PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence and risk factors for hospital-acquired infection among pediatric patients in a teaching hospital: a prospective study in southeast Ethiopia
AUTHORS	Sahiledengle, Biniyam; Seyoum, Fekadu; Abebe, Daniel; Geleta, Eshetu; Negash, Getahun; Kalu, Abdurhaman; Woldeyohannes, Demelash; Tekalegn, Yohannes; Zenbaba, Demisu; Edward Quisido, Bruce John

VERSION 1 – REVIEW

REVIEWER	Yallew, Walelegn University of Gondar College of Medicine and Health Sciences
REVIEW RETURNED	24-Mar-2020

GENERAL COMMENTS	Title : "Incidence and risk factors for healthcare-associated infection among pediatric patients in a teaching hospital: a prospective study in southeast Ethiopia. Article Number: Manuscript ID bmjopen-2020-037997 1. Line 124 page 6: " HAIs were confirmed by senior physician specialists working in the respective NICU and pediatrics ward" It is true that , for HAIs it needs laboratory blood culture to confirm the result ? is it valid as a scientific paper, better to include the method section the laboratory result as a guide in addition to the clinical criteria? 2. Line 143: Page 7 : " A Generalized Linear Model (GLM) , why not specific to logistic regression indicated in the paper? the researcher used multivariable logistic regression. GLM is broad term 3. Line 184 page 9" Incidence and type of healthcare-associated infection" 4. Line 198 page 10 : "Risk factors of hospital-acquired infections" It is clear that the terms are similar but use a uniform term either Hospital acquired infection or Health care associated infection" The term Health care associated infection includes care with geriatrics in some operational definition , but try to use uniform terms through out the paper either Hospital acquired infection or Healthcare associated infection?

	5. I advise the author try to refer and use the paper conducted in Ethiopia " https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181145 this may help for to high light risk factors for hospital acquired infection in teaching hospitals of Ethiopia.

REVIEWER	Cotton, Mark Stellenbosch University, Paediatrics & Child Health
REVIEW RETURNED	13-May-2020

GENERAL COMMENTS	Useful paper to document NI in hospitalised children. Page 2(abstract), line 42: There is no data on the reason for hospitalization. While it is likely that unnecessary hospitalization should be avoided, this conclusion was not validated. Page 6, line 61: The reference by Sheng is incorrectly interpreted: 80% of deaths were linked to nosocomial infection (NI) rather than 80% of those with NI died Page 6, line 112: Add 'patients' after 'paediatric' Page 7, line 92: Change 'And the overall incidence rate of 35.8 per 100 patients' to 'The overall incidence rate of 35.8 per 100 patients.' Page 8, line 50: Change 'pediatrics' to ;'children or pediatric patients' Page 10, line168: Add 'patients' after 'paediatric' Page 10, line 169: Why were asymptomatic patients excluded? Page 10, line 173: Replace 'fourthly' with 'forty' Page 10, line 180: Delete 'An underlying disease condition, which is' Page 11, line 172: Change 'remaining' to 'remainder' Table 3: What is a drainage tube? Is it a nasogastric tube? Table 1: How does a peripheral IV line differ from a peripheral vascular catheter? Page 12, line 204: Was duration of hospitalization correlated with underlying disease? Di any children have avoidable hospitalization? (this was addressed in 1st African pediatric NI study – (PIDJ 1989 [10] 676-83) Discussion: Were any organisms isolated? Is the antibiotic resistance profile known? This is important information

REVIEWER	Joanna Merckx McGill University, Canada employee, Medical Affairs bioMérieux Canada - no COI for the review of this paper
REVIEW RETURNED	01-Aug-2020

GENERAL COMMENTS	Sahiledengle et al report the results of their prospective study, over a period of 8 months, on the incidence of HAI in a tertiary care pediatric hospital in Ethiopia. The manuscript describes the patient population and provides epidemiologic cumulative incidence and incidence rate data for the composite outcome of HAI in both their NICU and pediatric wards. The group used valuable methods, using a prospective study design and using an individual patient chart investigation approach. In addition, the study aims to determine risk factors associated with HAI in the study population. While the overall results and the presented data are certainly of high value, mainly given the lack of epidemiologic data in the

