population who had access to improved WS sources and malaria incidence rate for each country across SSA (see Table 1 below). We found that the malaria incidence rates varied depending on the coverage of different WS sources. To this end, we applied the detailed information obtained by the Demographic Health Survey and Malaria Indicator Survey on each country across SSA in the first instance.

Considering the target date for the malaria roadmap and for the Sustainable Development Goals of universal access to basic WASH in communities, schools, and health care facilities being both 2030, we hypothesized whether redoubling of efforts to improve WS and its recognition as the new policy on the prevention and control malaria transmission can contribute to the achievement of malaria elimination targets in 2016-2030. To verify this indirect hypothesis, the first thing is to test the association between WS and malaria infection directly. Thus, we interest directly to "WS variable" as the leading risk factor for malaria infection even though there is some covariates factor national survey at this study. In our study, the other covariates included in multivariate logistic regression model were mainly due to their clinical importance and statistical significance in other previous studies.

We hope this explanation will help you better understand why we interest directly to "WS variable" as the leading risk factor for malaria infection even if there is some covariates factor national survey at this study

Table1 The proportion of population who used improved WAS sources and malaria incidence across SSA according to the WHO (2017)

Country	Proportion of Population Using Improved Drinking-Water Sources(%),2015[1]	Proportion of Population Using Improved Sanitation(%),2015[1]	Malaria Incidence(per 1000 Population at Risk),2015[2]
Angola	49	48	124
Benin	78	7	293·7
Burkina Faso	82	7	389·2
Burundi	76	<5·0	126·3
Cameroon	76	18	264·2
Congo Democratic Republic	52	6	246
Coate d'Ivoire	82	18	348·8
Ghana	89	21	266·4
Guinea	77	6	367·8
Kenya	63	6	166
Liberia	76	<5·0	246·2
Madagascar	52	<5·0	104·2
Malawi	90	<5·0	188·8
Mali	77	<5·0	448·6
Mozambique	51	<5·0	297·7
Nigeria	69	<5·0	380·8
Rwanda	76	<5·0	301·3
Senegal	79	36	97·6
Tanzania	56	<5·0	113·9
Togo	63	6	345·1
Uganda	79	<5·0	218·3

[1] WHO. Progress on sanitation and drinking water – 2015 update and MDG assessment. New York (NY): UNICEF; and Geneva: World Health Organization; 2015.http://apps.who.int/iris/bitstream/10665/177752/1/9789241509145_eng.pdf?ua=1
(accessed September 19, 2017)
[2] WHO. World Malaria Report 2016. Geneva: World Health Organization; 2016. http://www.who.int/malaria/publications/world-malaria-report-2016/report/en/ (accessed September 19, 2017).

LL 35
The writing of the numerical with the comma. In the English-speaking world, commas are commonly used in numbers of four or more digits every three decimal places, counting right to the left. 247,440

Response: Thank you for pointing this out. We have corrected them (see Lines 39, 234-236, and 240-242).
Methods
Outcome Definition
LL 121-123 and LL 159 - 162
It is better if this paper also creates a malaria infection map of the study area for a description of the area notably and clearly.

Response: Thank you for your suggestions. We definitely agree with your opinion. At first, we would have planned to draw a malaria infection map of SSA for our study. Unfortunately, in this study, the survey time node for each national DHS and MIS survey is different. Please forgive us we could not provide a malaria infection map of the study area.

Result
LL 204-217
Each DHS survey usually takes on average 18-20 months and is executed in four phases, correlation the text with your sample children who age 0-59 months. Please explain why you choose the age groups as your selected sample in connection with malaria infection.

Response: Thank you for pointing this out. We feel very sorry to put such important information somewhere in our original manuscript due to the word limits from Journal of Advanced Research. As you suggested, presently we put data sources and study design in Method section, and explain the reason for selecting children under 5 years old in Method section (Lines 120-124).

According to WHO records on the high-risk groups for malaria infection, children under 5 years of age are at considerably higher risk of contracting malaria and they (including infants) are also the most vulnerable group in high-transmission areas of the world (Ref# https://www.who.int/malaria/areas/high_risk_groups/en/). More importantly, only this age group was tested for malaria infection by all the DHS and MIS surveys.

Discussion
LL 316-325
Some essential references, in this case, are missing. Please see works of other similar papers. You can refer also adding other same articles from a large-scale study, for example at https://malariajournal.biomedcentral.com/articles/10.1186/s12936-019-2760-8 that also discussed the association of environmental sanitation that is Improved and unimproved of primary water source, water storage

facility, and wastewater disposal and malaria. Also, a similar paper at https://malariajournal.biomedcentral.com/articles/10.1186/s12936-018-2447-6 that revealed that most participants who use open sewage systems (domestic wastewater or municipal wastewater) at home and those without a sewage system are at higher odds of contracting the disease than participants who have closed sewage systems.

Response: Thank you for your expert suggestions and providing such essential references. We have studied these references carefully and considered them as the important evidences and backups for our study. As you suggested, we have discussed these two similar articles in our Discussion section (Lines 372-384).

The revision was shown as follows: Furthermore, Hasyim et al. indicated that individuals who lived in unimproved sanitation environments were more frequently infected with malaria than those who lived in improved sanitation environments, even though the association between environmental sanitation and malaria prevalence was not statistically significant (OR 1.13, 95% CI 0.99-1.31, P = 0.081). Finally, as Hasyim et al. also suggested, most individuals who used open sewage systems (domestic wastewater or municipal wastewater) at home and those who did not have a sewage system were at higher risk of malaria infection (OR 1.250, 95% CI 1.095-1.427, P = 0.001) than those who used closed sewage systems, further highlighting the significance of potential larval habitats near houses. All these studies were in line with our results; due to closed and clean systems, improved WS users had a decreased risk of malaria infection.
.
Conclusion
LL 433 - 437
Consider including in findings another co-variate factors with have the odds ratio greater than one that is a positive association.

Response: Thank you for providing these valuable suggestions. However, please forgive us that we could not figure out the real meanings of this sentence. If it is convenient, would you like to do us a favor to further explain this sentence so that we can further revise our manuscript?

Presently, we revised the Conclusion section slightly based on our own thoughts about your suggestion (see Lines 518-521) and the revision was shown as follows: In conclusion, WS conditions were important risk factors for malaria among children under five years old across SSA after adjustment for age, gender, IRS in the past 12 months and insecticide-treated use, house quality, and mother’s highest educational level.

Finally, we are apologized to provide the inconvenience for you and thank you very much again for reviewing our manuscript and providing many valuable revision suggestions and guidance in order to improve the quality of our study.

Reviewer #2: The paper presents a largely descriptive results about the risk of malaria among children aged less than five in sub-Sahara Africa. The data is meaningful as an empirical fact among specific population, but the paper does not present much general scientific knowledge. If the fact presented in the paper is contrary to any previous knowledge, such background and motivation of the study should be given. Beyond the factual report, not much of in-depth analysis is conducted that explores the underlying social dynamics or particular causes.

Response: Thank you very much for reviewing our manuscript and providing suggestions. Our study first revealed a connection: unimproved WS (unprotected water; no facility) as a most dominant risk factor adjusted by covariate factor for age, gender, indoor residual spraying, insecticide-treated net use, house quality, and mother's highest educational level for malaria infection among children under five years old across in sub-Saharan Africa (SSA) based on the national survey data.

As we indicated in Introduction section (Lines 73-88; Lines 100-109) and Discussion section (Lines 461-490), this study includes the large and comprehensive dataset analyzed from DHS and MIS, which was not performed before. The analysis aimed to elucidate the influence of WS on malaria risk stratified by socioeconomic status on a large scale for the first time. Additionally, a little researches exploring the association between WS and malaria infections have been found at present. Some similar articles were discussed and compared in Discussion section (Lines 362-384).

Unfortunately, please forgive us that we could not further perform in-depth analysis underlying social dynamics or particular causes in this study because there were not detailed variables associated with social researches in DHS and MIS.

Thank you very much again for reviewing our manuscript and providing many suggestions.

Reviewer #3: This is an interesting analysis of the importance of access to clean water and sanitation for minimising the risk of malaria infection in children. It contributes to the clear evidence that improved living conditions can help alleviate the burden of malaria. The analysis appears appropriate to the data resource although there are some questions to address prior to acceptance.

Response: Thank you very much for reviewing our manuscript and your appreciation.

There is not enough in the methods to allow the analysis to be repeated or fully appreciate the models fitted.

Response: Thank you for pointing this out. We definitely agree with your idea on providing detailed methods so that readers understand our study better. Please forgive us that we put some methods in Additional file 1 for the original manuscript because there are some word limits in Journal of Advanced Research.

According to your suggestions, we revised our Methods section, mainly adding Study Design and Data Sources (Lines 111-129). This part may clearly provide the specific data sources, the samples inclusion criteria, and the concise study design which may help other researchers to repeat our analysis in future.

Additionally, regarding the stratified analyses by household socioeconomic status, we have also put some information on how to conduct them (see Lines 194-203; 205-214). The detailed revisions were shown as follows: The main reasons for the retention of the above covariables in the “best” model were based on clinical or statistical significance in previous studies. Furthermore, for the stratified analyses, the population were first categorized into two groups, namely “poor” children and “nonpoor” children in each survey. Then the aORs revealing the associations between WS conditions and the odds of malaria infection in children aged 0-59 months in a logistic regression model for each survey were performed among those who were “poor” and “nonpoor”, respectively, adjusting for the above confounding factors for each DHS/MIS survey.

Finally, a meta-analysis method was performed to combine data from independent scientific trials as well as observational studies. In this study, each national survey was conducted independently. Using national survey data based on a random-effects meta-analysis might eliminate many biases typically related to pooling observational data, such as publication, selection, and measurement biases and selective outcome reporting bias. In this study, to determine the overall and the stratified aORs for WS among all the surveys, random-effect models in the meta-analysis were used to pool logistic regression results for the surveys which were calculated among total children, “poor” children, and “nonpoor” children, respectively.

We also set the statistical significant criterion: $P < 0.05$ for each overall aOR was considered statistically significant (see Lines 223-224).

There are necessary improvements that should be made to the writing - grammatical errors, clarity and paragraph structuring - which are essential for appropriately communicating the findings of the study as well as the analysis performed.

Response: Thank you for pointing this out. We have carefully double checked and revised the English writing. The paper was edited for grammar, phrasing, and punctuation. In addition, many edits were made to further improve the flow and readability of the text.

Finally, thank you very much again for reviewing our manuscript and providing many suggestions and guidance.

Responses to the editor and reviewers

Editor-in-Chief Decisions to Author:
The reviewers have commented on your above paper. They indicated that it is not acceptable for publication in its present form.

However, if you feel that you can suitably address the reviewers' comments (included below), I invite you to revise and resubmit your manuscript. Please carefully address the issues raised in the comments.

If you are submitting a revised manuscript, please also: a) outline each change made (point by point) as raised in the reviewer comments AND/OR b) provide a suitable rebuttal to each reviewer comment not addressed. To submit your revision, please do the following: 1. Go to: https://ees.elsevier.com/jare/ 2. Enter your login details 3. Click [Author Login] This takes you to the Author Main Menu. 4. Click [Submissions Needing Revision].

Your revision should be submitted before Sep 9 2019 12:00AM.

Response: We would like to thank you and the reviewers for reviewing our manuscript and making very insightful comments, all of which have been followed carefully in the preparation of this revision. We have highlighted the changes to our manuscript by marking the changes in RED (change-tracked version).

Reviewers' comments:

Reviewer #1: Reviewer reports

Manuscript Number: JARE-D-19-00908
Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling analysis of the national survey data

Overall Comments:
Overall, this manuscript is well written and provides useful information to help better understand the risk of malaria in this area. However, before recommending for publication, I have a few comments that ought to be considered.

The paper revealed a connection unimproved WS (unprotected water; no facility) as a most dominant risk factor adjusted by covariate factor for age, gender, indoor residual spraying, insecticide-treated net use, house quality, and mother's highest educational level for malaria infection among children under five years old across in sub-Saharan Africa (SSA) based on the national survey data.

General Remarks:
I think the analysis is worth publishing, but serious weaknesses should be acknowledged and addressed. The author was making a connection in this finding based on aOR value. The value odds ratio is higher than one that is a positive association.

Response: Thank you very much for reviewing our manuscript carefully and your appreciation to our study. We are appreciated that you have provided many expert, detailed, and valuable revisions and guidance in order to improve the quality of our manuscript.

However, we know a one-celled parasite called a Plasmodium causes malaria. When they feed on an infected person's blood, the parasite infects female mosquitoes. The mosquitoes and their ecosystems are significant spatial drivers for malaria transmission, so, based on the previous study if any, the authors need also briefly explore malaria prevalence in the same area related to the kind of Anopheles vector. Besides, distribution and 'bionomics' is used to cover both the ecology of a mosquito species (e.g. larval habitats) and its behaviour (e.g. host biting preferences).

Response: Thank you very much for your expert and detailed guidance. As you suggested, we have explored distribution and bionomics of mosquitoes in our study area. This information was included in **Discussion section (Lines 386-405)**.

According to the study of Hasyim et al. (Ref# Hasyim et al. Does livestock protect from malaria or facilitate malaria prevalence? A cross-sectional study in endemic rural areas of Indonesia. Malar J, 2018, 17: 302.), they indicated that ***zoopotentiation could also occur if the physical disturbances created by animals (e.g., puddles, hoof prints, watering sites) increase the potential for larval habitats and thus adult vector density near households.*** Considering the range and the form of human activities is greater and more diverse, we indicated that the potential larval habitats could be constructed due to the physical disturbances created by human fetching or storing unimproved drinking water (e.g., splashing water on the ground when fetching or storing unimproved water results in shallow puddles or footprints; additionally, storing unimproved drinking water creates stagnant water sources for nearby households), further increasing mosquito breeding and adult vector densities near households.

The top three vector species of human malaria in our study area included *Anopheles gambiae, An. arabiensis*, and *An. funestus* (Additional file 6; the data sources were derived from country profiles based on the World Health Organization (WHO) database online because the DHS and MIS did not include entomological surveys). Among these

Anopheles species, *An. gambiae* and *An. arabiensis* prefer to inhabit sunlit, shallow, temporary bodies of fresh water, such as puddles, pools, ground depressions, and hoof prints. In addition, water in these larval sites is often turbid or polluted. In contrast, *An. funestus* inhabits permanent or semipermanent bodies of fresh water with emergent vegetation, such as swamps, ponds, and lake edges. This evidence suggests that closed systems with improved water are relatively inappropriate environments for Anopheles.

However, due to the lack of the entomological survey in DHS and MIS, we could not explore malaria prevalence in the same area related to the kind of Anopheles vector directly. We only sorted out the major types of Anopheles in our studied areas based on "Country Profiles" from WHO online database (**see Additional file 6**) and found that the top three vector species of human malaria in our study area mainly included *An.gambiae, An.arabiensis*, and *An.funestus.* However, in this study, it is hardly seen that malaria prevalence is associated with types of Anopheles vector due to lack of the entomological survey which can provide more detailed information on the specific density of various kinds of Anopheles.

Additional File 6. Major types of Anopheles vector in sub-Saharan Africa.

Country and Year	Major anopheles species [1]	Parasite Rate (%) for children < 5 years*	
		Microscopy	RDT
Angola 2015-2016	*An.gambiae, An.funestus, An.nili*	-	16.5
Angola 2011	*An.gambiae, An.funestus, An.nili*	9.8	12.5
Angola 2006-2007	-	-	22.2
Benin 2011-2012	*An.gambiae, An.funestus, An.nili*	29.9	27.1
Burkina Faso 2014	*An.gambiae, An.funestus, An.arabiensis*	47.6	64.5
Burkina Faso 2010	-	65	75.6
Burundi 2016-2017	*An.gambiae, An.funestus, An.arabiensis*	24.4	34.8
Burundi 2012	*An.gambiae, An.funestus*	16.2	20.5
Cameroon 2011	*An.gambiae, An.funestus, An.arabiensis, An.moucheti*	-	32.6
Coate D Ivoire 2011-2012	*An.gambiae, An.funestus*	16.1	42
DRC 2013-2014	*An.gambiae, An.funestus, An.moucheti, An.nili*	26.3	35.9

Gambia 2013	*An.gambiae, An.funestus, An.arabiensis, An.melas, An.pharoensis, An.nili*	0.5	1.8
Ghana 2016	*An.gambiae, An.funestus, An.arabiensis*	23	32.5
Ghana 2014	*An.gambiae, An.funestus, An.arabiensis*	28.8	40.8
Guinea 2012	*An.gambiae, An.funestus,An.arabiensis*	43.8	45.7
Kenya 2015	*An.gambiae, An.arabiensis, An.funestus, An.merus*	5.3	9.4
Liberia 2016	*An.gambiae*	-	50.3
Liberia 2011	*An.gambiae*	32.5	52.3
Liberia 2009	*An.gambiae, An.funestus, An.hancocki, An.hargreavesi, An.pharoensis, An.nili*	33.3	37.4
Madagascar 2016	*An.gambiae, An.funestus, An.arabiensis*	5.5	3.7
Madagascar 2013	*An.gambiae, An.funestus, An.arabiensis*	6.5	7.5
Madagascar 2011	*An.gambiae, An.funestus, An.arabiensis*	4.1	6.2
Malawi 2017	*An.gambiae, An.funestus, An.arabiensis*	16.9	26
Malawi 2014	*An.gambiae, An.funestus, An.arabiensis*	26	29.9
Malawi 2012	*An.gambiae, An.funestus, An.arabiensis*	24.6	37.8
Mali 2015	*An.gambiae, An.funestus*	35	31.5
Mali 2012-2013	*An.gambiae, An.funestus*	48.7	44.1
Mozambique 2015	*An.gambiae, An.funestus, An.arabiensis*	-	31.7

Mozambique 2011	*An.gambiae, An.funestus, An.arabiensis*	29.9	34
Nigeria 2015	*An.gambiae, An.funestus, An.arabiensis, An.moucheti, An.nili, An.melas*	27.3	41.3
Nigeria 2010	-	38.3	46.3
Rwanda 2017	*An.gambiae, An.funestus, An.arabiensis*	6.6	10.9
Rwanda 2014-2015	*An.gambiae, An.funestus, An.arabiensis*	2.2	7.6
Rwanda 2010	*An.gambiae, An.funestus, An.arabiensis*	1.2	2.4
Senegal 2017	*An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas*	0.6	1.6
Senegal 2016	*An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas*	1	1.4
Senegal 2015	*An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas*	0.4	1
Senegal 2014	*An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas*	2.8	2.9
Senegal 2012-2013	*An.gambiae, An.funestus, An.arabiensis, An.pharoensis, An.melas*	3.7	4.1
Senegal 2010-2011	*An.gambiae, An.funestus, An.arabiensis, An.pharoensis*	3.7	3.3
Sierra Leone 2016	*An.gambiae, An.funestus, An.melas*	41.9	56.3
Tanzania 2017	*An.gambiae, An.funestus, An.arabiensis*	-	8.4

Tanzania 2015-2016	*An.gambiae, An.funestus, An.arabiensis*	5.1	12.7
Tanzania 2011-2012	*An.gambiae, An.funestus, An.arabiensis*	4.7	10
Togo 2017	*An.gambiae, An.funestus, An.arabiensis, An.melas*	29.6	47.2
Togo 2013-2014	*An.gambiae, An.funestus, An.arabiensis, An.melas*	37.8	39.3
Uganda 2016	*An.gambiae, An.funestus*	-	33.2
Uganda 2014-2015	*An.gambiae, An.funestus*	19.9	32.6
Uganda 2009	*An.gambiae, An.funestus, An.arabiensis, et al.*	43.6	53.1

[1] WHO. Malaria: Country Profiles. https://www.who.int/malaria/publications/country-profiles/en/ (accessed August 22, 2019)
*The Parasite Rate was calculated by ourselves based on DHS and MIS survey.

Through the entomological survey, particularly in the unimproved drinking water sources, and unimproved sanitation facilities at this study area, to ensure and justify that the condition has the risk of malaria associations were more pronounced among in this area. It is an important confounding factor to address as distinct species may have different ecological niches, and therefore, several factors may be necessary for various places.

Response: Thank you for your expert suggestions. We definitely agree with your opinions. Unfortunately, in DHS and MIS survey, the entomological surveys were not investigated, which might be the limitations of our study (**see Discussion section, Lines 506-512**).

Besides, the authors should check the English grammar errors of this script like tenses, punctuation, spellings, and others and the layout of the manuscript again.

Response: Thank you for pointing this out. We have carefully double checked and revised the English writing. The paper was edited for grammar, phrasing, and punctuation. In addition, many edits were made to further improve the flow and readability of the text.

Specific Remarks:
Comments by section

Title LL 1 - 3.

The "title" and the "abstract" are the "original impressions" of a research article and must be drawn up properly, carefully, accurately, and meticulously. Therefore, you need to pick a title that captures attention, describes your manuscript's contents correctly and makes individuals want to read more. The "title" should be descriptive, accurate, direct, suitable, appealing, concise, accurate, distinctive, and not misleading.