	studied setting, major limitations apply and the manuscript requires major changes prior to be suitable for publication. General comments: -The main objective for the study and the manuscript is stated as: the lack of a prior published manuscript on the topic. Epidemiological data on the incidence of HAI are necessary, because without a valid and precise baseline, the problem remains unnoticed and interventions are not designed nor implemented, and neither can their impact be assessed. Reformulation of the study objective with a sentence on the importance of regional HAI data for improvement of patient care is recommended. A link with AMR can be made. -The secondary objective to assess risk factors misses rigorous evaluation and interpretation of the results. Alternative statistical methodology and/or recognition of the limitations of current methods and correct interpretation of the results is suggested. -The methods are not clearly described and multiple details remain unclear eg. the moments and procedures followed for the data assessment and data collection, the definitions used and the availability of diagnostics for infectious processes (microbiology). -Clinical diagnosis of HAI is made. Can the authors describe the methods available for pathogen identification? -There is no description on how biases were addressed during the different study phases: protocol development, data analysis and result interpretation. Which are the remaining biases that need to be taken into account interpreting the results? Only a comment is made about possibly missing cases that manifested after discharge. -The outcome HAI is a composite outcome: better description of the different components of HAI and which where assessed, including the validity of the assessment, would improve the understanding of the HAI. The different HAI are now only reported in the supplemental table, bringing these data to the main paper might be considered. -An important issue is the variable: length of stay (LOS), in the study: “duration of hospitalization”. This variable, being continuous, is used as a binary variable “6 days” or more (chosen based on the median LOS). *It is not completely clear which time contributes and which time does not contribute to the denominator. More detailed reporting on the calculation of the incidence rate is necessary. *In the discussion and conclusion, duration of hospitalization is interpreted as a causal factor, which if avoided and taken out, will lead to a direct decrease of the HAI rate and HAI cumulative incidence. This conclusion is not correct and flawed. *There are multiple issues with the LOS variable: from being a possible collider, outcome (effect of HAI- reversed causation) and being confounded. *The used analysis also does not take any time-varying risk into account. *With the present analysis methods, an association between duration of admission and HAI incidence can be concluded, but no further causal, nor speculations regarding the impact of decreasing length of stay on HAI can be made using the present data and analysis. -It is clear that events within the first 48h of admission, as is the consensus, are censored. It is unclear if the first 2 days are counted in the denominator of time at risk for the patients that do not get excluded from the study.

	-The time at risk for the different HAI is not clear. Presenting the device-specific rate for lines, urinary catheter, mechanical ventilation would be informative. It is not clear if these risks are calculated by their time of exposure or the total duration of hospitalization is used. -There is no reflection on the mortality of the patients and if these were patients with diagnosed HAI or not. -It is good that also the absolute effect measures are communicated. -Severe malnutrition and infection risk, including HAI, is a separate discussion. Given the lack of microbiology data endogenous infections will be misclassified as HAI. This aspect is not touched upon in the manuscript. For this particular subgroup, data on CLABSI – BSI vs HAP are of interest. -For neonates: no report on prematurity or (V)LBW status is given. These variables are important baseline characteristics of the study population when describing HAI in a NICU unit. -The manuscript would benefit from help with the English language. Past and present tense are often mixed. Below in the comments I refer to some particular sentences or words used. Detailed comments: -Abstract: -line 20-24 - Objectives: wording “infections among admitted pediatric in Ethiopia. “ – to change to admitted children or pediatric patients. -Design: prospective cohort study. -line 38-39: The 13 in 100 is not a rate but a cumulative incidence or proportion as the authors report correctly in the results, it is misleading to call it a morbidity rate in the abstract. -line 41: ” Avoiding unnecessary length of stay could save lives and minimize the occurrence of healthcare-acquired infections. “: there is no proof that this will help, this is not a conclusion you can make from the study. There is only an association found, this is not a proof that decreasing the length of stay in children from 5 to 4 days will do the job, neither from 7 to 6 or 6 to 5. Moreover because it is even written in the introduction that there is evidence that HAI cause prolonged length of stay. Revered causation can thus be one out of the mechanisms why this prolonged LOS is associated with HAI. -Attention to English: “Pediatric and neonates inpatients were recruited and followed-up“ and “The full burden of healthcare-associated infections could not be captured in this specific study as our study, was limited to in-hospital assessment only and leaving outpatients who may potentially develop an infection after discharge. “ -Reporting of p-values in the abstract does not add value. -Introduction: -Faster focussing on HAI in the pediatric population and the absence of regional data would make the introduction more concise and to the point. -It remains unclear if in the hospital or the region any surveillance program is set up or will be set up and where we can situate the collection – measurement of HAI in the near future in the region. -line 75: take out “as well” -line 78: “the” change to that -line 80: “correct “highlighted” -line 83: “in lieu” not correctly used -line 92: is not a rate if not over patient days

	-Methods: -line 107: NICU introduced as abbreviation and only later written full -line 108: change were to are -line 112: the word “pediatric” is often used for pediatric patients or children – please correct -line 112: can you explain what is meant with the patients “becoming asymptomatic within the first 48h” means – are those not already excluded? -line 115: it is unclear when consent was sought and when data collection was precisely performed. It is unclear when HAI were “diagnosed”: at the moment of presentation or after discharge – was there daily chart review? Were the study nurses – clinicians contacted to review the charts daily? -line 118: is this clinical history or what was collected? It is unclear if there were data collected through interview with the parents or all data come from patient chart review. -Was the data collection piloted? Is the CDC tool in use outside this study? -line 122: word pediatrics -line 137: “underline” - underlying disease – however: be specific if co-morbidity is meant or admission diagnosis or discharge diagnosis. -HIV status: measured for every patient on admission? -The operational definitions can maybe be introduced earlier. -line 151: what is “an adverse reaction to the presence of an infectious agent” -line 156: where does the definition of late-onset neonatal sepsis comes from: this is related to time since birth – age of the patient – not time since admission. Unclear. Are children on the pediatrics ward at risk for early onset or late onset neonatal sepsis? Are they admitted to the ward? -patient involvement can be summarized in 1 sentence -Results: -There are little social determinant variables measured – all described variables, except origin from a rural or urban site are rather general demographics. -A flow chart would be informative. -line 181: unclear if the diagnosis of SAM is made by a questionnaire of medically assessed – re-write “reported by” -The use of antimicrobials is an important variable. Is there more granular data on: antimicrobials prior to admission – during total admission – treatment for HAI – po versus IV versus IM. The description “at the time of the study” is unclear -line 186: time of onset of HAI – time of diagnosis? -line 192-193: wording - pediatrics -line 200: “statistically associated”: does not make sense. -line 204: it is important to write out what was adjusted for. -The only underlying condition included in the analysis is SAM – please name as such. Regarding SAM: type of HAI? Their time at risk – more time with IV? -line 208: It is stated that clinical related confounders were not statistically significantly associated with the presence of HAI. Which of the variables are defined as confounders – is there certainty that the confounders are not mediaters nor colliders? A DAG can be of value. Or:

	Are the variables “assumed” confounders dependent of their “statistical significant” result in the bivariate analysis? Thanks for clarification. -Where there patients with more than 1 episode of HAI? -Discussion: -line 220: word pediatrics and incorrect reporting of the 18 per 1000 as a proportion. -line 222: point? -When comparing data can it be made clear if the comparator are pediatric data only or combined pediatric and adult data. In addition: NICU and pediatrics have difference incidence and incidence rate – there is little discussion and direct comparison. What is also unclear is if the studies used for comparison are all cohort studies or include point-prevalence surveys or are part of structured infection prevention and control structures. Some more detail and grouping of comparisons is more informative compared to the many different data that are now written out in the paragraph. -Differences by sex: this is compared with a study on surgical site infections – how does this pediatric and neonatal population directly relate to this study? Is in the neonatal population this difference important? -little attention goes to how many of the HAP are VAP. -For the discussion on the association between length of hospitalization and HAI incidence I refer to the major comments. The discussion, acknowledging biases is warranted. -line 257: typo: thru. -Conclusions: -line 271: the word community is oddly used, given these are nosocomial infections – but of course, our hospitalized patients always originally come from and within a community. -line: 273: incorrect conclusion as discussed prior -Table 1: -the age categories vary widely in the number of months. A figure might be more informative for this variable – presentation of the mean and median can make more sense. -antimicrobials: needs to be clear in the legend if this is IV or po or all – prior – ever (for those who only look at the table) – antibiotics – etc. -reformulate: with drainage -Because only severe malnutrition is used for the underlying pathologies, just write it as such in the table -HIV status: were all the children tested on admission? Is this part of the admission tests? -One column can present both the total number (here called frequency- often presented as n=; and the % (percent). -Table 2: The table represents the Type of HAI; add in the legend: CI: Confidence Interval; “a including ventilator-associated pneumonia in pediatrics patients”: what is meant by adding in pediatric patients? Not in neonates? -Table 3: the column with p-values does not add any value, neither “starring” of statistical significant results; it needs to be added if these RR are from bivariate (crude estimates) or multivariate analysis – if adjusted: add in variables (it is clear to me that it is crude, because there is an additional table 4 – however this needs to be more clear in the legend or with the title of the table; also in

	this table write directly severe malnutrition as the investigated underlying illness. -Table 4: -Add in the legend the variables adjusted for – and if different models were used or not. -Not necessary or additional value of reporting the p-value. -eTable 3: The Chi-square test does not add much value to the table.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: walelegn
Institution and Country:
University of Gondar
Institute of Public Health
Ethiopia
Competing interests: None

Please leave your comments for the authors below
Title : "Incidence and risk factors for healthcare-associated infection among pediatric patients in a teaching hospital: a prospective study in southeast Ethiopia.
Article Number: Manuscript ID bmjopen-2020-037997

1. Line 124 page 6: " HAIs were confirmed by senior physician specialists working in the respective NICU and pediatrics ward"

It is true that , for HAIs it needs laboratory blood culture to confirm the result ? is it valid as a scientific paper, better to include the method section the laboratory result as a guide in addition to the clinical criteria?