Consider adding Logistic regression.

Title: Drinking water and sanitation sources are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A modelling Logistic regression analysis of the national survey data.

The title started with a catchy primary title, followed by a subtitle that provides data on the study's content and method, and this is a short, easy to understand, and conveys the essential aspects of the research.

Response: Thank you for providing the expert suggestions on how to write a catchy title. As you suggested, we have revised our title and the new title is shown as follows: Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data (**Lines 1-3**).

LL 27-51

Abstract

The abstract as a miniature manuscript must be smooth clear, unbiased, frank, concise, accurate, stand-alone, complete, (ideally) organised, and not misrepresented, and the abstract should answer these questions about your manuscript: What was done? Why did you do it? What did you find? Why are these findings useful and essential? Replying these queries lets readers grasp the first important points regarding your study and helps them determine whether or not they desire to examine the remainder of the paper. Make certain you observe the appropriate journal manuscript formatting tips when preparing your abstract.

Response: Thank you for providing these valuable experiences and suggestions on how to write a clear, unbiased, frank, concise, accurate, stand-alone, and complete abstract. We have revised our original abstract point by point according to your valuable suggestions below (**see Abstract section, Lines 24-39**).

LL 27-29

Duration of the data should be precise.

Data were acquired through surveys published starting from …. up to 18

September 2018.

Response: Thank you for pointing this out. We have revised it in Abstract (**Line 30**), Methods (**Line 113**), and Results (**Line 228**). The revision is shown as follows: between 2006 and 2018.

LL 34-35
The final survey-specific results were combined through meta-analysis with a random effect.

However, it is not clear the source of meta-analysis in this paper. Meta-analysis is a method for synthesising evidence from various sources. It can be the analysis of individual data combined from two or more studies or the interpretation of summary measures obtained from two or more reports (usually from the published literature). Further, traditionally, meta-analysis strategies have been developed and used to mix data from quite a few independent scientific trials as nicely as observational studies; however, they have not been as extensively used in survey research.

You can briefly the argument using of meta-analysis based national the national survey data in background or method section

Response: Thank you for pointing this out. We definitely agree with your opinion. As you suggested, we have added why using meta-analysis based on national survey data in Method section (**Lines 205-214**).

The revision was shown as follows: a meta-analysis method was performed to combine data from independent scientific trials as well as observational studies. In this study, each national survey was conducted independently. Using national survey data based on a random-effects meta-analysis might eliminate many biases typically related to pooling observational data, such as publication, selection, and measurement biases and selective outcome reporting bias. In this study, to determine the overall and the stratified aORs for WS and malaria risks among all the surveys, random-effect models in the meta-analysis were used to pool logistic regression results for the surveys which were calculated among total children, "poor" children, and "nonpoor" children, respectively.

LL 29 - 30
Why the author interest directly to "WS variable" as the leading risk factor for malaria infection due to there is some covariates factor national survey at this study?

Response: Thank you for pointing this out. To briefly explain why we are interested directly to WS as the leading risk factor for malaria infection, in this study, we revised the first sentence in our original Abstract (**Lines 24-27**). Then, we will explain our initial thoughts on conducting the study on WS and malaria at length below.

Good hygiene is universally known as one of the most efficacious and straightforward measures to prevent disease transmission. To date, the water, sanitation, and hygiene (WASH) component of the strategy has received little attention and the potential to link efforts on WASH and malaria and many neglected tropical diseases (NTDs) has also been largely untapped. A remarkable progress has been made on the prevention of malaria and waterborne diseases in SSA. However, both diarrhea (DALYs [000s] 44,483) and malaria (DALYs [000s] 35,615) remain on the 20 top diseases with the highest DALYs globally. Diarrhea and malaria also rank as third and fourth in the region of Africa according to the WHO, respectively. If we add up the DALYs of the above two diseases, then their sum would rank them first. These two main diseases have threaten children's lives seriously. At first, we hypothesized whether improving WS might provide double efforts to prevent malaria and diarrhea.

Additionally, many studies indicated that unimproved WS users may indirectly increase the likelihood of *P.falciparum* risk through increasing the risk of other waterborne parasitic diseases such as soil transmitted diseases. The latter kind of disease is more frequently found in unimproved WS users. To crucially test our idea about the association between WS and malaria, we first summarized the latest WHO statistics and obtained the proportion of population who had access to improved WS sources and malaria incidence rate for each country across SSA (**see Table 1 below**). We found that the malaria incidence rates varied depending on the coverage of different WS sources. To this end, we applied the detailed information obtained by the Demographic Health Survey and Malaria Indicator Survey on each country across SSA in the first instance.

Considering the target date for the malaria roadmap and for the Sustainable Development Goals of universal access to basic WASH in communities, schools, and health care facilities being both 2030, we hypothesized whether redoubling of efforts to improve WS and its recognition as the new policy on the prevention and control malaria transmission can contribute to the achievement of malaria elimination targets in 2016-2030. To verify this indirect hypothesis, the first thing is to test the association between WS and malaria infection directly. Thus, we interest directly to "WS variable" as the leading risk factor for malaria infection even though there is some covariates factor national survey at this study. In our study, the other covariates included in multivariate logistic regression model were mainly due to their clinical importance and statistical significance in other previous studies.

We hope this explanation will help you better understand why we interest directly to "WS variable" as the leading risk factor for malaria infection even if there is some covariates factor national survey at this study

Table1 The proportion of population who used improved WAS sources and malaria

incidence across SSA according to the WHO (2017)

Country	**Proportion of Population Using Improved Drinking-Water Sources(%),2015[1]**	**Proportion of Population Using Improved Sanitation(%),2015[1]**	**Malaria Incidence(per 1000 Population at Risk),2015[2]**
Angola	49	48	124
Benin	78	7	293·7
Burkina Faso	82	7	389·2
Burundi	76	<5·0	126·3
Cameroon	76	18	264·2
Congo Democratic Republic	52	6	246
Coate d'Ivoire	82	18	348·8
Ghana	89	21	266·4
Guinea	77	6	367·8
Kenya	63	6	166
Liberia	76	<5·0	246·2
Madagascar	52	<5·0	104·2
Malawi	90	<5·0	188·8
Mali	77	<5·0	448·6
Mozambique	51	<5·0	297·7
Nigeria	69	<5·0	380·8
Rwanda	76	<5·0	301·3
Senegal	79	36	97·6
Tanzania	56	<5·0	113·9
Togo	63	6	345·1
Uganda	79	<5·0	218·3

[1] WHO. Progress on sanitation and drinking water – 2015 update and MDG assessment. New York (NY): UNICEF; and Geneva: World Health Organization; 2015.http://apps.who.int/iris/bitstream/10665/177752/1/9789241509145_eng.pdf?ua=1 (accessed September 19, 2017)

[2] WHO. World Malaria Report 2016. Geneva: World Health Organization; 2016. http://www.who.int/malaria/publications/world-malaria-report-2016/report/en/ (accessed September 19, 2017).

LL 35

The writing of the numerical with the comma. In the English-speaking world, commas are commonly used in numbers of four or more digits every three decimal places, counting right to the left. 247,440

Response: Thank you for pointing this out. We have corrected them (**see Lines 39, 234-236, and 240-242**).

Methods

Outcome Definition
LL 121-123 and LL 159 - 162
It is better if this paper also creates a malaria infection map of the study area for a description of the area notably and clearly.

Response: Thank you for your suggestions. We definitely agree with your opinion. At first, we would have planned to draw a malaria infection map of SSA for our study. Unfortunately, in this study, the survey time node for each national DHS and MIS survey is different. Please forgive us we could not provide a malaria infection map of the study area.

Result
LL 204-217
Each DHS survey usually takes on average 18-20 months and is executed in four phases, correlation the text with your sample children who age 0-59 months. Please explain why you choose the age groups as your selected sample in connection with malaria infection.

Response: Thank you for pointing this out. We feel very sorry to put such important information somewhere in our original manuscript due to the word limits from *Journal of Advanced Research*. As you suggested, presently we put data sources and study design in Method section, and explain the reason for selecting children under 5 years old in Method section (**Lines 120-124**).

According to WHO records on the high-risk groups for malaria infection, children under 5 years of age are at considerably higher risk of contracting malaria and they (including infants) are also the most vulnerable group in high-transmission areas of the world (Ref# https://www.who.int/malaria/areas/high_risk_groups/en/). More importantly, only this age group was tested for malaria infection by all the DHS and MIS surveys.

Discussion
LL 316-325
Some essential references, in this case, are missing. Please see works of other similar papers. You can refer also adding other same articles from a large-scale study, for example at https://malariajournal.biomedcentral.com/articles/10.1186/s12936-019-2760-8 that also discussed the association of environmental sanitation that is Improved and unimproved of primary water source, water storage facility, and wastewater disposal and malaria. Also, a similar paper at https://malariajournal.biomedcentral.com/articles/10.1186/s12936-018-2447-6 that revealed that most participants who use open sewage systems (domestic wastewater or municipal wastewater) at home and those without a sewage system are at higher odds of contracting the disease than participants who have closed sewage systems.

Response: Thank you for your expert suggestions and providing such essential references. We have studied these references carefully and considered them as the important evidences and backups for our study. As you suggested, we have discussed these two similar articles in our Discussion section (**Lines 372-384**).

The revision was shown as follows: Furthermore, Hasyim et al. indicated that individuals who lived in unimproved sanitation environments were more frequently infected with malaria than those who lived in improved sanitation environments, even though the association between environmental sanitation and malaria prevalence was not statistically significant (OR 1.13, 95% CI 0.99-1.31, *P* = 0.081). Finally, as Hasyim et al. also suggested, most individuals who used open sewage systems (domestic wastewater or municipal wastewater) at home and those who did not have a sewage system were at higher risk of malaria infection (OR 1.250, 95% CI 1.095-1.427, *P* = 0.001) than those who used closed sewage systems, further highlighting the significance of potential larval habitats near houses. All these studies were in line with our results; due to closed and clean systems, improved WS users had a decreased risk of malaria infection.

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Conclusion

LL 433 – 437

Consider including in findings another co-variate factors with have the odds ratio greater than one that is a positive association.

Response: Thank you for providing these valuable suggestions. However, please forgive us that we could not figure out the real meanings of this sentence. If it is convenient, would you like to do us a favor to further explain this sentence so that we can further revise our manuscript?

Presently, we revised the Conclusion section slightly based on our own thoughts about your suggestion (**see Lines 518-521**) and the revision was shown as follows: In conclusion, WS conditions were important risk factors for malaria among children under five years old across SSA after adjustment for age, gender, IRS in the past 12 months and insecticide-treated use, house quality, and mother’s highest educational level.

Finally, we are apologized to provide the inconvenience for you and thank you very much again for reviewing our manuscript and providing many valuable revision suggestions and guidance in order to improve the quality of our study.

Reviewer #2: The paper presents a largely descriptive results about the risk of malaria among children aged less than five in sub-Sahara Africa. The data is meaningful as an empirical fact among specific population, but the paper does not present much general scientific knowledge. If the fact presented in the paper is contrary to any previous knowledge, such background and motivation of the study should be given. Beyond the factual report, not much of in-depth analysis is conducted that explores the underlying social dynamics or particular causes.

Response: Thank you very much for reviewing our manuscript and providing suggestions. Our study first revealed a connection: unimproved WS (unprotected water; no facility) as a most dominant risk factor adjusted by covariate factor for age, gender, indoor residual spraying, insecticide-treated net use, house quality, and mother's highest educational level for malaria infection among children under five years old across in sub-Saharan Africa (SSA) based on the national survey data.

As we indicated in Introduction section (**Lines 73-88; Lines 100-109**) and Discussion section (**Lines 461-490**), this study includes the large and comprehensive dataset analyzed from DHS and MIS, which was not performed before. The analysis aimed to elucidate the influence of WS on malaria risk stratified by socioeconomic status on a large scale for the first time. Additionally, a little researches exploring the association between WS and malaria infections have been found at present. Some similar articles were discussed and compared in Discussion section (**Lines 362-384**).

Unfortunately, please forgive us that we could not further perform in-depth analysis underlying social dynamics or particular causes in this study because there were not detailed variables associated with social researches in DHS and MIS.

Thank you very much again for reviewing our manuscript and providing many suggestions.

Reviewer #3: This is an interesting analysis of the importance of access to clean water and sanitation for minimising the risk of malaria infection in children. It contributes to the clear evidence that improved living conditions can help alleviate the burden of malaria. The analysis appears appropriate to the data resource although there are some questions to address prior to acceptance.

Response: Thank you very much for reviewing our manuscript and your appreciation.

There is not enough in the methods to allow the analysis to be repeated or fully appreciate the models fitted.

Response: Thank you for pointing this out. We definitely agree with your idea on providing detailed methods so that readers understand our study better. Please forgive us that we put some methods in Additional file 1 for the original manuscript because there are some word limits in *Journal of Advanced Research*.

According to your suggestions, we revised our Methods section, mainly adding *Study Design and Data Sources* (**Lines 111-129**). This part may clearly provide the specific data sources, the samples inclusion criteria, and the concise study design which may help other researchers to repeat our analysis in future.

Additionally, regarding the stratified analyses by household socioeconomic status, we have also put some information on how to conduct them (**see Lines 194-203; 205-214**). The detailed revisions were shown as follows: The main reasons for the retention of the above covariables in the "best" model were based on clinical or statistical significance in previous studies. Furthermore, for the stratified analyses, the population were first categorized into two groups, namely "poor" children and "nonpoor" children in each survey. Then the aORs revealing the associations between WS conditions and the odds of malaria infection in children aged 0-59 months in a logistic regression model for each survey were performed among those who were "poor" and "nonpoor", respectively, adjusting for the above confounding factors for each DHS/MIS survey.

Finally, a meta-analysis method was performed to combine data from independent scientific trials as well as observational studies. In this study, each national survey was conducted independently. Using national survey data based on a random-effects meta-analysis might eliminate many biases typically related to pooling observational data, such as publication, selection, and measurement biases and selective outcome reporting bias. In this study, to determine the overall and the stratified aORs for WS among all the surveys, random-effect models in the meta-analysis were used to pool logistic regression results for the surveys which were calculated among total children, "poor" children, and "nonpoor" children, respectively.

We also set the statistical significant criterion: $P < 0.05$ for each overall aOR was considered statistically significant (**see Lines 223-224**).

There are necessary improvements that should be made to the writing - grammatical errors, clarity and paragraph structuring - which are essential for appropriately communicating the findings of the study as well as the analysis performed.

Response: Thank you for pointing this out. We have carefully double checked and revised the English writing. The paper was edited for grammar, phrasing, and punctuation. In addition, many edits were made to further improve the flow and readability of the text.

Finally, thank you very much again for reviewing our manuscript and providing many suggestions and guidance.

Title: Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data

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Abstract

Current efforts for the prevention of malaria have resulted in notable reductions in the global malaria burden; however, they are not enough. Good hygiene is universally known as one of the most efficacious and straightforward measures to prevent disease transmission. This work analyzed whether improved drinking water and sanitation (WS) conditions were associated with a decreased risk of malaria infection. Data were acquired through surveys published between 2006 and 2018 from the Demographic and Health Program in sub-Saharan Africa (SSA). Multiple logistic regression was used for each national survey to identify the associations between WS conditions and malaria infection diagnosed by microscopy or a malaria rapid diagnostic test (RDT) among children (0-59 months), with adjustment for age, gender, indoor residual spraying (IRS), insecticide-treated net (ITN) use, house quality, and the mother's highest educational level. Individual nationally representative survey odds ratios (ORs) were combined to obtain a summary OR using a random-effects meta-analysis. Among the 247,440 included children, 18.8% and 24.2% were positive for malaria infection based on microscopy and RDT results, respectively. Across all surveys, both unprotected water and no facility users were associated with increased malaria risks (unprotected water: aOR 1.17, 95% CI 1.07-1.27, *P* = 0.001; no facilities: aOR 1.35, 95% CI 1.24-1.47, *P* < 0.001; respectively), according to microscopy, whereas the odds of malaria infection were 48% and 49% less among piped water and flush-toilet users, respectively (piped water: aOR 0.52, 95% CI 0.45-0.59, $P < 0.001$; flush toilets: aOR 0.51, 95% CI 0.43-0.61, $P < 0.001$). The trends of individuals diagnosed by RDT were consistent with those of individuals diagnosed by microscopy. Risk associations were more pronounced among children with a "nonpoor" socioeconomic status who were unprotected water or no facility users. WS conditions are a vital risk factor for malarial infection among children (0-59 months) across SSA. Improved WS conditions should be considered a potential intervention for the prevention of malaria in the long term.

Keywords

drinking water; sanitation; malaria; risk; children; sub-Saharan Africa

Introduction

Malaria is one of the most severe public health problems, posing significant risks to the lives of children, especially in sub-Saharan Africa (SSA). Although cases of malaria decreased by an estimated 20 million since 2010 [1], there was no significant progress in reducing the number of global cases from 2015 to 2017 [1]. Current efforts for preventing malaria mainly include preventive and symptomatic treatment with antimalarial compounds, consisting of artemisinin-based combination therapies [2], as well as vector control with long-lasting insecticidal mosquito nets (LLINs) and indoor residual spraying (IRS) [3, 4]; these methods have resulted in reductions in case incidence and mortality. However, increasing evidence has revealed that these efforts can only go so far [1, 5]. Therefore, we need to determine and invest in additional effective measures to tackle the complex challenges.

Good hygiene is universally known as one of the most efficacious and straightforward measures to prevent disease transmission [6]. To date, the water, sanitation and hygiene (WASH) component of the strategy has received little attention, and the potential to link WASH efforts with malaria and neglected tropical disease (NTD) transmission has been largely untapped [7]. Some studies explored the effect of water and sanitation (WS) on malaria in Ethiopia and Kenya on a small scale [8-11], but there are no clear existing studies that have comprehensively evaluated the association between different types of WS conditions and malaria infection among children under five years old across a broad epidemic region, such as SSA. Considering the target date for the malaria roadmap and for the Sustainable Development Goal (SDG) of universal access to basic WASH in communities, schools, and health care facilities is both 2030 [7, 12], the primary hypothesis was whether the redoubling of efforts to improve WS and its recognition as a new policy for the prevention and control of malaria transmission can contribute to the achievement of malaria elimination targets from 2016 to 2030.

It is well known that Demographic and Health Survey (DHS) and Malaria Indicator Survey (MIS) are national cross-sectional surveys that provide data for many indicators in the areas of health, populations, and nutrition [13-15]. Each DHS survey usually takes an average of 18-20 months and is executed in four phase [13]. Although most of the collected variables are different in each survey [14, 15], the types of WS sources used by children under five years old are meticulously classified, and the available data provide a convenient condition to comprehensively evaluate the effect of WS conditions on the risk of malaria on a large scale.

In this study, using all the available data derived from DHS and MIS in SSA, a model analysis of the relationship between WS and malaria was performed. Specifically, the hypothesis that the odds of malaria infection in children under

5 years old with access to improved WS conditions across SSA are lower than those in children with access to unimproved WS conditions across SSA was tested. This is the most comprehensive study of the relationship between WS conditions and malaria across SSA to date, and it is also the first to demonstrate the effects between drinking water and sanitation use in relation to malaria prevalence stratified by household socioeconomic status on a large scale.

Methods

Study Design and Data Sources

A model analysis of individual-level data that were acquired through surveys published between 2006 and 2018 and performed by the DHS Program in SSA was conducted. The cross-sectional survey data used in this study had been provided by the DHS Program. First, surveys were excluded if the data on malaria infection in children or information on WS conditions were not complete. Second, participants in each survey were excluded if there was no data or ambiguous data on their WS use (these variables in the DHS and MIS were always represented in the form of “do not know” or “others”) or if their age was over 59 months. Only children under five years old were included in this study because children under 5 years of age (including infants) are the most vulnerable group, especially in high-transmission areas of the world [16]. More importantly, only this age group was tested for malaria infection during all the DHS and MIS surveys. Then, each national DHS and MIS survey on the exposure to various WS conditions and risk of malaria was separately analyzed for the outcome definition, exposure and covariate groupings, and stratified analysis by household socioeconomic status. Finally, to obtain a summary OR, individual national survey ORs obtained by multivariable logistic regression were synthesized through a random-effects meta-analysis.

Outcome Definition

The endpoint was the participants' malaria status as measured by a malaria rapid diagnostic test (RDT) or microscopy using thick or thin blood smears. A positive result by either of these two test methods indicated a malaria case. Considering that microscopy results of the participants from Angola 2015-2016, Angola 2006-2007, Cameroon 2011, Liberia 2016, Mozambique 2015, Tanzania 2017, and Uganda 2016 were not available, only the RDT results for these participants were recorded in the aforementioned years.

Exposure: Drinking Water and Sanitation (WS)

The DHS and MIS classified drinking water sources into five groups (piped water, tube well water, dug well, surface water, others), and they categorized sanitation sources into three groups (flush or pour flush-toilet, pit latrine toilet, and no facility). In this study, the DHS/MIS sanitation classifications were used. However, drinking water sources were condensed into three groups (piped water in accordance with the DHS/MIS definition, protected water, and unprotected water) [10]. Protected water was obtained from a tube well or borehole, protected well, protected spring, tanker truck, cart with a small tank, bicycle with jerrycans, bottles, or sachets [10]. Unprotected water was obtained from an unprotected well, unprotected spring, river, dam, lake, pond, stream or the rain [10].

Covariates

Information on the participants' age, gender, IRS in the past 12 months, insecticide-treated net (ITN) use, house quality, mother's highest educational level, and socioeconomic status was collected. For these covariates, age (in months) was treated as a continuous variable. Gender was categorized into two groups (male versus female). IRS in the past 12 months was treated as a dichotomized variable (yes/no). ITN use was grouped into three categories (ITNs or LLINs, untreated nets, or no nets). Specifically, if ITNs were >1 year old or were not retreated within a year before the survey [13, 17] or LLINs were 3 years old at the time of survey, these nets were considered "untreated nets" [13, 18-20]. House quality was divided into two groups (modern versus traditional). Houses built with finished walls, a finished roof, and a finished floor were categorized as "modern", while all other houses were categorized as "traditional" [13]. Mother's highest educational level was classified into four groups (no education, primary, secondary, or higher), which were in accordance with the DHS/MIS definitions. The DHS and MIS classified the population’s socioeconomic status into five categories, namely, “poorest”, “poor”, “middle”, “rich”, and “richest”. In this study, the total population was classified into two groups for further stratified analyses, namely, “poor” (poorest + poor) and “nonpoor” (middle + rich + richest). No missing values were observed for all the other covariates in each survey, except for IRS in the past 12 months and mother’s highest educational level in some surveys (no data on IRS in the past 12 months in Angola 2011, DRC 2013-2014, Kenya 2015, Liberia 2009, Madagascar 2016, Malawi 2017, Rwanda 2014-2015, Rwanda 2010, Tanzania 2017, Togo 2017, Togo 2013-2014, Uganda 2009; no data on mother’s highest educational level in Rwanda 2017).

Stratified Analyses by Household Socioeconomic Status

For descriptive analyses, chi-square (χ^2) tests or Fisher’s exact tests were used for each survey to compare the prevalence of unprotected water and piped water with that of protected water, and the prevalence of flush toilets and no facility sources with that of pit latrine toilets among the total population. Chi-square (χ^2) tests or Fisher’s exact tests were also used to compare the proportion of “poor” associated with different WS conditions for each survey.

Second, a logistic regression model was used to conduct the primary analysis of the total population to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) of the associations between different WS conditions and malaria infection for each survey, considering protected water and pit latrine toilets as reference. In these regression analyses, aORs were adjusted for (i) age in months, (ii) gender, (iii) IRS in the past 12 months, (iv) ITN use, (v) house quality, and (vi) mother's highest educational level. The main reasons for the retention of the above covariables in the "best" model were based on clinical or statistical significance in previous studies [13, 17, 21]. Furthermore, for the stratified analyses, the population were first categorized into two groups, namely "poor" children and "nonpoor" children in each survey. Then, the aORs revealing the associations between WS conditions and the odds of malaria infection in children aged 0-59 months in a logistic regression model were performed for each DHS/MIS survey among those who were "poor" and "nonpoor", respectively, adjusting for the above confounding factors.

Finally, a meta-analysis method was performed to combine data from independent scientific trials as well as observational studies. In this study, each national survey was conducted independently. Using national survey data based on a random-effects meta-analysis might eliminate many biases typically related to pooling observational data, such as publication, selection, and measurement biases and selective outcome reporting bias. In this study, to determine the overall and the stratified aORs for WS and malaria risks among all the surveys, random-effect models in the meta-analysis were used to pool logistic regression results for the surveys which were calculated among total children, “poor” children, and “nonpoor” children, respectively. Furthermore, to investigate the heterogeneity among the survey-specific effects, Tau-squared statistics, I^2 statistics and *P*-values were analyzed with chi-square and Cochran’s Q tests.

All analyses were conducted using SPSS Statistics version 22.0 (IBM Co., Armonk, NY, USA), except for the meta-analysis and forest plots, which were performed using STATA version 15.0 (StataCorp, College Station, TX, 77845, USA) and relating line diagrams and bar charts in GRAPHPAD PRISM version 7.0 (GraphPad Software, Inc., La Jolla, CA, USA). $P < 0.05$ for each overall aOR was considered statistically significant.

Results

Study Population

After screening 189 identified surveys (136 DHS, 27 MIS, and 26 others) published between 2006 and 2008, none of 138 surveys met the inclusion criteria because they did not document malaria infection status (Additional file 1). After the removal of 138 surveys, 2 surveys were further excluded because they did not contain data on WS use (Additional file 1). Finally, 49 surveys (23 DHS, 24 MIS, and 2 others) including data for 307,365 individuals from 23 countries (Additional file 1) were identified. Among the identified individuals, 6,058 did not record information on WS use, and the age of 53,867 individuals was over 59 months; thus, these 59,925 individuals were excluded (Additional file 1). Overall, 49 eligible surveys comprising data for 247,440 individuals were included in the analysis (Additional file 1).

Table 1 provides the descriptive statistics for the health outcomes and covariates. Of the included individuals, 213,920 children aged 0-59 months were tested for malaria infection using microscopy, and the prevalence was 18.8%, whereas 59,988 (24.2%) positive cases were identified in 247,440 children by RDTs (Table 1). Across all surveys, the average age of the children was 32.6 months, and 50.2% were male (Table 1). Nearly half (47.3%) of the mother's had no education, and the proportion ranged from 10.1% (Malawi 2017) to 83.0% (Burkina Faso 2010). With regard to preventive measures targeting vectors, data on the use of ITNs and IRS for each survey were extracted. As shown in Table 1, it is clear that ITN usage was less than half (45.8%) overall and ranged from 15.2% (Cameroon 2011) to 71.5% (Burkina Faso 2014). Among the households surveyed, 12.5% experienced IRS in the past 12 months. With regard to house quality, the majority of the overall houses were traditional (69.7%), ranging from 38.1% (Ghana 2014) to 100% (Uganda 2009).

<Table 1>

Drinking Water and Sanitation (WS) and Household Socioeconomic Status

Fig. 1 represents the proportion of WS in the 23 countries in this study. Across all surveys, 35.4% of the included children had access to unprotected water, followed by protected water (32.5%) and piped water (32.1%) (Fig. 1A). Additionally, Fig. 1B demonstrates that most children utilized pit latrine toilets (62.4%), followed by no facilities (26.8%) and flush toilets (10.8%). The proportion of households with a “poor” (versus “nonpoor”) socioeconomic statuses was 48.6% overall and ranged from 31.8% (Malawi 2017) to 61.4% (Liberia 2011) (Table 1). The greatest proportion of children who were classified as having a “poor” socioeconomic status were unprotected water users (69.6%), followed by protected water users (46.5%) and piped water users (26.7%) ($P < 0.001$) (Fig. 2A). Additionally, Fig. 2B illustrates that the proportion of children with “poor” socioeconomic status who were no facility users (77.7%) was higher than the proportions of those who were pit latrine toilet users (42.6%) and flush-toilet users (8.6%) ($P < 0.001$).

<Figure 1>

<Figure 2>

Association Between Drinking Water and Sanitation (WS) and Malaria Infection

Across all surveys, the comparison of malaria infections diagnosed by microscopy among those with different WS access in different countries revealed that the prevalence rates of malaria in the unprotected water users (22.6%) and piped water users (7.5%) were both significantly lower than that in the protected water users (22.6% versus 26.8%, $p < 0.001$; 7.6% versus 26.8%, $P < 0.001$); however, this trend was not always consistent with all the surveys (Fig. 3A). Children who used no facilities were more likely to have malaria than children who used pit latrine toilets (Fig. 3B) according to microscopy (27.7% versus 17.4%, $P < 0.001$), whereas children who used flush toilets had a low tendency for malaria infection (4.5% versus 17.4%, $P < 0.001$); this trend was consistent in each survey (Fig. 3B). Data on malaria infections measured by RDTs in exposed and unexposed groups were provided by a survey, as shown in Additional file 2.

<Figure 3>

For the total population, the specific regression results for each survey based on the logistic regression model are shown in the forest plot (Fig. 4, Additional file 3). Across all surveys, unprotected water users were associated with a significantly increased malaria prevalence (aOR 1.17, 95% CI 1.07-1.27, $P = 0.001$) as measured by microscopy (Table 2, Fig. 4A), while piped water users were associated with a significantly decreased malaria prevalence (aOR 0.52, 95% CI 0.45-0.59, $P < 0.001$) as measured by microscopy (Table 2, Fig. 4B). Both results were retained when adjustments were made for age, gender, IRS in the past 12 months (when measured), ITN use, house quality, and mother's highest educational level (when measured). Moreover, no facility users had increased odds and flush-toilet users had decreased odds of malaria risk as measured by microscopy (Table 2, Fig. 4C, 4D). The overall aORs for no facility users and flush-toilet users were 1.35 (95% CI 1.24-1.47, $P < 0.001$), and 0.51 (95% CI 0.43-0.61, $P < 0.001$), respectively (Table 2, Figs. 4C, 4D). The trends of individuals diagnosed by RDTs were consistent with those of microscopy (Table 2, Additional file 3).

<Figure 4>

<Table 2>

For the stratified results, the specific regression results for each survey stratified by household socioeconomic status are shown in the forest plot (Figs. 5, 6, Additional files 4, 5). In children with a “poor” socioeconomic status, no overall associations with malaria risk were observed in the unprotected water users compared to protected water users (microscopy: aOR 1.09, 95% CI 0.99-1.21, $P = 0.083$; RDT: aOR 1.02, 95% CI 0.93-1.13, $P = 0.652$) (Fig. 5A, Additional file 4A), whereas in children with a “nonpoor” socioeconomic status, the risk of malaria in the unprotected water users was more pronounced than that in protected water users (microscopy: aOR 1.21, 95% CI 1.10-1.32, $P < 0.001$; RDT: aOR 1.24, 95% CI 1.11-1.38, $P < 0.001$) (Fig. 5B, Additional file 4B). In children with a “poor” socioeconomic status, the protective effects of piped water were still significant, and the overall aORs of the piped water users were 0.65 (95% CI 0.53-0.80, $P < 0.001$) in those diagnosed by microscopy (Fig. 5C) and 0.68 (95% CI 0.56-0.82, $P < 0.001$) in those diagnosed by RDTs

(Additional file 4C). In children with a "nonpoor" socioeconomic status, the aORs of the piped water users were 0.57 (95% CI 0.49-0.65, *P* < 0.001) in those diagnosed by microscopy (Fig. 5D) and 0.53 (95% CI 0.46-0.60, *P* < 0.001) in those diagnosed by RDTs (Additional file 4D)

<Figure 5>

Similarly, for children with a "poor" socioeconomic status who were pit latrine toilet users, the overall aORs of the no facility users were 1.14 (95% CI 1.03-1.26, *P* = 0.010) in those diagnosed by microscopy (Fig. 6A) and 1.15 (95% CI 1.05-1.25, *P* = 0.002) in those diagnosed by RDTs (Additional file 5A); for the children with a "nonpoor" socioeconomic status, the aORs were 1.46 (95% CI 1.32-1.61, *P* < 0.001) in those diagnosed by microscopy (Fig. 6B) and 1.54 (95% CI 1.38-1.72, *P* < 0.001) in those diagnosed by RDTs (Additional file 5B). Additionally, in children with a "poor" socioeconomic status, the flush-toilet users did not have significant protection from malaria infection according to microscopy; the aOR of the flush-toilet users was 0.80 (95% CI 0.55-1.17, *P* = 0.250) (Fig. 6C). In the children with a "nonpoor" socioeconomic status, the protective effects of flush-toilets (considering both microscopy and RDTs) were significant (microscopy: aOR 0.57, 95% CI 0.49-0.66, *P* < 0.001; RDT: aOR 0.53, 95% CI 0.47-0.60, *P* < 0.001) in relation to malaria risk (Fig. 6D, Additional file 5D).

<Figure 6>

Discussion

To our knowledge, this is the first analysis of the associations between WS conditions and risk of malaria among children under five years old across SSA employing data from multi-country, cross-sectional surveys. This analysis of 49 surveys (23 DHS, 24 MIS, and 2 others) found that compared to protected water and pit latrine toilets, piped water and flush toilets were associated with significantly reduced malaria prevalence rates, whereas unprotected water and no facilities were related to an increased risk of malaria after adjusting for potential confounders. However, this association was mostly influenced by the household socioeconomic status. In children with a “poor” socioeconomic status, no significant associations were observed between unprotected water and flush toilets in relation to malaria infection, whereas in children with a “nonpoor” socioeconomic status, the associations between unimproved WS conditions (including unprotected water or no facilities) and the risk of malaria appeared to be pronounced.

These findings are in line with several previous studies [8-11, 22, 23]; for example, Ayele et al. assessed various WS conditions as indicators of socioeconomic status on the prevalence of malaria in Ethiopia from December 2006 to January 2007 using a generalized additive mixed model, generalized linear mixed model with spatial covariance structure, and generalized linear mode [8-10]. All of the articles found that malaria disproportionately affected people who had a poor socioeconomic status and limited access to clean drinking water sources [8-10]. Similarly, Kinuthia et al. also observed an increased number of malaria cases associated with inappropriate WS conditions in Njoro District, Kenya, using chi-squared tests and confidence limits [11]. Furthermore, Hasyim et al. indicated that individuals who lived in unimproved sanitation environments were more frequently infected with malaria than those who lived in improved sanitation environments, even though the association between environmental sanitation and malaria prevalence was not statistically significant (OR 1.13, 95% CI 0.99-1.31, P = 0.081) [22]. Finally, as Hasyim et al. also suggested, most individuals who used open sewage systems (domestic wastewater or municipal wastewater) at home and those who did not have a sewage system were at higher risk of malaria infection (OR 1.250, 95% CI 1.095-1.427, P = 0.001) than those who used closed sewage systems, further highlighting the significance of potential larval habitats near houses [23]. All these studies were in line with our results; due to closed systems, improved WS users had a decreased risk of malaria infection.

It is well known that mosquitoes and their ecosystems are significant spatial drivers of malaria transmission. The potential larval habitats could be constructed due to the physical disturbances created by human fetching or storing unimproved drinking water (e.g., splashing water on the ground when fetching or storing unimproved water results in shallow puddles or footprints; additionally, storing unimproved drinking water creates stagnant water sources for nearby households), further increasing mosquito breeding and adult vector densities near households. The top three vector species of human malaria in our study area included *Anopheles gambiae, An. arabiensis,* and *An. funestus* (Additional file 6; the data sources were derived from country profiles based on the World Health Organization (WHO) database online because the DHS and MIS did not include entomological surveys). Among these Anopheles species, *An. gambiae* and *An. arabiensis* prefer to inhabit sunlit, shallow, temporary bodies of fresh water, such as puddles, pools, ground depressions, and hoof prints [24]. In addition, water in these larval sites is often turbid or polluted [25-27]. In contrast, *An. funestus* inhabits permanent or semipermanent bodies of fresh water with emergent vegetation, such as swamps, ponds, and lake edges [24]. This evidence suggests that closed systems with improved water are relatively inappropriate environments for Anopheles.

The association between improved WS (including protected and piped water; pit latrines and flush toilets) and the reduced risk of malaria in this study could be explained by several potential mechanisms. There are data that indicate that wealth is probably protective against malaria risk [28-34], as prevention and treatment are affordable [35-37]. In this study, among the total participants, socioeconomic status (a confounder) determined access to improved water, sanitation and hygiene practices and malaria prevention practices, all of which affected the level of malaria risk [8-10]. We can easily see that the highest proportion of children with a “poor” socioeconomic status were unimproved WS users (Fig. 2). To address the confounding nature of socioeconomic status, the results of WS conditions and prevalence of malaria in children under five years old were stratified by household socioeconomic status, and the aORs within each socioeconomic level were calculated. In the stratified results, the mixed effects of wealth weighed heavily upon the WS conditions related to malaria risk in the children with a “poor” socioeconomic status (Table 2). This nonsignificant phenomenon was mostly attributed to the decreased proportion of improved water access in children with a “poor” socioeconomic status (Fig. 2). This result simply showed that malaria infection rates were the highest among the poorest populations who had little or no access to safe drinking water and toilets.

Regarding the overall OR results between children with a “poor” or “nonpoor” socioeconomic status, the effects of WS and malaria infections were more obvious in the children with a “nonpoor” socioeconomic status (Table 2), demonstrating that it is urgent to improve WS conditions in nonpoor populations if economic circumstances permit. The important finding in this study was that in the children with a “nonpoor” socioeconomic status, the effects of WS conditions were still significant even without the confounding effects of socioeconomic status. This may be explained by the fact that unimproved WS users may indirectly increase the likelihood of contracting *Plasmodium falciparum* by increasing the risk of other waterborne parasitic diseases, such as soil transmitted helminth diseases (STHs, such as *hookworm, Strongyloides stercoralis*) or *Schistosoma haematobium* infections directly [38-42].

According to previous studies, we hypothesize that children who have STHs or schistosomiasis may be more susceptible to malaria infection [38-45]. There are many mechanisms to support this theory. For example, *Strongyloides stercoralis* could increase the risk of *Plasmodium* infection because of the predominance of Th2 responses in young children [38, 39]. Furthermore, schistosomiasis infection alone or in combination with trichiasis or hookworm infection can apparently increase the risk of *P. falciparum* by modulating the immune system [41-43]. Additionally, helminth-infected individuals can present decreased cutaneous reactivity to anopheline bites, which may theoretically facilitate the success of sporozoite introduction [44, 45]. There are also many previous studies exploring the risk factors of STH or *Schistosoma haematobium* and malaria coinfections, and all these articles indicate that unsafe WASH conditions are the primary risk factors associated with such coinfections [38, 46, 47]; this suggest that clean WS conditions can help prevent malaria infections. Finally, the most important distinction between unimproved water and improved water is whether drinking water is treated. In this study, it was apparent that a high proportion of disposed unprotected water was linked to a relatively low prevalence of malaria (Additional file 7).

The strength of this study includes the large and comprehensive dataset obtained from the DHS and MIS. The analysis aimed to elucidate the influence of household WS on malaria risk stratified by household socioeconomic status on a large scale for the first time. Some studies have indicated that many high-income countries eliminated malaria without malaria-specific interventions; for example, malaria in Europe and North America declined as a result of improved living conditions and increased wealth [48]. As Lucy Tusting et al. stated, halting existing malaria control efforts is not recommended; however, we believe there is a need to increase investment in interventions that support socioeconomic development [33]. Although wealth status is a combination of multiple factors, it is important to know which specific aspect of wealth affects malaria infection. In this study, the mixed effects of socioeconomic status were eliminated, and we focused on exploring the relationship between WS and malaria. Water-associated vector-borne diseases (including malaria and many NTDs) continue to be a major public health problem in many developing countries [7]. However, remarkable and significant progress in the prevention and control of water-related vector-borne diseases has been made in many regions, primarily through the strengthening of vector control strategies, case detection, and treatment methods [1, 7]. These present strategies must be expanded. Strengthening of intersectoral links with improving WASH may provide a method to increase the pace of malaria elimination. Although the SDGs have offered unprecedented opportunities to improve health by dramatically increasing the availability and use of WASH services [7], the coverage of safe WASH in SSA is still very low. These findings suggest that efforts should be redoubled to improve WS conditions, which should be considered an important component of malaria prevention and control. Finally, the use of pooled observational multicountry data eliminated many biases, including publication, selection, and measurement biases and selective outcome reporting, which are typically present in traditional systematic reviews and meta-analyses.

This study has several limitations. First, it did not explore the association between drinking water storage sites and malaria infection. However, data on drinking water storage sites were absent in many surveys in this study, making it too difficult to link the various types of drinking water sources with their storage sites. Further studies are needed to investigate the influence of storage sites in depth. Second, although the results of WS conditions and malaria prevalence among children under 5 years old were stratified by household socioeconomic level, this stratification (“poor” versus “nonpoor”) in this study was not very prudent because of the original stratifications in the

DHS and MIS were grouped into five categories, namely, “poorest, poor, middle, rich, and richest”. There may still be residual confounding caused by wealth status in our study. However, considering the proportion of children with a “poor” socioeconomic status (approximately 50%) (Table 1), this study classified the total children into two groups to avoid an uneven sample distribution. Furthermore, entomological surveys, particularly among unimproved drinking water sources and unimproved sanitation facilities in SSA, are important to understand how the type of Anopheles species and the behavior of Anopheles species affect malaria transmission and to assist in addressing confounding factors involving the various ecological niches of distinct species. Unfortunately, in the DHS and MIS surveys, entomological surveys were not conducted. Finally, due to the lack of examination for other parasitic diseases, such as STHs or schistosomiasis, in the DHS Program, the proposed effect of coinfections is still under speculation in this study; it would be beneficial to add coinfection investigations to the DHS and MIS in the future.

Conclusions

In conclusion, WS conditions were important risk factors for malaria among children under five years old across SSA after adjustment for age, gender, IRS in the past 12 months and insecticide-treated use, house quality, and mother’s highest educational level; Unimproved WS access (unprotected water; no facility) was related to a relatively high risk of malaria. Furthermore, this association was mostly influenced by socioeconomic status. However, the malaria risk associated with unimproved WS was more pronounced among the children with a “nonpoor” socioeconomic status. These findings indicated incremental improvements to WS in SSA might be considered a potential intervention for the prevention and control of malaria in the long term.

Abbreviations

SSA: sub-Saharan Africa; LLINs: long-lasting insecticidal mosquito nets; ITNs: insecticide treated nets; IRS: indoor residual spraying; WHO: World Health Organization; WASH: Water, Sanitation, and Hygiene; NTDs: neglected tropical diseases; WS: drinking water and sanitation; SDGs: Sustainable Development Goals; DHS: Demographic and Health Survey; MIS: Malaria Indicator Surveys; RDT: rapid diagnostic test; aOR: adjusted odds ratio; 95% CI: 95% confidence interval; STHs: soil transmitted helminth diseases

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Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

The DHS Program has the compliance with ethics requirements.

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Figure Legends

Figure 1. Proportion of children under 5 years old who used various WS conditions

(A) drinking water, (B) sanitation.

Figure 2. The percentage of children with a “poor” socioeconomic status and different WS sources for each national survey

(A) The association between socioeconomic status and drinking water sources.

(B) The association between socioeconomic status and sanitation conditions.

Chi-square (χ^2) tests were used for assessing the differences in the proportion of children with a “poor” socioeconomic status among the various WS conditions. The *P*-values of all the χ^2 tests in Fig. 2 were less than 0.001. WS = Drinking Water and Sanitation.

Figure 3. Prevalence of malaria infection in different WS users identified by microscopy for each national survey

(A) The association between malaria prevalence and different drinking water sources. (B) The association between malaria prevalence and different sanitation conditions. Chi-square (χ^2) tests or Fisher’s exact tests were used to assess the differences in malaria infection between the various WS users. The infections were determined by microscopy. #*P*-values were obtained with Fisher’s exact test. *P*-values (> 0.05) were obtained with χ^2 tests or Fisher’s exact tests; all unmarked *P*-values are less than 0.001. WS = Drinking Water and Sanitation.

Figure 4. Forest plots of the effects of WS conditions on malaria infection among the total children diagnosed by microscopy

The ORs and 95% CIs for the risk of infection as determined by microscopy in relation to (A) Unprotected Water, (B) Piped Water, (C) No Facility, and (D) Flush toilets in each survey were measured by logistic regression models with adjustment for age, gender, IRS, ITN use, house quality, and mother's highest educational level. The datapoints, lines, boxes, and vertical dashed lines represent the ORs, 95% CIs, weight that each survey contributed to the overall OR, and overall 95% CIs, respectively. WS = Drinking Water and Sanitation; OR = Odds Ratio; 95% CI = 95% Confidence Interval.

Figure 5. Forest plots of the effects of drinking water sources on malaria infection diagnosed by microscopy based on socioeconomic status

(A) Unprotected Water among children with a "poor" socioeconomic status, (B) Piped Water among children with a "poor" socioeconomic status, (C) Unprotected Water among children with a "nonpoor" socioeconomic status, (D) Piped Water among children with a "nonpoor" socioeconomic status. Malaria infections were determined by microscopy. Datapoints, lines, boxes, and vertical dashed lines represent ORs, 95% CIs, weight that each survey contributed to the overall OR, and overall 95% CIs, respectively. OR = Odds Ratio; 95% CI = 95% Confidence Interval.

Figure 6. Forest plots of the effects of sanitation conditions on malaria infection diagnosed by microscopy based on socioeconomic status

(A) No Facility among children with a “poor” socioeconomic status, (B) Flush toilet among children with a “poor” socioeconomic status, (C) No Facility among children with a “nonpoor” socioeconomic status, (D) Flush toilets among children with a “nonpoor” socioeconomic status. Malaria infections were diagnosed by microscopy. Datapoints, lines, boxes, and vertical dashed lines represent ORs, 95% CIs, weight that each survey contributed to the overall OR, and overall 95% CIs, respectively. OR = Odds Ratio; 95% CI = 95% Confidence Interval.

Table Legends

Table 1. Characteristics of children under five years old across SSA who were included in the analysis

All surveyed children were 0-59 months. *Valid percent was measured among the valid records because some records on the mother’s highest educational level and IRS were missing in some surveys. RDT = Rapid Diagnostic Test; DRC = Democratic Republic of the Congo. ITN = Insecticide-treated Net; IRS = Indoor Residual Spraying.

Table 2. Meta-analysis of the associations between WS conditions and malaria infections among the total children, children with a “poor” socioeconomic status, and children with a “poor” socioeconomic status

*Some surveys were excluded in the meta-analysis due to the unavailability of logistic regression results. Each logistic regression model was adjusted for age, gender, IRS, ITN use, house quality, and mother’s highest educational level.

OR = Odds Ratio; 95% CI = 95% Confidence Interval; WS = Drinking Water and Sanitation; RDT = Rapid Diagnostic Test.

Table 1

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Country and Year	N	Mean Age (Months)	Male (%)	Mother's Highest Educational Level (No Education Valid Percent)*	ITN Use (%)	IRS in Past 12 mo (Valid Percent)*	Traditional House (%)	Socioeconomic Status (The Poor Percent)	Parasite Rate (%)	
									Microscopy	RDT
Angola 2015-2016	6746	31.9	50.4	36.8	21.2	1.4	71.2	53.3	-	16.5
Angola 2011	3259	32.1	48.1	35.4	21.9	-	69.8	47.1	9.8	12.5
Angola 2006-2007	2573	32.2	44.1	32.3	17.8	4.2	61.6	54.4	-	22.2
Benin 2011-2012	3709	33.2	51.7	74.7	69.6	12.6	62.3	44.9	29.9	27.1
Burkina Faso 2014	6090	32.5	50.8	81.6	71.5	0.7	82.4	44.7	47.6	64.5
Burkina Faso 2010	6088	32.1	51.4	83.0	44.5	1.6	77.5	40.9	65.0	75.6
Burundi 2016-2017	5755	32.5	50.3	44.0	36.8	0.8	84.3	40.0	24.4	34.8
Burundi 2012	3710	32.8	50.3	47.6	48.0	4.5	86.2	42.0	16.2	20.5
Cameroon 2011	5367	31.7	49.1	23.3	15.2	3.1	63.0	43.1	-	32.6
Coate D Ivoire 2011-2012	3762	31.6	43.6	67.9	37.0	1.4	43.0	50.5	16.1	42.0
DRC 2013-2014	8159	32.5	49.8	22.0	46.0	-	89.8	49.9	26.3	35.9
Gambia 2013	3104	31.4	52.0	66.0	38.1	59.1	47.5	54.4	0.5	1.8
Ghana 2016	3071	32.3	51.2	34.8	52.0	18.8	58.8	55.5	23.0	32.5
Ghana 2014	2705	32.7	52.1	36.8	38.9	21.6	38.1	54.0	28.8	40.8
Guinea 2012	3192	32.3	52.3	79.7	20.3	1.8	57.8	44.3	43.8	45.7
Kenya 2015	3352	33.3	50.5	21.3	45.1	-	98.5	53.0	5.3	9.4
Liberia 2016	2569	33.3	49.6	43.5	39.2	0.8	67.5	54.7	-	50.3
Liberia 2011	2888	33.1	50.5	49.9	32.8	10.3	75.7	61.4	32.5	52.3
Liberia 2009	4766	32.5	49.5	54.4	25.0	-	77.1	55.7	33.3	37.4
Madagascar 2016	6734	32.5	51.6	26.8	69.6	-	90.3	50.1	5.5	3.7

Madagascar 2013	5322	32.7	50.9	32.3	37.7	41.4	92.6	47.6	6.5	7.5
Madagascar 2011	6132	33.7	50.6	32.6	70.5	50.7	90.2	50.0	4.1	6.2
Malawi 2017	2295	33.7	50.2	10.1	54.6	-	65.5	31.8	16.9	26.0
Malawi 2014	1893	32.4	50.5	12.7	62.4	7.0	71.0	38.2	26.0	29.9
Malawi 2012	2074	32.3	47.1	18.3	44.4	8.9	74.9	37.8	24.6	37.8
Mali 2015	7277	32.7	50.9	78.0	62.8	6.6	78.2	43.5	35.0	31.5
Mali 2012-2013	4653	33.1	50.9	82.9	62.4	8.3	84.1	41.3	48.7	44.1
Mozambique 2015	4429	32.4	48.8	27.1	38.3	15.1	74.8	36.7	-	31.7
Mozambique 2011	4874	31.8	49.0	34.8	28.6	23.3	79.9	36.9	29.9	34.0
Nigeria 2015	5530	32.8	50.4	44.0	34.2	1.6	49.6	40.2	27.3	41.3
Nigeria 2010	4907	32.6	50.7	47.3	27.5	1.0	58.5	37.5	38.3	46.3
Rwanda 2017	2615	32.2	52.1	-	58.9	17.2	75.9	40.3	6.6	10.9
Rwanda 2014-2015	3416	32.1	51.0	14.9	55.8	-	82.1	45.9	2.2	7.6
Rwanda 2010	3931	33.4	50.6	19.0	63.2	-	87.2	43.3	1.2	2.4
Senegal 2017	9772	32.6	50.7	60.8	57.6	8.7	49.1	55.2	0.6	1.6
Senegal 2016	12091	32.9	50.7	71.4	57.2	10.0	52.9	59.6	1.0	1.4
Senegal 2015	6046	32.8	50.5	71.6	51.5	9.7	50.6	58.0	0.4	1.0
Senegal 2014	12118	32.5	50.3	72.2	42.2	15.6	55.9	57.7	2.8	2.9
Senegal 2012-2013	5889	32.2	50.1	72.1	44.7	18.4	55.5	53.7	3.7	4.1
Senegal 2010-2011	3852	32.6	52.4	74.9	39.0	14.8	58.4	56.4	3.7	3.3
Sierra Leone 2016	6328	32.1	50.5	64.2	36.9	1.3	66.7	51.5	41.9	56.3
Tanzania 2017	7125	32.4	50.3	24.7	44.9	-	69.0	47.4	-	8.4
Tanzania 2015-2016	10047	35.7	50.1	21.9	45.7	9.3	66.7	43.6	5.1	12.7
Tanzania 2011-2012	7361	32.1	50.6	24.7	59.7	27.6	76.6	44.2	4.7	10.0
Togo 2017	3174	32.3	49.7	44.8	59.9	-	46.8	54.8	29.6	47.2
Togo 2013-2014	3181	32.5	50.6	47.5	29.9	-	59.0	53.2	37.8	39.3

Uganda 2016	4711	32.5	50.4	13.3	44.3	11.3	75.9	47.2	-	33.2
Uganda 2014-2015	4831	30.2	49.0	22.8	67.3	8.6	80.1	52.7	19.9	32.6
Uganda 2009	3967	30.2	49.5	23.6	28.0	-	100.0	46.2	43.6	53.1
Total	247,440	32.6	50.2	47.3	45.8	12.5	69.7	48.6	18.8	24.2

Table 1. Characteristics of children under five years old across SSA who were included in the analysis

All surveyed children were 0-59 months. *Valid percent was measured among the valid records because some records on the mother's highest educational level and IRS were missing in some surveys. RDT = Rapid Diagnostic Test; DRC = Democratic Republic of the Congo. ITN = Insecticide-treated Net; IRS = Indoor Residual Spraying.

Table 2
Click here to view linked References

Table 2. Meta-analysis of the associations between WS conditions and malaria infections among the total children, children with a "poor" socioeconomic status, and children with a "poor" socioeconomic status

	Number of surveys*	Total Children OR (95%CI)	Number of surveys*	Poor Children OR (95%CI)	Number of surveys*	Non-poor Children OR (95%CI)
Microscopy						
Protected water (Reference)	-	1.00	-	1.00	-	1.00
Unprotected water	41	1.17 (1.07, 1.27)	41	1.09 (0.99, 1.21)	39	1.21 (1.10, 1.32)
Piped water	41	0.52 (0.45, 0.59)	40	0.65 (0.53, 0.80)	40	0.57 (0.49, 0.65)
Pit latrine (Reference)	-	1.00	-	1.00	-	1.00
No facility	40	1.35 (1.24, 1.47)	39	1.14 (1.03, 1.26)	35	1.46 (1.32, 1.61)
Flush toilet	32	0.51 (0.43, 0.61)	14	0.80 (0.55, 1.17)	32	0.57 (0.49, 0.66)
RDT						
Protected water (Reference)	-	1.00	-	1.00	-	1.00
Unprotected water	48	1.11 (1.02, 1.22)	48	1.02 (0.93, 1.13)	47	1.24 (1.11, 1.38)
Piped water	47	0.49 (0.43, 0.57)	46	0.68 (0.56, 0.82)	47	0.53 (0.46, 0.60)
Pit latrine	-	1.00	-	1.00	-	1.00

(Reference)						
No facility	48	1.38 (1.27, 1.50)	48	1.15 (1.05, 1.25)	42	1.54 (1.38, 1.72)
Flush toilet	44	0.46 (0.39, 0.53)	24	0.71 (0.56, 0.91)	44	0.53 (0.47, 0.60)

*Some surveys were excluded in the meta-analysis due to the unavailability of logistic regression results. Each logistic regression model was adjusted for age, gender, IRS, ITN use, house quality, and mother’s highest educational level.

OR = Odds Ratio; 95% CI = 95% Confidence Interval; WS = Drinking Water and Sanitation; RDT = Rapid Diagnostic Test.

Fig1

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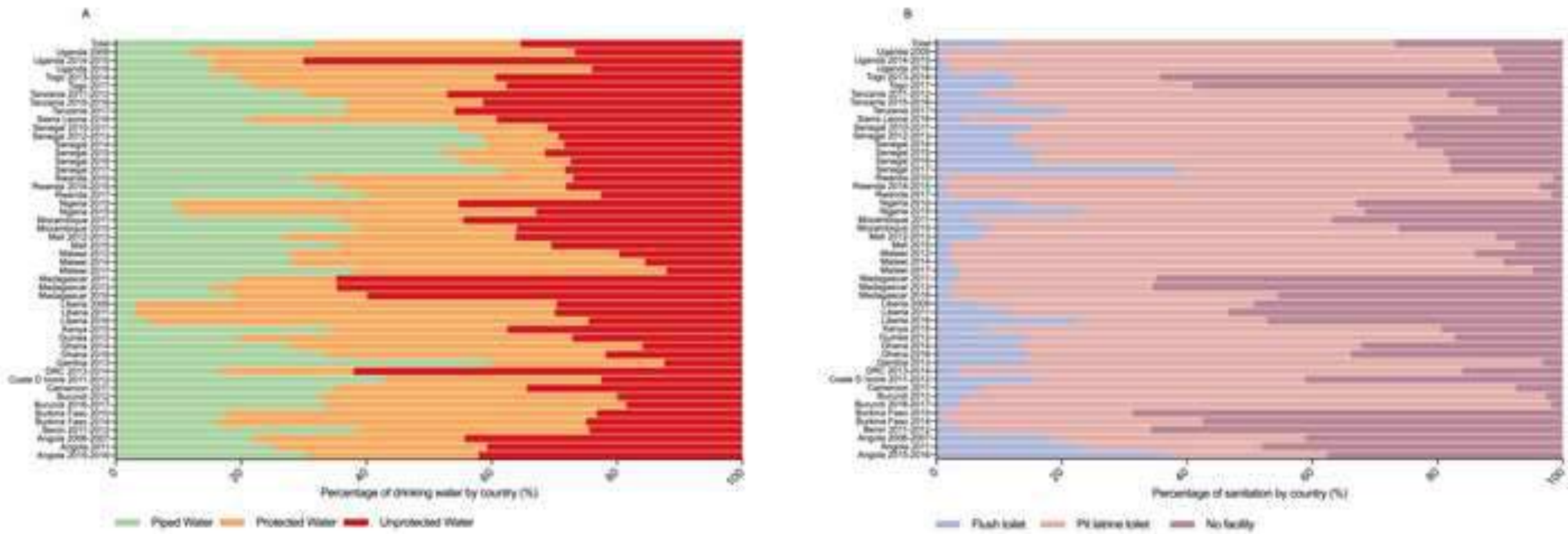

Fig2
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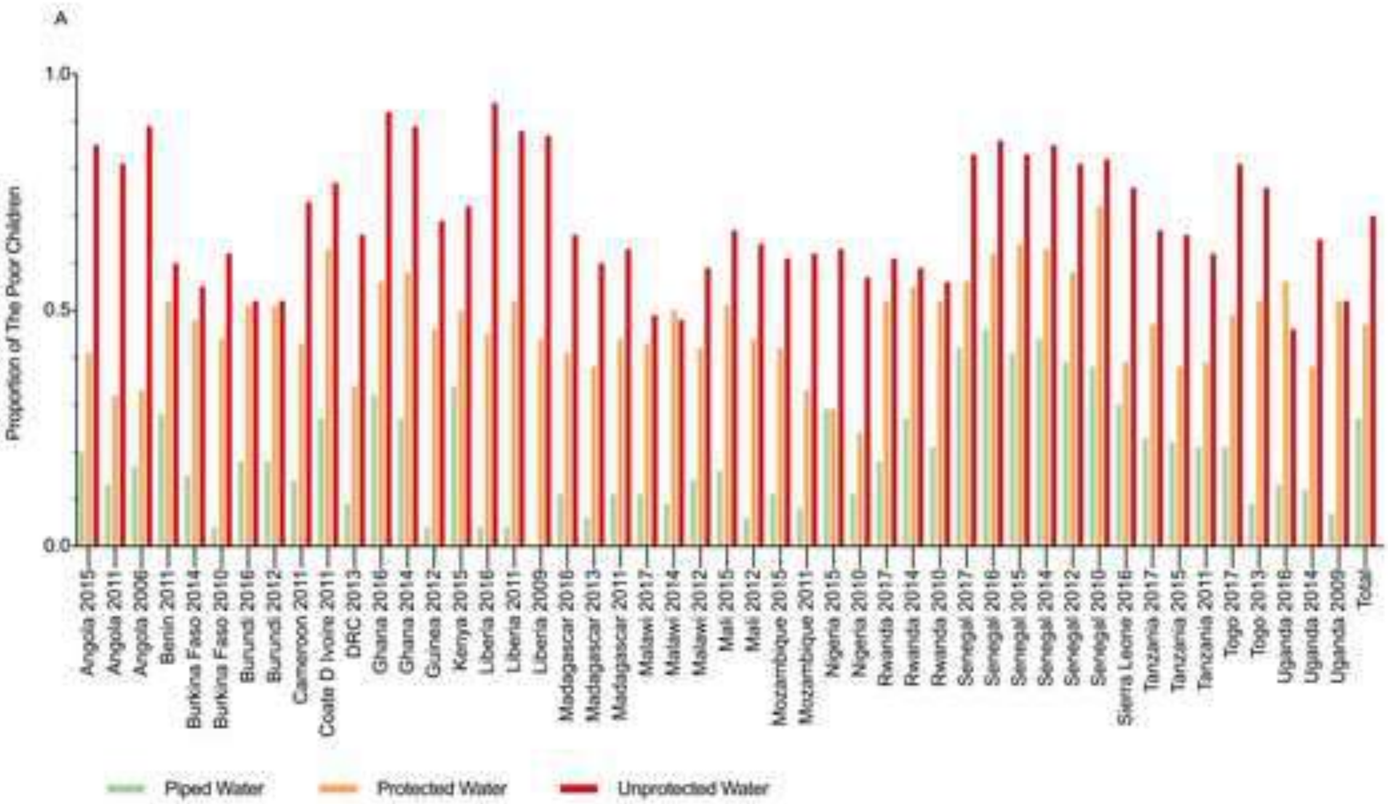

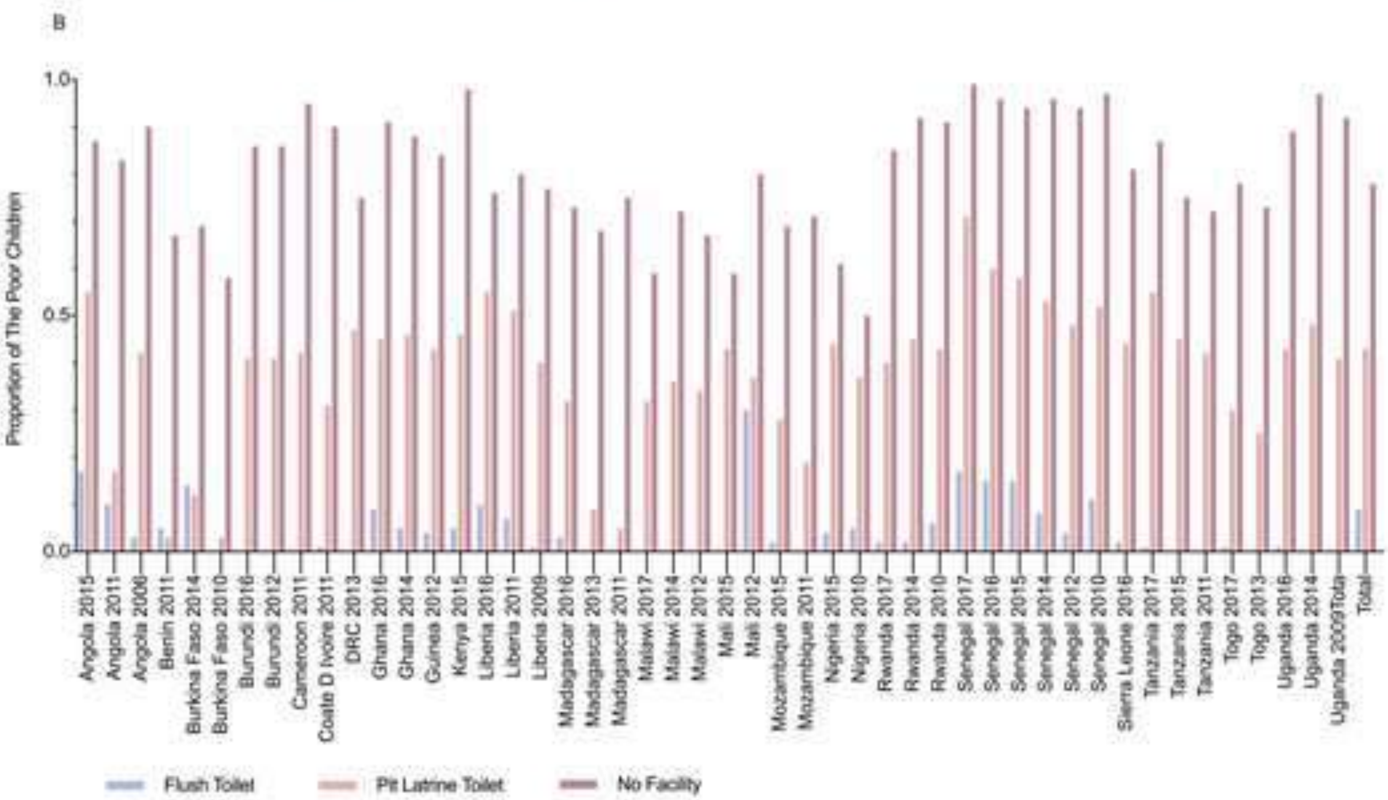

Fig3

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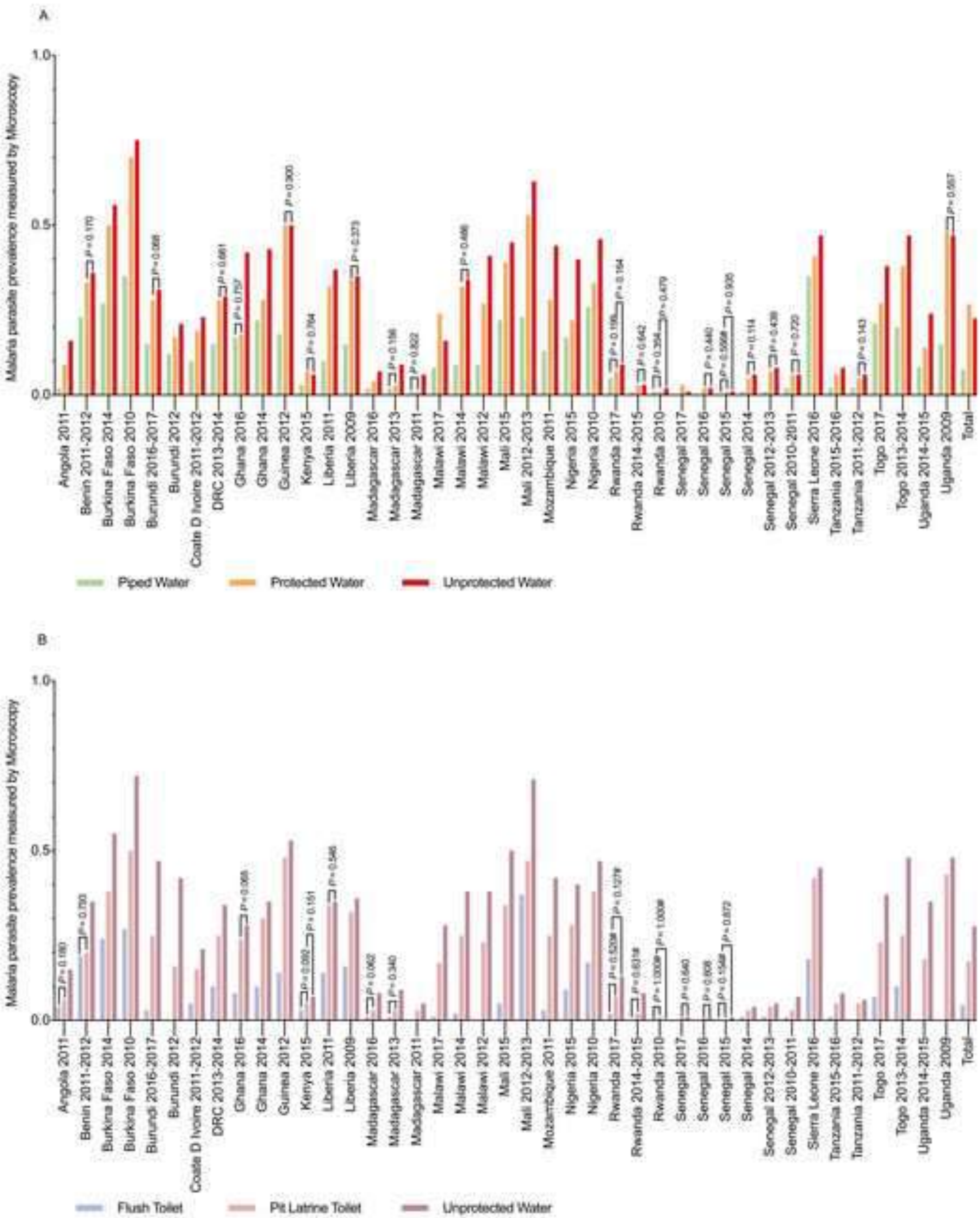


Fig4

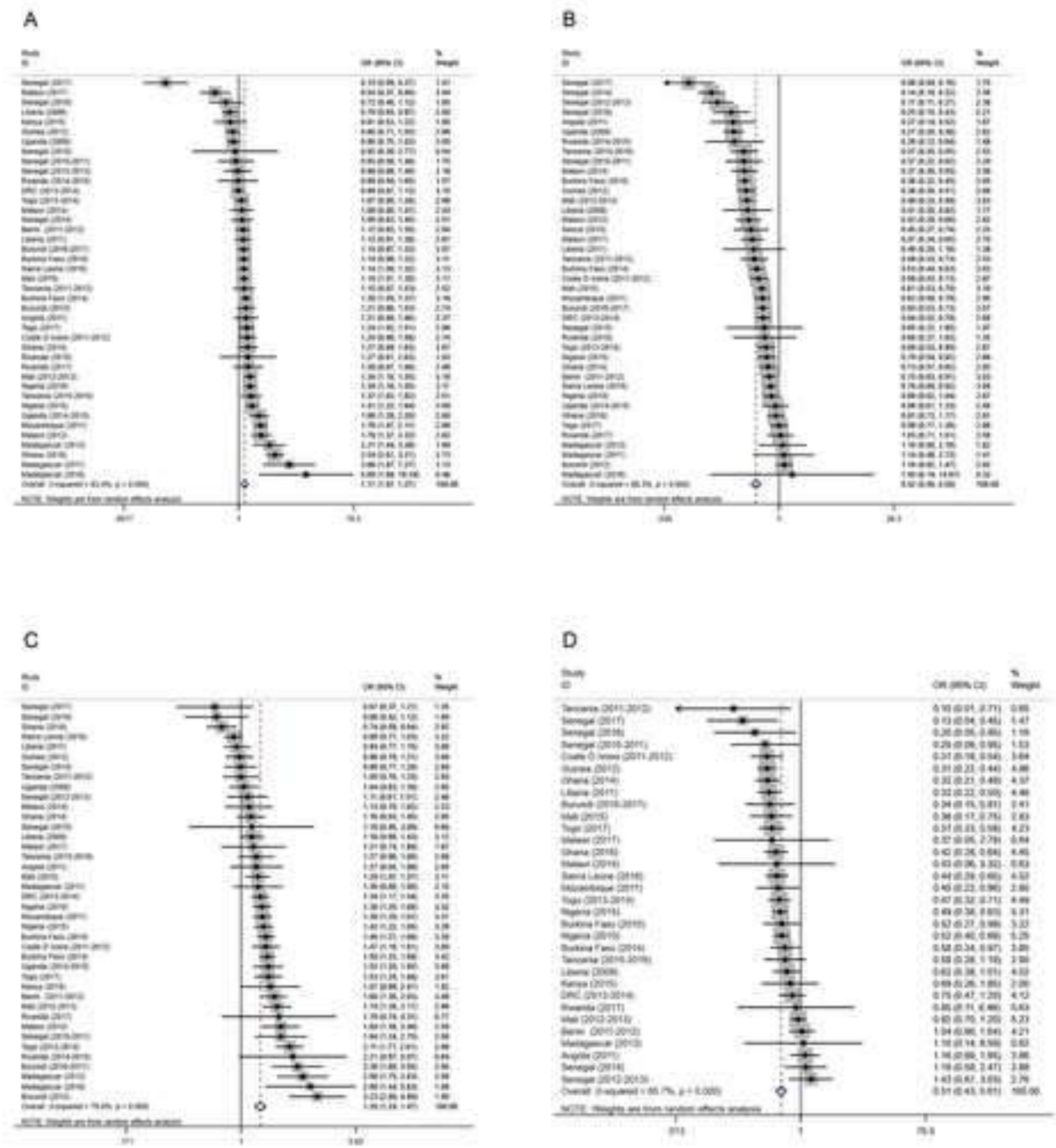


Fig5

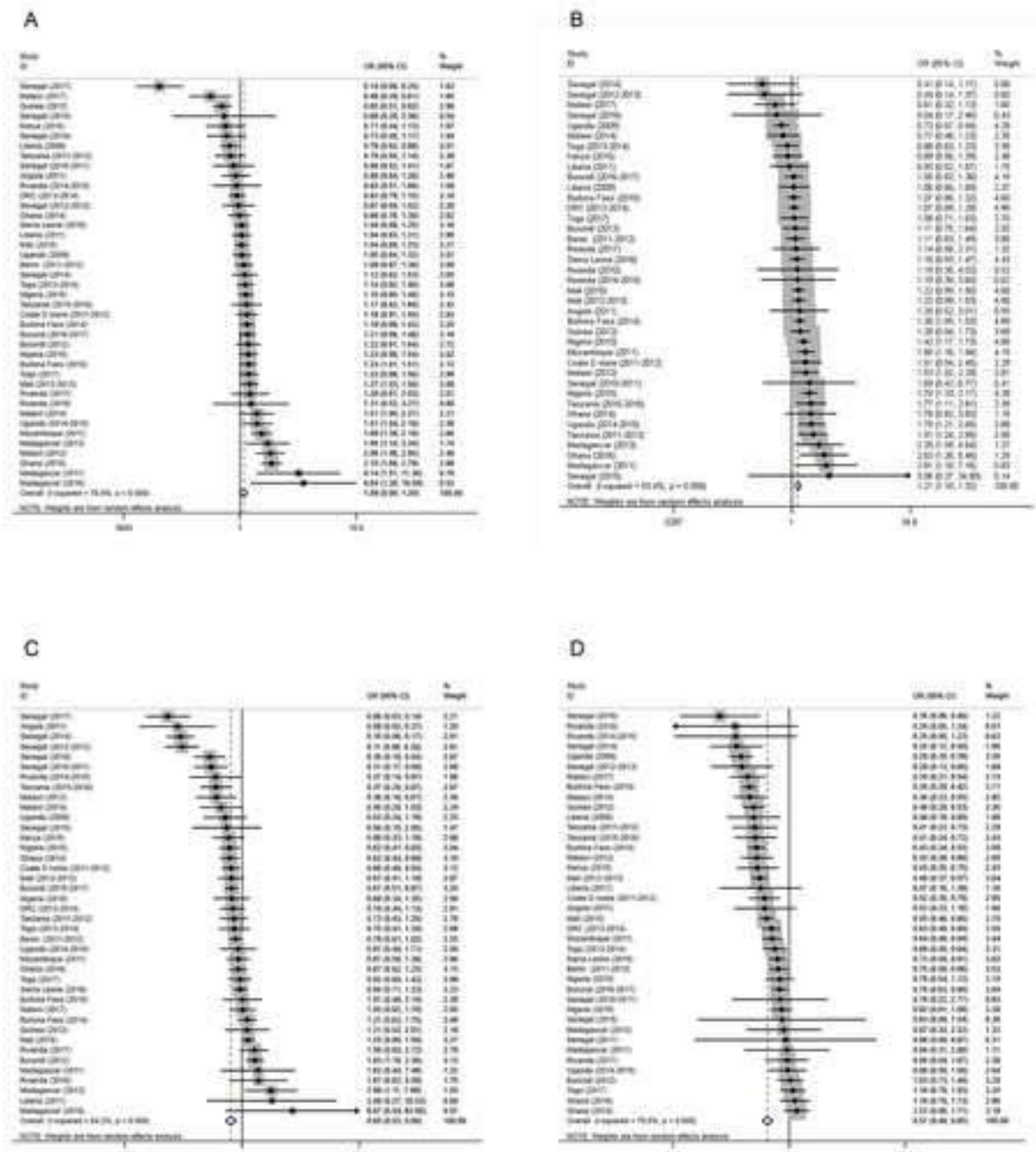
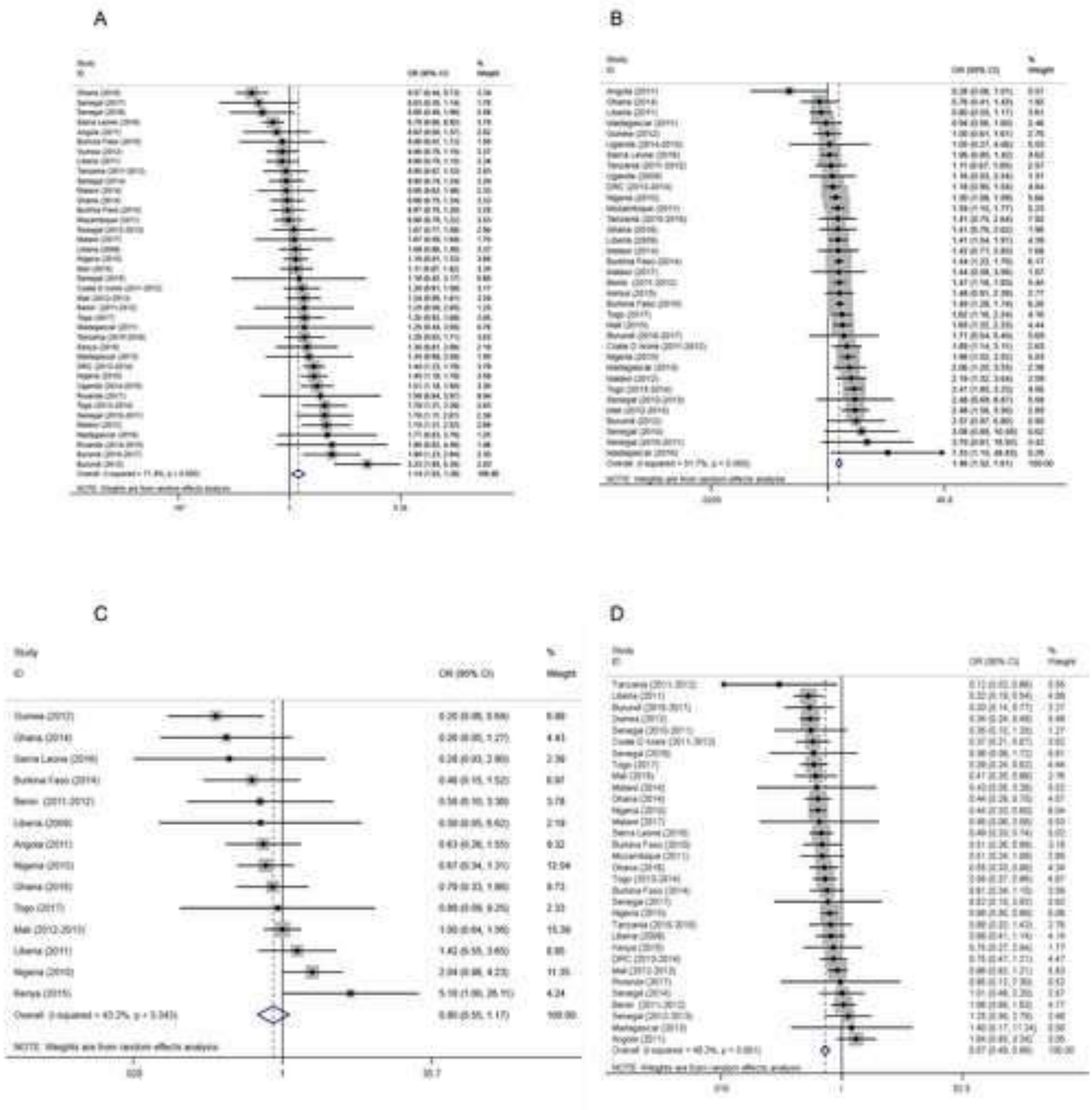


Fig6



***Conflict of interest**

Conflict of Interest

The authors have declared no conflict of interest

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Compliance with Ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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Research Highlights

1. Drinking water and sanitation is a risk factor to malaria infection.

2. Wealth brought mixed effects of the relationship between WS and malaria.

3. The associations between WS and malaria were more pronounced among the non-poor children.

4. This pooling multi-country data eliminates many bias seen in traditional meta-analysis.

5. Improved drinking water and sanitation seemed to be promising in preventing malaria.

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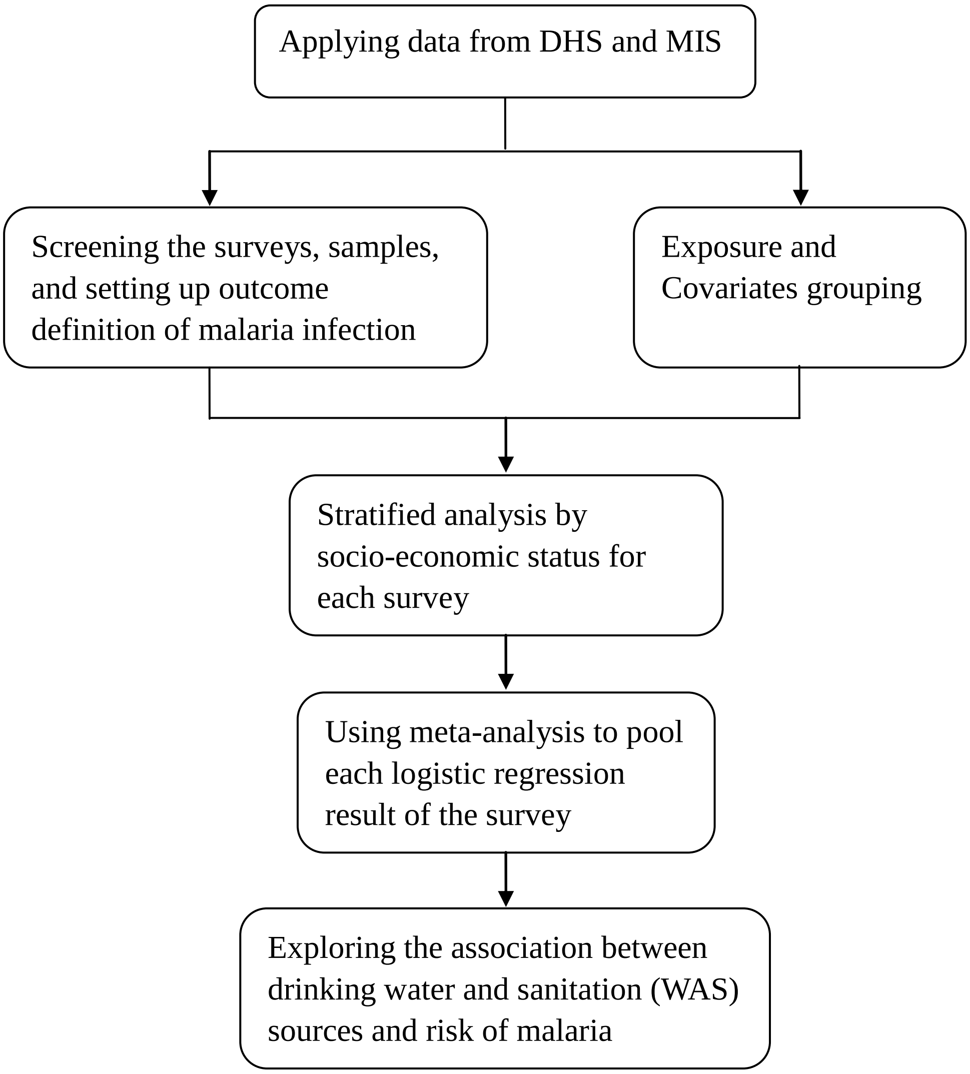
*Graphical Abstract

Graphical Abstract

Flowchart of the method to explore the association between the type of WS and malaria infection among children under five years across sub-Saharan Africa



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Drinking water and sanitation conditions are associated with the risk of malaria among children under five years old in sub-Saharan Africa: A logistic regression model analysis of national survey data

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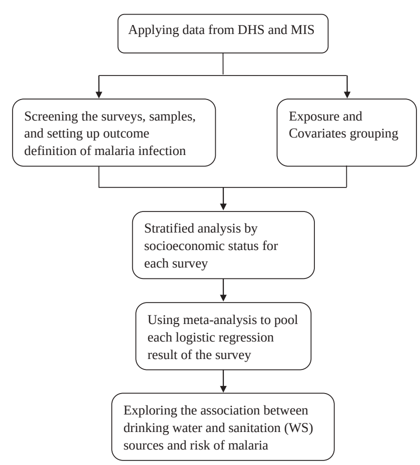
HIGHLIGHTS

- Drinking water and sanitation is a risk factor to malaria infection.
- Wealth brought mixed effects of the relationship between WS and malaria.
- The associations between WS and malaria were more pronounced among the non-poor children.
- This pooling multi-country data eliminates many bias seen in traditional meta-analysis.
- Improved drinking water and sanitation seemed to be promising in preventing malaria.

GRAPHICAL ABSTRACT

Flowchart of the method to explore the association between the type of WS and malaria infection among children under five years across sub-Saharan Africa.



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ABSTRACT

Current efforts for the prevention of malaria have resulted in notable reductions in the global malaria burden; however, they are not enough. Good hygiene is universally considered one of the most efficacious and straightforward measures to prevent disease transmission. This work analyzed whether improved drinking water and sanitation (WS) conditions were associated with a decreased risk of malaria infection. Data were acquired through surveys published between 2006 and 2018 from the Demographic and Health Program in sub-Saharan Africa (SSA). Multiple logistic regression was used for each national

Abbreviations: SSA, sub-Saharan Africa; LLINs, long-lasting insecticidal mosquito nets; ITNs, insecticide treated nets; IRS, indoor residual spraying; WHO, World Health Organization; WASH, water, sanitation, and hygiene; NTDs, neglected tropical diseases; WS, drinking water and sanitation; SDGs, sustainable development goals; DHS, Demographic and Health Survey; MIS, Malaria Indicator Surveys; RDT, rapid diagnostic test; aOR, adjusted odds ratio; 95% CI, 95% confidence interval; STHs, soil transmitted helminth diseases.

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survey to identify the associations between WS conditions and malaria infection diagnosed by microscopy or a malaria rapid diagnostic test (RDT) among children (0–59 months), with adjustments for age, gender, indoor residual spraying (IRS), insecticide-treated net (ITN) use, house quality, and the mother's highest educational level. Individual nationally representative survey odds ratios (ORs) were combined to obtain a summary OR using a random-effects meta-analysis. Among the 247,440 included children, 18.8% and 24.2% were positive for malaria infection based on microscopy and RDT results, respectively. Across all surveys, both unprotected water and no facility users were associated with increased malaria risks (unprotected water: aOR 1.17, 95% CI 1.07–1.27, $P = 0.001$; no facilities: aOR 1.35, 95% CI 1.24–1.47, $P < 0.001$; respectively), according to microscopy, whereas the odds of malaria infection were 48% and 49% less among piped water and flush-toilet users, respectively (piped water: aOR 0.52, 95% CI 0.45–0.59, $P < 0.001$; flush toilets: aOR 0.51, 95% CI 0.43–0.61, $P < 0.001$). The trends of individuals diagnosed by RDT were consistent with those of individuals diagnosed by microscopy. Risk associations were more pronounced among children with a "nonpoor" socioeconomic status who were unprotected water or no facility users. WS conditions are a vital risk factor for malarial infection among children (0–59 months) across SSA. Improved WS conditions should be considered a potential intervention for the prevention of malaria in the long term.

Introduction

Malaria is one of the most severe public health problems, posing significant risks to the lives of children, especially in sub-Saharan Africa (SSA). Although cases of malaria have decreased by an estimated 20 million since 2010 [1], there was no significant progress in reducing the number of global cases from 2015 to 2017 [1]. Current efforts to prevent malaria mainly include preventive and symptomatic treatment with antimalarial compounds, consisting of artemisinin-based combination therapies [2], as well as vector control with long-lasting insecticidal mosquito nets (LLINs) and indoor residual spraying (IRS) [3,4]; these methods have resulted in reductions in case incidence and mortality. However, increasing evidence has revealed that these efforts can only go so far [1,5]. Therefore, we need to determine and invest in additional effective measures to tackle the complex challenges.

Good hygiene is universally known as one of the most efficacious and straightforward measures to prevent disease transmission [6]. To date, the water, sanitation and hygiene (WASH) component of the strategy has received little attention, and the potential to link WASH efforts with malaria and neglected tropical disease (NTD) transmission has been largely untapped [7]. Some studies explored the effect of water and sanitation (WS) on malaria in Ethiopia and Kenya on a small scale [8–11], but there are no clear existing studies that have comprehensively evaluated the association between different types of WS conditions and malaria infection among children under five years old across a broad epidemic region, such as SSA. Considering the target date for the malaria roadmap and for the Sustainable Development Goal (SDG) of universal access to basic WASH in communities, schools, and health care facilities is both 2030 [7,12], the primary hypothesis was whether the redoubling of efforts to improve WS and its recognition as a new policy for the prevention and control of malaria transmission can contribute to the achievement of malaria elimination targets from 2016 to 2030.

It is well known that Demographic and Health Survey (DHS) and Malaria Indicator Survey (MIS) are national cross-sectional surveys that provide data for many indicators in the areas of health, populations, and nutrition [13–15]. Each DHS survey usually takes an average of 18–20 months and is executed in four phase [13]. Although most of the collected variables are different in each survey [14,15], the types of WS sources used by children under five years old are meticulously classified, and the available data provide a convenient condition to comprehensively evaluate the effect of WS conditions on the risk of malaria on a large scale.

In this study, using all the available data derived from DHS and MIS in SSA, a model analysis of the relationship between WS and malaria was performed. Specifically, the hypothesis that the odds of malaria infection in children under 5 years old with access to improved WS conditions across SSA are lower than those in children with access to unimproved WS conditions across SSA was tested. This is the most comprehensive study of the relationship between WS conditions and malaria across SSA to date, and it is also the first to demonstrate the effects between drinking water and sanitation use in relation to malaria prevalence stratified by household socioeconomic status on a large scale.

Methods

Study design and data sources

A model analysis of individual-level data that were acquired through surveys published between 2006 and 2018 and performed by the DHS Program in SSA was conducted. The cross-sectional survey data used in this study had been provided by the DHS Program. First, surveys were excluded if the data on malaria infection in children or information on WS conditions were not complete. Second, participants in each survey were excluded if there was no data or ambiguous data on their WS use (these variables in the DHS and MIS were always represented in the form of "do not know" or "others") or if their age was over 59 months. Only children under five years old were included in this study because they (including infants) are the most vulnerable group, especially in high-transmission areas of the world [16]. More importantly, only this age group was tested for malaria infection during all the DHS and MIS surveys. Then, each national DHS and MIS survey on the exposure to various WS conditions and risk of malaria was separately analyzed for the outcome definition, exposure and covariate groupings, and stratified analysis by household socioeconomic status. Finally, to obtain a summary OR, individual national survey ORs obtained by multivariable logistic regression were synthesized through a random-effects meta-analysis.

Outcome definition

The endpoint was the participants' malaria status as measured by a malaria rapid diagnostic test (RDT) or microscopy using thick or thin blood smears. A positive result by either of these two test methods indicated a malaria case. Because the microscopy results of the participants from Angola 2015–2016, Angola 2006–2007, Cameroon 2011, Liberia 2016, Mozambique 2015, Tanzania 2017, and Uganda 2016 were not available, only the RDT results for these participants were recorded in the aforementioned years.

Exposure: drinking water and sanitation (WS)

The DHS and MIS classified drinking water sources into five groups (piped water, tube well water, dug well, surface water, others), and they categorized sanitation sources into three groups (flush or pour flush-toilet, pit latrine toilet, and no facility). In this study, the DHS/MIS sanitation classifications were used. However, drinking water sources were condensed into three groups (piped water in accordance with the DHS/MIS definition, protected water, and unprotected water) [10]. Protected water was obtained from a tube well or borehole, protected well, protected spring, tanker truck, cart with a small tank, bicycle with jerrycans, bottles, or sachets [10]. Unprotected water was obtained from an unprotected well, unprotected spring, river, dam, lake, pond, stream or the rain [10].

Covariates

Information on the participants' age, gender, IRS in the past 12 months, insecticide-treated net (ITN) use, house quality, mother's highest educational level, and socioeconomic status was collected. For these covariates, age (in months) was treated as a continuous variable. Gender was categorized into two groups (male versus female). IRS in the past 12 months was treated as a dichotomized variable (yes/no). ITN use was grouped into three categories (ITNs or LLINs, untreated nets, or no nets). Specifically, if ITNs were >1 year old or were not retreated within a year before the survey [13,17] or if LLINs were 3 years old at the time of survey, these nets were considered "untreated nets" [13,18–20]. House quality was divided into two groups (modern versus traditional). Houses built with finished walls, a finished roof, and a finished floor were categorized as "modern", while all other houses were categorized as "traditional" [13]. Mother's highest educational level was classified into four groups (no education, primary, secondary, or higher), which were in accordance with the DHS/MIS definitions. The DHS and MIS classified the population's socioeconomic status into five categories, namely, "poorest", "poor", "middle", "rich", and "richest". In this study, the total population was classified into two groups for further stratified analyses, namely, "poor" (poorest + poor) and "nonpoor" (middle + rich + richest). No missing values were observed for all the other covariates in each survey, except for IRS in the past 12 months and mother's highest educational level in some surveys (no data on IRS in the past 12 months in Angola 2011, DRC 2013–2014, Kenya 2015, Liberia 2009, Madagascar 2016, Malawi 2017, Rwanda 2014–2015, Rwanda 2010, Tanzania 2017, Togo 2017, Togo 2013–2014, Uganda 2009; no data on mother's highest educational level in Rwanda 2017).

Stratified analyses by household socioeconomic status

For descriptive analyses, chi-square (χ^2) tests or Fisher's exact tests were used for each survey to compare the prevalence of unprotected water and piped water with that of protected water, and the prevalence of flush toilets and no facility sources with that of pit latrine toilets among the total population. Chi-square (χ^2) tests or Fisher's exact tests were also used to compare the proportion of "poor" associated with different WS conditions for each survey.

Second, a logistic regression model was used to conduct the primary analysis of the total population to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) of the associations between different WS conditions and malaria infection for each survey, considering protected water and pit latrine toilets as reference. In these regression analyses, aORs were adjusted for (i) age in months, (ii) gender, (iii) IRS in the past 12 months, (iv) ITN use, (v) house quality, and (vi) mother's highest educational level. The main reasons for the retention of the above covariables in the "best" model were based on clinical or statistical significance in previous studies [13,17,21]. Furthermore, for the stratified analyses, the population was first categorized into two groups, namely, "poor" children and "nonpoor" children in each survey. Then, the aORs revealing the associations between WS conditions and the odds of malaria infection in children aged 0–59 months in a logistic regression model were performed for each DHS/MIS survey among those who were "poor" and "nonpoor", respectively, adjusting for the above confounding factors.

Finally, a meta-analysis method was performed to combine data from independent scientific trials as well as observational studies. In this study, each national survey was conducted independently. Using national survey data based on a random-effects meta-analysis might eliminate many biases typically related to pooling observational data, such as publication, selection, and measurement biases and selective outcome reporting bias. In this study, to determine the overall and the stratified aORs for WS and malaria risks among all the surveys, random-effect models in the meta-analysis were used to pool logistic regression results for the surveys which were calculated among total children, "poor" children, and "nonpoor" children, respectively. Furthermore, to investigate the heterogeneity among the survey-specific effects, Tau-squared statistics, I^2 statistics and *P*-values were analyzed with chi-square and Cochran's Q tests.

All analyses were conducted using SPSS Statistics version 22.0 (IBM Co., Armonk, NY, USA), except for the meta-analysis and forest plots, which were performed using STATA version 15.0 (StataCorp, College Station, TX, 77845, USA) and relating line diagrams and bar charts in GRAPHPAD PRISM version 7.0 (GraphPad Software, Inc., La Jolla, CA, USA). $P < 0.05$ for each overall aOR was considered statistically significant.

Results

Study population

After screening 189 identified surveys (136 DHS, 27 MIS, and 26 others) published between 2006 and 2008, none of 138 surveys met the inclusion criteria because they did not document malaria infection status (Additional file 1). After the removal of 138 surveys, 2 surveys were further excluded because they did not contain data on WS use (Additional file 1). Finally, 49 surveys (23 DHS, 24 MIS, and 2 others) including data for 307,365 individuals from 23 countries (Additional file 1) were identified. Among the identified individuals, 6,058 did not record information on WS use, and the age of 53,867 individuals was over 59 months; thus, these 59,925 individuals were excluded (Additional file 1). Overall, 49 eligible surveys comprising data for 247,440 individuals were included in the analysis (Additional file 1).

Table 1 provides the descriptive statistics for the health outcomes and covariates. Of the included individuals, 213,920 children aged 0–59 months were tested for malaria infection using microscopy, with a prevalence of 18.8%, whereas 59,988 (24.2%) positive cases were identified in 247,440 children by RDTs (Table 1). Across all surveys, the average age of the children was 32.6 months, and 50.2% were male (Table 1). Nearly half (47.3%) of the mothers had no education, this proportion ranged from 10.1% (Malawi 2017) to 83.0% (Burkina Faso 2010). With regard to preventive measures targeting vectors, data on the use of ITNs and IRS for each survey were extracted. As shown in Table 1, it is

Table 1
Characteristics of children under five years old across SSA who were included in the analysis.

Country and year	N	Mean age (Months)	Male (%)	Mother's highest educational level (no education valid percent)*	ITN use (%)	IRS in Past 12 mo (Valid Percent)*	Traditional house (%)	Socioeconomic status (the poor percent)	Parasite rate (%)	
									Microscopy	RDT
Angola 2015–2016	6746	31.9	50.4	36.8	21.2	1.4	71.2	53.3	–	16.5
Angola 2011	3259	32.1	48.1	35.4	21.9	–	69.8	47.1	9.8	12.5
Angola 2006–2007	2573	32.2	44.1	32.3	17.8	4.2	61.6	54.4	–	22.2
Benin 2011–2012	3709	33.2	51.7	74.7	69.6	12.6	62.3	44.9	29.9	27.1
Burkina Faso 2014	6090	32.5	50.8	81.6	71.5	0.7	82.4	44.7	47.6	64.5
Burkina Faso 2010	6088	32.1	51.4	83.0	44.5	1.6	77.5	40.9	65.0	75.6
Burundi 2016–2017	5755	32.5	50.3	44.0	36.8	0.8	84.3	40.0	24.4	34.8
Burundi 2012	3710	32.8	50.3	47.6	48.0	4.5	86.2	42.0	16.2	20.5
Cameroon 2011	5367	31.7	49.1	23.3	15.2	3.1	63.0	43.1	–	32.6
Coate D Ivoire 2011–2012	3762	31.6	43.6	67.9	37.0	1.4	43.0	50.5	16.1	42.0
DRC 2013–2014	8159	32.5	49.8	22.0	46.0	–	89.8	49.9	26.3	35.9
Gambia 2013	3104	31.4	52.0	66.0	38.1	59.1	47.5	54.4	0.5	1.8
Ghana 2016	3071	32.3	51.2	34.8	52.0	18.8	58.8	55.5	23.0	32.5
Ghana 2014	2705	32.7	52.1	36.8	38.9	21.6	38.1	54.0	28.8	40.8
Guinea 2012	3192	32.3	52.3	79.7	20.3	1.8	57.8	44.3	43.8	45.7
Kenya 2015	3352	33.3	50.5	21.3	45.1	–	98.5	53.0	5.3	9.4
Liberia 2016	2569	33.3	49.6	43.5	39.2	0.8	67.5	54.7	–	50.3
Liberia 2011	2888	33.1	50.5	49.9	32.8	10.3	75.7	61.4	32.5	52.3
Liberia 2009	4766	32.5	49.5	54.4	25.0	–	77.1	55.7	33.3	37.4
Madagascar 2016	6734	32.5	51.6	26.8	69.6	–	90.3	50.1	5.5	3.7
Madagascar 2013	5322	32.7	50.9	32.3	37.7	41.4	92.6	47.6	6.5	7.5
Madagascar 2011	6132	33.7	50.6	32.6	70.5	50.7	90.2	50.0	4.1	6.2
Malawi 2017	2295	33.7	50.2	10.1	54.6	–	65.5	31.8	16.9	26.0
Malawi 2014	1893	32.4	50.5	12.7	62.4	7.0	71.0	38.2	26.0	29.9
Malawi 2012	2074	32.3	47.1	18.3	44.4	8.9	74.9	37.8	24.6	37.8
Mali 2015	7277	32.7	50.9	78.0	62.8	6.6	78.2	43.5	35.0	31.5
Mali 2012–2013	4653	33.1	50.9	82.9	62.4	8.3	84.1	41.3	48.7	44.1
Mozambique 2015	4429	32.4	48.8	27.1	38.3	15.1	74.8	36.7	–	31.7
Mozambique 2011	4874	31.8	49.0	34.8	28.6	23.3	79.9	36.9	29.9	34.0
Nigeria 2015	5530	32.8	50.4	44.0	34.2	1.6	49.6	40.2	27.3	41.3
Nigeria 2010	4907	32.6	50.7	47.3	27.5	1.0	58.5	37.5	38.3	46.3
Rwanda 2017	2615	32.2	52.1	–	58.9	17.2	75.9	40.3	6.6	10.9
Rwanda 2014–2015	3416	32.1	51.0	14.9	55.8	–	82.1	45.9	2.2	7.6
Rwanda 2010	3931	33.4	50.6	19.0	63.2	–	87.2	43.3	1.2	2.4
Senegal 2017	9772	32.6	50.7	60.8	57.6	8.7	49.1	55.2	0.6	1.6
Senegal 2016	12,091	32.9	50.7	71.4	57.2	10.0	52.9	59.6	1.0	1.4
Senegal 2015	6046	32.8	50.5	71.6	51.5	9.7	50.6	58.0	0.4	1.0
Senegal 2014	12,118	32.5	50.3	72.2	42.2	15.6	55.9	57.7	2.8	2.9
Senegal 2012–2013	5889	32.2	50.1	72.1	44.7	18.4	55.5	53.7	3.7	4.1
Senegal 2010–2011	3852	32.6	52.4	74.9	39.0	14.8	58.4	56.4	3.7	3.3
Sierra Leone 2016	6328	32.1	50.5	64.2	36.9	1.3	66.7	51.5	41.9	56.3
Tanzania 2017	7125	32.4	50.3	24.7	44.9	–	69.0	47.4	–	8.4
Tanzania 2015–2016	10,047	35.7	50.1	21.9	45.7	9.3	66.7	43.6	5.1	12.7
Tanzania 2011–2012	7361	32.1	50.6	24.7	59.7	27.6	76.6	44.2	4.7	10.0
Togo 2017	3174	32.3	49.7	44.8	59.9	–	46.8	54.8	29.6	47.2
Togo 2013–2014	3181	32.5	50.6	47.5	29.9	–	59.0	53.2	37.8	39.3
Uganda 2016	4711	32.5	50.4	13.3	44.3	11.3	75.9	47.2	–	33.2
Uganda 2014–2015	4831	30.2	49.0	22.8	67.3	8.6	80.1	52.7	19.9	32.6
Uganda 2009	3967	30.2	49.5	23.6	28.0	–	100.0	46.2	43.6	53.1
Total	247,440	32.6	50.2	47.3	45.8	12.5	69.7	48.6	18.8	24.2

All surveyed children were 0–59 months.

* Valid percent was measured among the valid records because some records on the mother's highest educational level and IRS were missing in some surveys. RDT = Rapid Diagnostic Test; DRC = Democratic Republic of the Congo. ITN = Insecticide-treated Net; IRS = Indoor Residual Spraying.

clear that ITN usage was less than half (45.8%) overall and ranged from 15.2% (Cameroon 2011) to 71.5% (Burkina Faso 2014). Among the households surveyed, 12.5% experienced IRS in the past 12 months. With regard to house quality, the majority of the overall houses were traditional (69.7%), ranging from 38.1% (Ghana 2014) to 100% (Uganda 2009).

Drinking water and sanitation (WS) and household socioeconomic status

Fig. 1 presents the proportion of WS in the 23 countries in this study. Across all surveys, 35.4% of the included children had access to unprotected water, followed by protected water (32.5%) and piped water (32.1%) (Fig. 1A). Additionally, Fig. 1B demonstrates that most children utilized pit latrine toilets (62.4%), followed by no facilities (26.8%) and flush toilets (10.8%). The proportion of households with a "poor" (versus "nonpoor") socioeconomic status was 48.6% overall and ranged from 31.8% (Malawi 2017) to 61.4% (Liberia 2011) (Table 1). The greatest proportion of children who were classified as having a "poor" socioeconomic status were unprotected water users (69.6%), followed by protected water users (46.5%) and piped water users (26.7%) ($P < 0.001$) (Fig. 2A). Additionally, Fig. 2B illustrates that the proportion of children with "poor" socioeconomic status who were no facility users (77.7%) was higher than the proportions of those who were pit latrine toilet users (42.6%) and flush-toilet users (8.6%) ($P < 0.001$).

Association between drinking water and sanitation (WS) and malaria infection

Across all surveys, the comparison of malaria infections diagnosed by microscopy among individuals with different WS access in different countries revealed that the prevalence rates of malaria among the unprotected water users (22.6%) and piped water users (7.5%) were both significantly lower the prevalence rate among the protected water users (22.6% versus 26.8%, $p < 0.001$; 7.6% versus 26.8%, $P < 0.001$); however, this trend was not always consistent in all the surveys (Fig. 3A). Children who used no facilities were more likely to have malaria than children who used pit latrine toilets (Fig. 3B) according to microscopy (27.7% versus 17.4%, $P < 0.001$), whereas children who used flush toilets had a low tendency of malaria infection (4.5% versus 17.4%, $P < 0.001$); this trend was consistent in each survey (Fig. 3B). Data on malaria infections measured by RDTs in exposed and unexposed groups were provided by a survey, as shown in Additional file 2.

For the total population, the specific regression results for each survey based on the logistic regression model are shown in the forest plot (Fig. 4, Additional file 3). Across all surveys, unprotected water users were associated with a significantly increased prevalence of malaria (aOR 1.17, 95% CI 1.07–1.27, $P = 0.001$) as measured by microscopy (Table 2, Fig. 4A), while piped water users were associated with a significantly decreased prevalence of malaria (aOR 0.52, 95% CI 0.45–0.59, $P < 0.001$) as measured by microscopy (Table 2, Fig. 4B). Both results were retained when adjustments were made for age, gender, IRS in the past 12 months (when measured), ITN use, house quality, and mother's highest educational level (when measured). Moreover, no facility users had increased odds and flush-toilet users had decreased odds of malaria risk as measured by microscopy (Table 2, Fig. 4C, D). The overall aORs for no facility users and flush-toilet users were 1.35 (95% CI 1.24–1.47, $P < 0.001$), and 0.51 (95% CI 0.43–0.61, $P < 0.001$), respectively (Table 2, Fig. 4C, D). The trends of individuals diagnosed by RDTs were consistent with those of microscopy (Table 2, Additional file 3).

For the stratified results, the specific regression results for each survey stratified by household socioeconomic status are shown in the forest plot (Figs. 5, 6, Additional files 4, 5). In children with a "poor" socioeconomic status, no overall associations with malaria risk were observed in the unprotected water users compared to protected water users (microscopy: aOR 1.09, 95% CI 0.99–1.21, $P = 0.083$; RDT: aOR 1.02, 95% CI 0.93–1.13, $P = 0.652$) (Fig. 5A, Additional file 4A), whereas in children with a "nonpoor" socioeconomic status, the risk of malaria in the unprotected water users was more pronounced than that in protected water users (microscopy: aOR 1.21, 95% CI 1.10–1.32, $P < 0.001$; RDT: aOR 1.24, 95% CI 1.11–1.38, $P < 0.001$) (Fig. 5B, Additional file 4B). In children with a "poor" socioeconomic status, the protective effects of piped water were still significant, and the overall aORs of the piped water users were 0.65 (95% CI 0.53–0.80, $P < 0.001$) in those diagnosed by microscopy (Fig. 5C) and 0.68 (95% CI 0.56–0.82, $P < 0.001$) in those diagnosed by RDTs (Additional file 4C). In children with a "nonpoor" socioeconomic status, the aORs of the piped water users were 0.57 (95% CI 0.49–0.65, $P < 0.001$) in those diagnosed by microscopy (Fig. 5D) and 0.53 (95% CI 0.46–0.60, $P < 0.001$) in those diagnosed by RDTs (Additional file 4D)

For children with a "poor" socioeconomic status who were pit latrine toilet users, the overall aORs of the no facility users were 1.14 (95% CI 1.03–1.26, $P = 0.010$) in those diagnosed by microscopy (Fig. 6A) and 1.15 (95% CI 1.05–1.25, $P = 0.002$) in those diagnosed by RDTs (Additional file 5A); for the children with a "non-

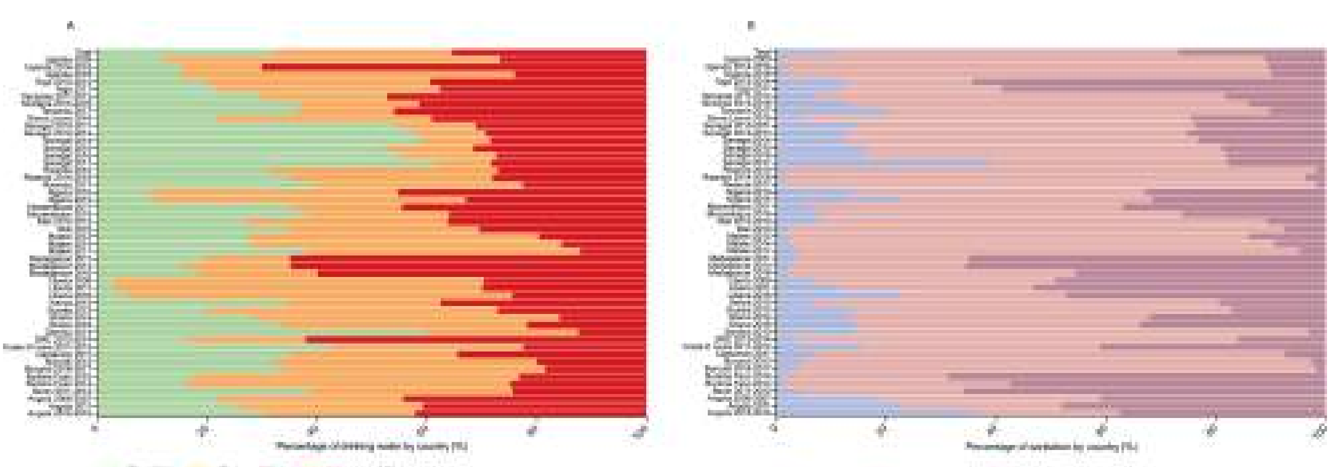

Fig. 1. Proportion of children under 5 years old who used various WS conditions. (A) drinking water, (B) sanitation.

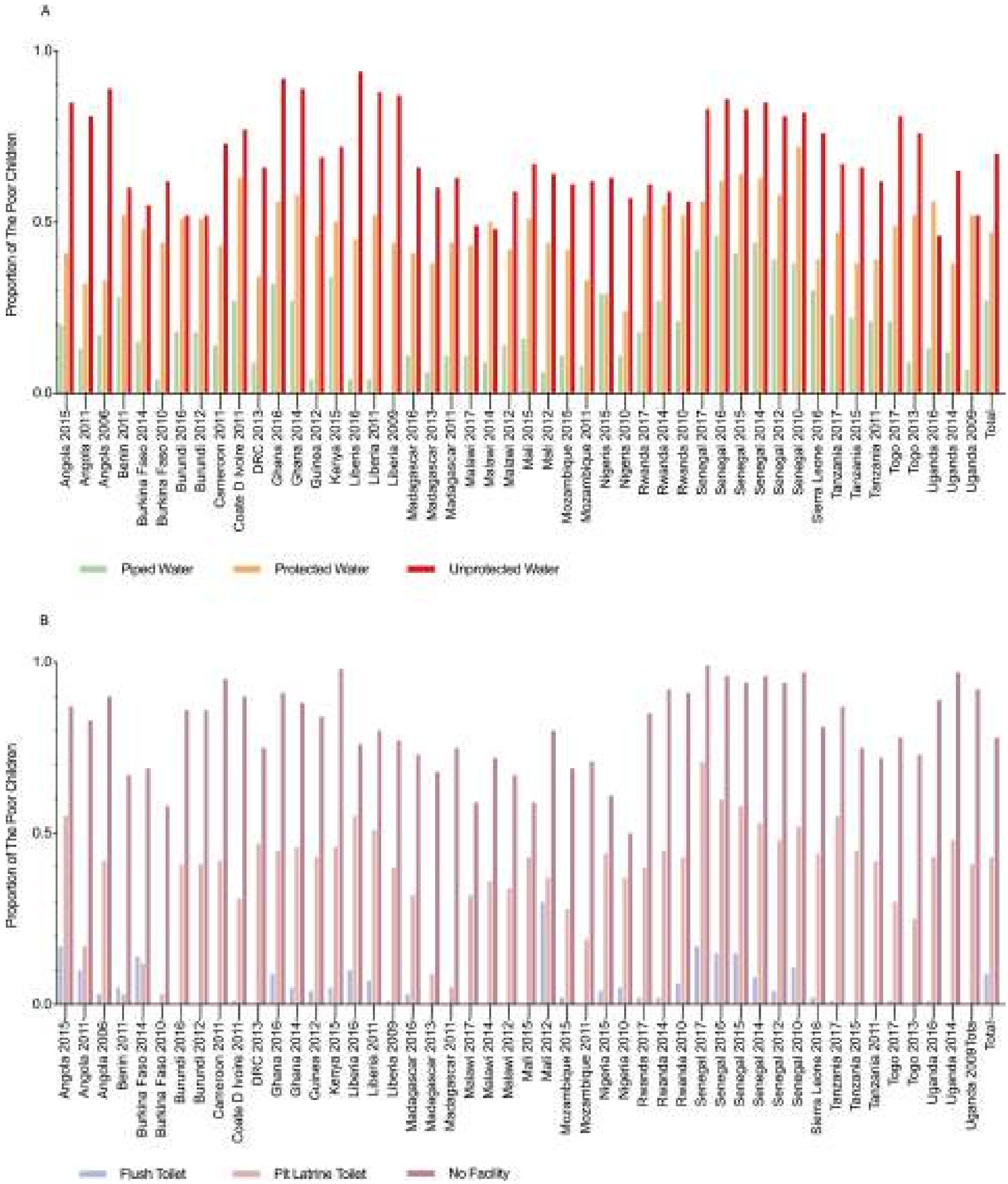

Fig. 2. The percentage of children with a "poor" socioeconomic status and different WS sources for each national survey. (A) The association between socioeconomic status and drinking water sources. (B) The association between socioeconomic status and sanitation conditions. Chi-square (χ^2) tests were used for assessing the differences in the proportion of children with a "poor" socioeconomic status among the various WS conditions. The *P*-values of all the χ^2 tests in Fig. 2 were less than 0.001. WS = Drinking Water and Sanitation.

poor" socioeconomic status, the aORs were 1.46 (95% CI 1.32–1.61, $P < 0.001$) in those diagnosed by microscopy (Fig. 6B) and 1.54 (95% CI 1.38–1.72, $P < 0.001$) in those diagnosed by RDTs (Additional file 5B). Additionally, in children with a "poor" socioeconomic status, the flush-toilet users did not have significant protection from malaria infection according to microscopy; the aOR of the flush-toilet users was 0.80 (95% CI 0.55–1.17, $P = 0.250$) (Fig. 6C). In the children with a "nonpoor" socioeconomic status, the protective effects of flush-toilets (considering both microscopy and RDTs) were significant (microscopy: aOR 0.57, 95% CI 0.49–0.66, $P < 0.001$; RDT: aOR 0.53, 95% CI 0.47–0.60, $P < 0.001$) in relation to malaria risk (Fig. 6D, Additional file 5D).

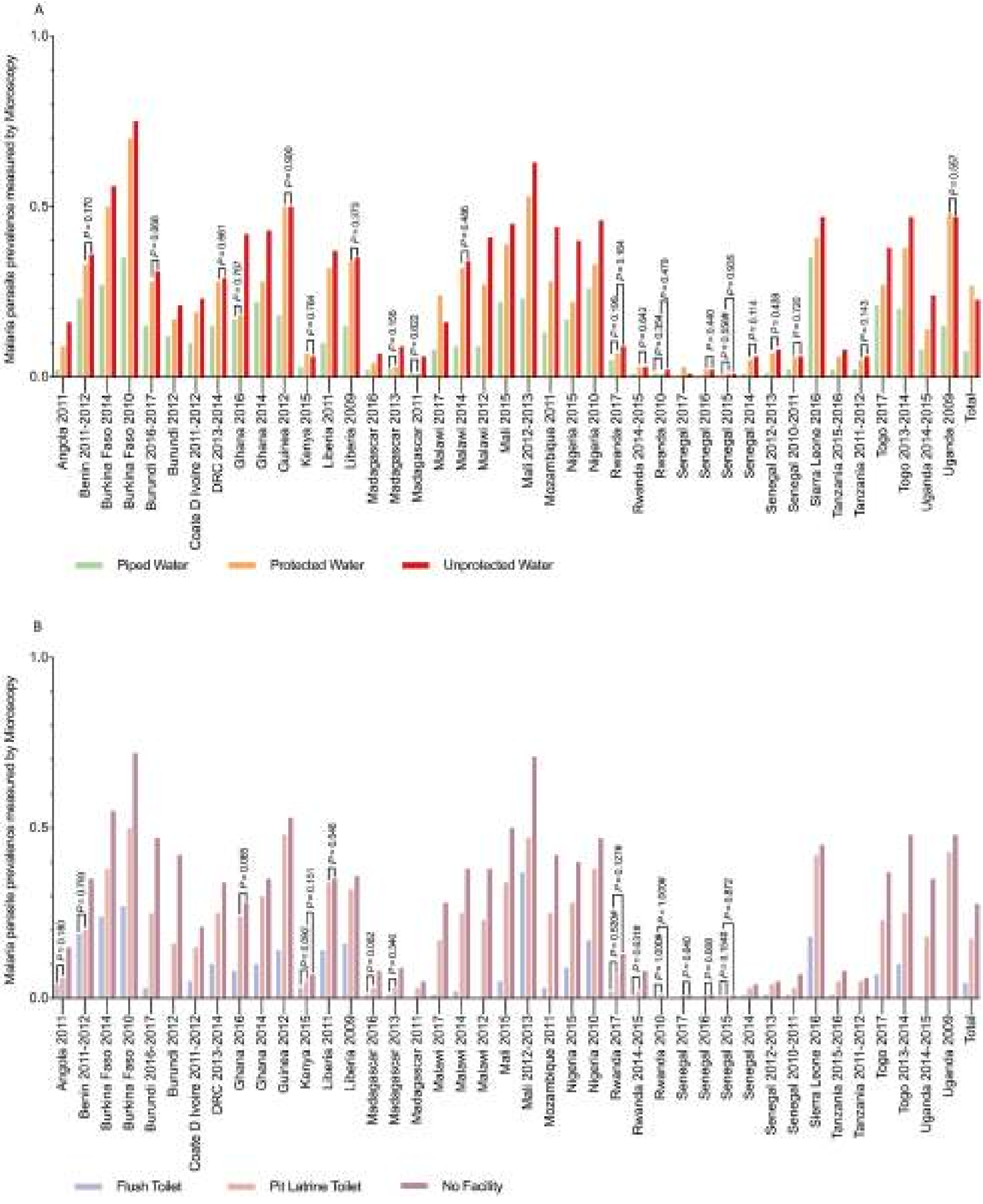

Fig. 3. Prevalence of malaria infection in different WS users identified by microscopy for each national survey. (A) The association between malaria prevalence and different drinking water sources. (B) The association between malaria prevalence and different sanitation conditions. Chi-square (χ^2) tests or Fisher's exact tests were used to assess the differences in malaria infection between the various WS users. The infections were determined by microscopy. #*P*-values were obtained with Fisher's exact test. *P*-values (>0.05) were obtained with χ^2 tests or Fisher's exact tests; all unmarked *P*-values are less than 0.001. WS = Drinking Water and Sanitation.

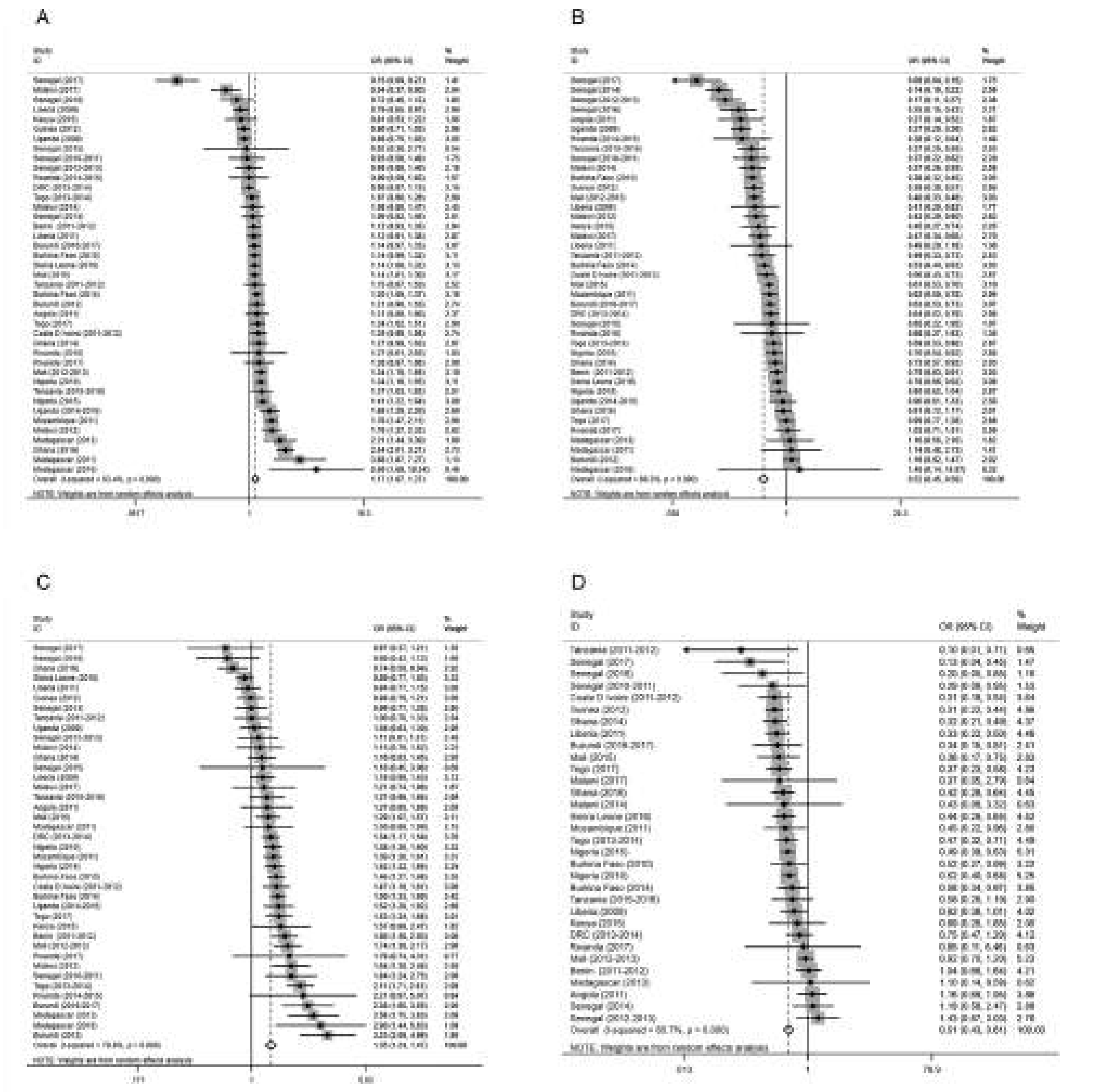

Fig. 4. Forest plots of the effects of WS conditions on malaria infection among the total children diagnosed by microscopy. The ORs and 95% CIs for the risk of infection as determined by microscopy in relation to (A) Unprotected Water, (B) Piped Water, (C) No Facility, and (D) Flush toilets in each survey were measured by logistic regression models with adjustments for age, gender, IRS, ITN use, house quality, and mother's highest educational level. The datapoints, lines, boxes, and vertical dashed lines present the ORs, 95% CIs, weight that each survey contributed to the overall OR, and overall 95% CIs, respectively. WS = Drinking Water and Sanitation; OR = Odds Ratio; 95% CI = 95% Confidence Interval.

Discussion

To our knowledge, this is the first analysis of the associations between WS conditions and the risk of malaria among children under five years old across SSA employing data from multi-country, cross-sectional surveys. This analysis of 49 surveys (23 DHS, 24 MIS, and 2 others) found that compared to protected water and pit latrine toilets, piped water and flush toilets were associated with significantly reduced malaria prevalence rates, whereas unprotected water and no facilities were related to an increased risk of malaria after adjusting for potential confounders. However, this association was mostly influenced by the household socioeconomic status. In children with a "poor" socioeconomic status, no significant associations were observed between unprotected water and flush toilets in relation to malaria infection, whereas in children with a "nonpoor" socioeconomic status, the associations between unimproved WS conditions (including unprotected water or no facilities) and the risk of malaria appeared to be pronounced.

These findings are in line with several previous studies [8–11,22,23]; for example, Ayele et al. assessed various WS conditions as indicators of socioeconomic status on the prevalence of malaria in Ethiopia from December 2006 to January 2007 using a general-

Table 2
Meta-analysis of the associations between WS conditions and malaria infections among the total children, children with a "poor" socioeconomic status, and children with a "poor" socioeconomic status.

	Number of surveys*	Total children OR (95%CI)	Number of surveys*	Poor children OR (95%CI)	Number of surveys*	Non-poor children OR (95%CI)
Microscopy						
Protected water (Reference)	–	1.00	–	1.00	–	1.00
Unprotected water	41	1.17 (1.07, 1.27)	41	1.09 (0.99, 1.21)	39	1.21 (1.10, 1.32)
Piped water	41	0.52 (0.45, 0.59)	40	0.65 (0.53, 0.80)	40	0.57 (0.49, 0.65)
Pit latrine (Reference)	–	1.00	–	1.00	–	1.00
No facility	40	1.35 (1.24, 1.47)	39	1.14 (1.03, 1.26)	35	1.46 (1.32, 1.61)
Flush toilet	32	0.51 (0.43, 0.61)	14	0.80 (0.55, 1.17)	32	0.57 (0.49, 0.66)
RDT						
Protected water (Reference)	–	1.00	–	1.00	–	1.00
Unprotected water	48	1.11 (1.02, 1.22)	48	1.02 (0.93, 1.13)	47	1.24 (1.11, 1.38)
Piped water	47	0.49 (0.43, 0.57)	46	0.68 (0.56, 0.82)	47	0.53 (0.46, 0.60)
Pit latrine (Reference)	–	1.00	–	1.00	–	1.00
No facility	48	1.38 (1.27, 1.50)	48	1.15 (1.05, 1.25)	42	1.54 (1.38, 1.72)
Flush toilet	44	0.46 (0.39, 0.53)	24	0.71 (0.56, 0.91)	44	0.53 (0.47, 0.60)

* Some surveys were excluded in the meta-analysis due to the unavailability of logistic regression results. Each logistic regression model was adjusted for age, gender, IRS, ITN use, house quality, and mother's highest educational level. OR = Odds Ratio; 95% CI = 95% Confidence Interval; WS = Drinking Water and Sanitation; RDT = Rapid Diagnostic Test.

ized additive mixed model, generalized linear mixed model with spatial covariance structure, and generalized linear mode [8–10]. All of these studies found that malaria disproportionately affected people who had a poor socioeconomic status and limited access to clean drinking water sources [8–10]. Similarly, Kinuthia et al. also observed an increased number of malaria cases associated with inappropriate WS conditions in Njoro District, Kenya, using chi-squared tests and confidence limits [11]. Furthermore, Hasyim et al. indicated that individuals who lived in unimproved sanitation environments were more frequently infected with malaria than those who lived in improved sanitation environments, even though the association between environmental sanitation and malaria prevalence was not statistically significant (OR 1.13, 95% CI 0.99–1.31, $P = 0.081$) [22]. Finally, as Hasyim et al. also suggested, most individuals who used open sewage systems (domestic wastewater or municipal wastewater) at home and those who did not have a sewage system were at higher risk of malaria infection (OR 1.250, 95% CI 1.095–1.427, $P = 0.001$) than those who used closed sewage systems, further highlighting the significance of potential larval habitats near houses [23]. The results of all of these studies were in line with our results; due to closed systems, improved WS users had a decreased risk of malaria infection.

It is well known that mosquitoes and their ecosystems are significant spatial drivers of malaria transmission. Potential larval habitats may occur due to the physical disturbances created by human fetching or storing of unimproved drinking water (e.g., splashing water on the ground when fetching or storing unimproved water results in shallow puddles or footprints; additionally, storing unimproved drinking water creates stagnant water sources for nearby households), further increasing mosquito breeding and adult vector densities near households. The top three vector species of human malaria in our study area included *Anopheles gambiae, An. arabiensis,* and *An. funestus* (Additional file 6; the data sources were derived from country profiles based on the World Health Organization (WHO) database online because the DHS and MIS did not include entomological surveys). Among these Anopheles species, *An. gambiae* and *An. arabiensis* prefer to inhabit sunlit, shallow, temporary bodies of fresh water, such as puddles, pools, ground depressions, and hoof prints [24]. In addition, water in these larval sites is often turbid or polluted [25–27]. In contrast, *An. funestus* inhabits permanent or semipermanent bodies of fresh water with emergent vegetation, such as swamps, ponds, and lake edges [24]. This evidence suggests that closed systems with improved water are relatively inappropriate environments for Anopheles.

The association between improved WS (including protected and piped water; pit latrines and flush toilets) and the reduced risk of malaria in this study could be explained by several potential mechanisms. There are data that indicate that wealth is probably protective against malaria risk [28–34], as prevention and treatment are affordable [35–37]. In this study, among the total participants, socioeconomic status (a confounder) determined access to improved water, sanitation and hygiene practices and malaria prevention practices, all of which affected the level of malaria risk [8–10]. We can easily see that the highest proportion of children with a "poor" socioeconomic status were unimproved WS users (Fig. 2). To address the confounding nature of socioeconomic status, the results of WS conditions and prevalence of malaria in children under five years old were stratified by household socioeconomic status, and the aORs within each socioeconomic level were calculated. In the stratified results, the mixed effects of wealth weighed heavily upon the WS conditions related to malaria risk in the children with a "poor" socioeconomic status (Table 2). This nonsignificant phenomenon was mostly attributed to the decreased proportion of improved water access in children with a "poor" socioeconomic status (Fig. 2). This result simply showed that malaria infection rates were the highest among the poorest populations who had little or no access to safe drinking water and toilets.

Regarding the overall OR results between children with a "poor" or "nonpoor" socioeconomic status, the effects of WS and malaria infections were more obvious in the children with a "nonpoor" socioeconomic status (Table 2), demonstrating that it is urgent to improve WS conditions in nonpoor populations if economic circumstances permit. The important finding in this study was that in the children with a "nonpoor" socioeconomic status, the effects of WS conditions were still significant even without the confounding effects of socioeconomic status. This may be explained by the fact that unimproved WS users may indirectly increase the likelihood of contracting *Plasmodium falciparum* by increasing the risk

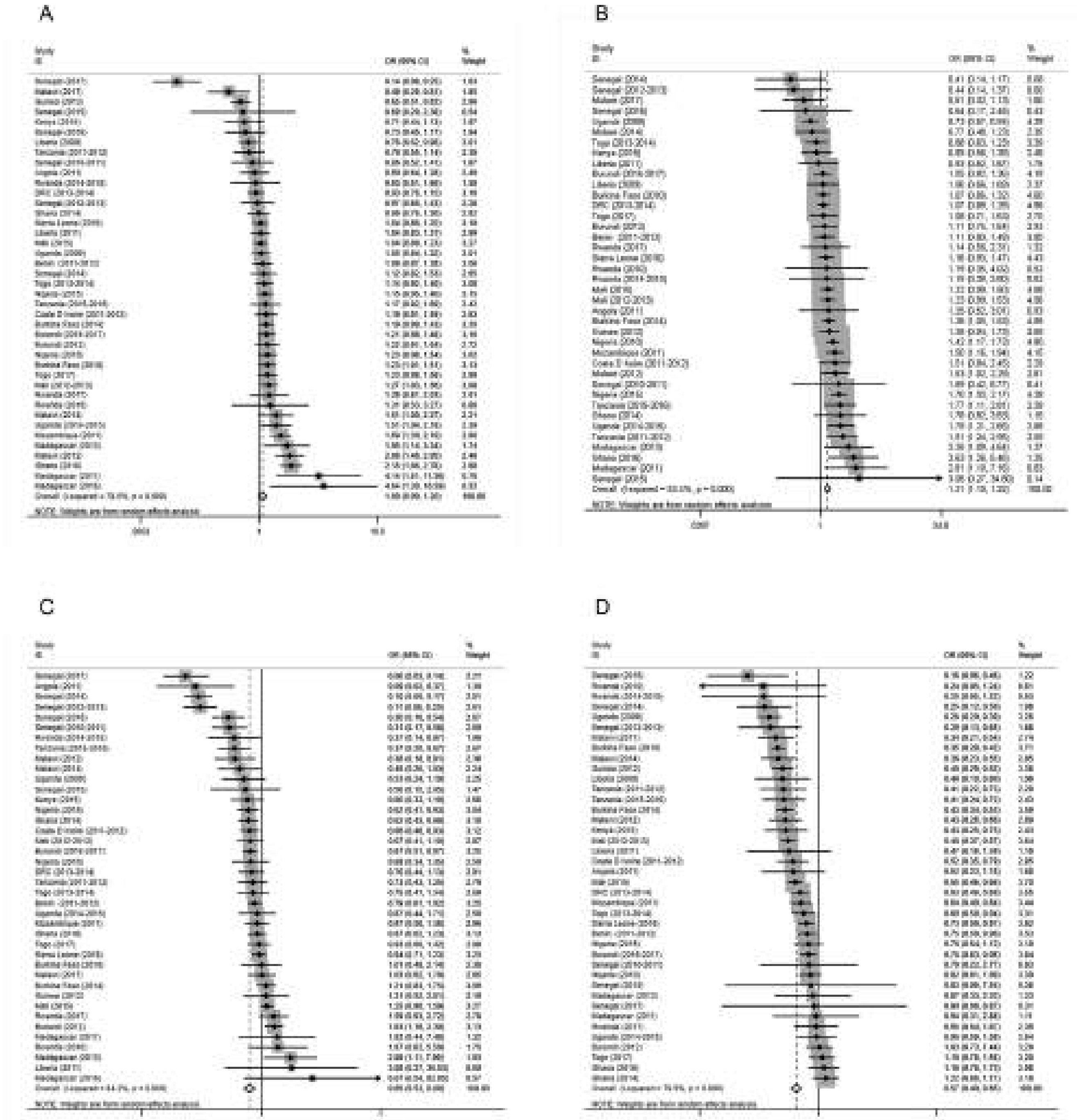

Fig. 5. Forest plots of the effects of drinking water sources on malaria infection diagnosed by microscopy based on socioeconomic status. (A) Unprotected Water among children with a "poor" socioeconomic status, (B) Unprotected Water among children with a "nonpoor" socioeconomic status, (C) Piped Wateramongchildrenwitha"poor"socioeconomicstatus, (D) Piped Water among children with a "nonpoor" socioeconomic status. Malaria infections were determined by microscopy. Datapoints, lines, boxes, and vertical dashed lines represent ORs, 95%CIs,weight that each survey contributed to the overall OR, and overall 95% CIs, respectively. OR = Odds Ratio; 95% CI = 95% Confidence Interval..

of other waterborne parasitic diseases, such as soil transmitted helminth diseases (STHs, such as *hookworm, Strongyloides stercoralis*) or *Schistosoma haematobium* infections directly [38–42].

According to previous studies, we hypothesize that children who have STHs or schistosomiasis may be more susceptible to malaria infection [38–45]. There are many mechanisms to support this theory. For example, *Strongyloides stercoralis* could increase the risk of *Plasmodium* infection because of the predominance of Th2 responses in young children [38,39]. Furthermore, schistosomiasis infection alone or in combination with trichiasis or hookworm infection can apparently increase the risk of *P. falciparum* by modulating the immune system [41–43]. Additionally, helminth-infected individuals can present decreased cutaneous reactivity to anopheline bites, which may theoretically facilitate the success of sporozoite introduction [44,45]. There are also many previous studies exploring the risk factors of STH or *Schistosoma haemato-*

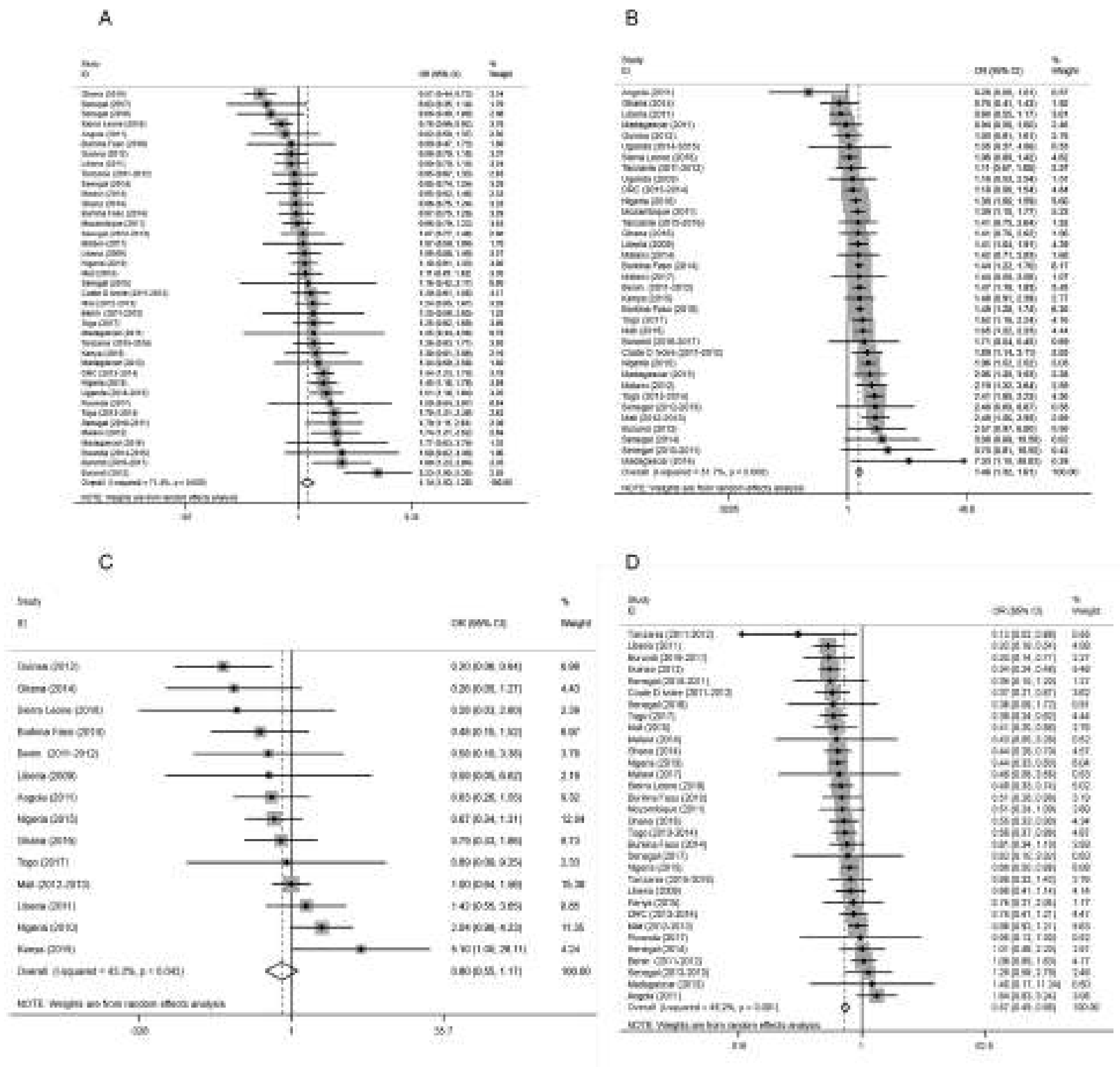

Fig. 6. Forest plots of the effects of sanitation conditions on malaria infection diagnosed by microscopy based on socioeconomic status. (A) No Facility among children with a "poor" socioeconomic status, (B) No Facilityamongchildrenwitha"nonpoor"socioeconomicstatus, (C) Flush toilet among children with a "poor" socioeconomic status, (D) Flush toilets among children with a "nonpoor" socioeconomic status. Malaria infections were diagnosed by microscopy. Datapoints, lines, boxes, and vertical dashed lines represent ORs, 95% CIs, weight that eachsurvey contributed to the overall OR, and overall 95% CIs, respectively. OR = Odds Ratio; 95% CI = 95% Confidence Interval.

bium and malaria coinfections, and all these articles indicate that unsafe WASH conditions are the primary risk factors associated with such coinfections [38,46,47], suggesting that clean WS conditions can help to prevent malaria infections. Finally, the most important distinction between unimproved water and improved water is whether drinking water is treated. In this study, it was apparent that a high proportion of disposed unprotected water was linked to a relatively low prevalence of malaria (Additional file 7).

The strength of this study includes the large and comprehensive dataset obtained from the DHS and MIS. The analysis aimed to elucidate the influence of household WS on malaria risk stratified by household socioeconomic status on a large scale for the first time. Some studies have indicated that many high-income countries eliminated malaria without malaria-specific interventions; for example, malaria in Europe and North America declined as a result of improved living conditions and increased wealth [48]. As Lucy Tusting et al. stated, halting existing malaria control efforts is not recommended; however, we believe there is a need to increase investment in interventions that support socioeconomic development [33]. Although wealth status is a combination of multiple factors, it is important to know which specific aspect of wealth affects malaria infection. In this study, the mixed effects of socioeconomic status were eliminated, and we focused on exploring the relationship between WS and malaria. Water-associated vector-borne diseases (including malaria and many NTDs) continue to be a major public health problem in many developing countries [7]. However, remarkable and significant progress in the prevention and control of water-related vector-borne diseases has been made in many regions, primarily through the strengthening of vector control strategies, case detection, and treatment methods [1,7]. These present strategies must be expanded. Strengthening of intersectoral links with improving WASH may provide a method to increase the pace of malaria elimination. Although the SDGs have offered unprecedented opportunities to improve health by dramatically increasing the availability and use of WASH services [7], the coverage of safe WASH in SSA is still very low. These findings suggest that efforts should be redoubled to improve WS conditions, which should be considered an important component of malaria prevention and control. Finally, the use of pooled observational multicountry data eliminated many biases, including publication, selection, and measurement biases and selective outcome reporting, which are typically presented in traditional systematic reviews and meta-analyses.

This study has several limitations. First, it did not explore the association between drinking water storage sites and malaria infection. However, in this study data on drinking water storage sites were absent in many surveys, making it too difficult to link the various types of drinking water sources with their storage sites. Further studies are needed to investigate the influence of storage sites in depth. Second, although the results of WS conditions and malaria prevalence among children under 5 years old were stratified by household socioeconomic level, the stratification (''poor" versus ''nonpoor") in this study was not very prudent because of the original stratifications in the DHS and MIS were grouped into five categories, namely, ''poorest", ''poor", ''middle", ''rich", and ''richest". There may still be residual confounding caused by wealth status in our study. However, considering the proportion of children with a ''poor" socioeconomic status (approximately 50%) (Table 1), this study classified the total children into two groups to avoid an uneven sample distribution. Furthermore, entomological surveys, particularly among unimproved drinking water sources and unimproved sanitation facilities in SSA, are important to understand how the type and the behavior of Anopheles species affect malaria transmission and to assist in addressing confounding factors involving the various ecological niches of distinct species. Unfortunately, entomological surveys were not conducted in the DHS and MIS surveys. Finally, due to the lack of examination in the DHS Program of other parasitic diseases, such as STHs or schistosomiasis, the proposed effect of coinfections is still under speculation in this study. It would be beneficial to add coinfection investigations to the DHS and MIS in the future.

Conclusions

In conclusion, WS conditions were important risk factors for malaria among children under five years old across SSA after adjustments for age, gender, IRS in the past 12 months and insecticide-treated use, house quality, and mother's highest educational level. Unimproved WS access (unprotected water; no facility) was related to a relatively high risk of malaria. Furthermore, this association was mostly influenced by socioeconomic status. However, the malaria risk associated with unimproved WS was more pronounced among the children with a ''nonpoor" socioeconomic status. These findings indicated incremental improvements to WS in SSA might be considered a potential intervention for the prevention and control of malaria in the long term.

Compliance with Ethics Requirements

The DHS Program has the compliance with ethics requirements.

Declaration of Competing Interest

The authors have declared no conflict of interest.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2019.09.001.

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