Response 1:

Our respect reviewer Dr. walelegn thank you for your comment. We completely agree with your suggestion. Since the study was conducted for 8 months and due to financial constraint we did not use laboratory culture to identify HAIs. We also have limited laboratory facilities and expertise; for this reason, we only adhere to the clinical criteria (confirmed by senior pediatrician specialists). This is one of the limitations of the present study and we included this issue in the study limitation section. Please see the revised manuscript limitation section. We included this statement "Finally, we did not use laboratory blood culture to confirm the results of HAIs as a guide in addition to the clinical criteria because of financial constraint"

2. Line 143: Page 7 : " A Generalized Linear Model (GLM) , why not specific to logistic regression indicated in the paper? the researcher used multivariable logistic regression. GLM is broad term

Response 2:

Thank our respect reviewer Dr. walelegn. As per your wise advice, it is corrected accordingly. Please see the revised manuscript data processing and analysis section. We included a statement "Multivariable logistic regression was used to identify factors with increased risk of HAIs."

3. Line 184 page 9" Incidence and type of healthcare-associated infection"
4. Line 198 page 10 : "Risk factors of hospital-acquired infections"

It is clear that the terms are similar but use a uniform term either Hospital acquired infection or Health care associated infection" The term Health care associated infection includes care with geriatrics in some operational definition , but try to use uniform terms through out the paper either Hospital acquired infection or Healthcare associated infection?

Response 3 & 4:

Thank our respect reviewer Dr. walelegn. Please accept our apologies for this inconsistency. As per your wise advice, we corrected all inconsistencies throughout the manuscript. Please see the revised manuscript result section.

5. I advise the author try to refer and use the paper conducted in Ethiopia " https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181145 this may help for to high light risk factors for hospital acquired infection in teaching hospitals of Ethiopia.

Response 5:

Thank our respect reviewer Dr. walelegn. As per your wise advice we cited the stated interesting article and we also highlighted the risk factors for hospital-acquired infection in teaching hospitals in Ethiopia. Please see the revised manuscript introduction section.

We included this narration "Surgery since admission [23,26], underlying medical conditions [23,25], patients' with catheter [23,25,26], patient put on mechanical ventilation [26] , immune deficient patients [23,25], patient age [26,32,33], hospital type [32], the type of ward [33], and prolonged hospitalization [33] were found to be important factors associated with increased risk of HAIs in Ethiopia."

Dear Dr. walelegn we are so glad to have your comments. As per your advice, we corrected your comments accordingly. If there is anything you can comment we are ready and willing to learn from you. Thank you with all respect.

Reviewer: 2

Reviewer Name: M Cotton
Institution and Country:
Stellenbosch University
South Africa
Competing interests: None declared

Please leave your comments for the authors below
Useful paper to document NI in hospitalised children.
Page 2(abstract), line 42: There is no data on the reason for hospitalization. While it is likely that unnecessary hospitalization should be avoided, this conclusion was not validated.

Response:

Thank our respect reviewer Dr. M Cotton. As per your wise advice we revised the conclusion as "The present study has revealed that hospital-acquired infections affected 13 in 100 admitted pediatric patients – which is a significant burden in the morbidity rate among pediatric patients. Length of stay in the hospital and the presence of underlying diseases were found to be important factors associated with increased risk of hospital-acquired infections." Please see the revised manuscript abstract section.

Page 6, line 61: The reference by Sheng is incorrectly interpreted: 80% of deaths were linked to nosocomial infection (NI) rather than 80% of those with NI died

Response:

Thank our respect reviewer Dr. M Cotton. Following your recommendation, we amended accordingly. We amended as "A study by Sheng et al. reported that 80% of hospitalized patient's deaths were linked to nosocomial infection (NI)[9]." Please see the revised manuscript introduction section.

Page 6, line 112: Add 'patients' after 'paediatric'

Response:

Thank our respect reviewer Dr. M Cotton. It is corrected accordingly. Thank you for your support. Please see the revised manuscript method section.

Page 7, line 92: Change 'And the overall incidence rate of 35.8 per 100 patients' to 'The overall incidence rate of 35.8 per 100 patients.'

Response:

Thank our respect reviewer Dr. M Cotton. It is corrected accordingly. Thank you for your support. Please see the revised manuscript method section.

Page 8, line 50: Change 'pediatrics' to ;'children or pediatric patients'

Response:

Thank our respect reviewer Dr. M Cotton. It is corrected accordingly. Thank you for your support. Please see the revised manuscript method section.

Page 10, line168: Add 'patients' after 'paediatric'

Response:

Thank our respect reviewer Dr. M Cotton. It is corrected accordingly. Please see the revised manuscript method section.

Page 10, line 169: Why were asymptomatic patients excluded?

Response:

Thank our respect reviewer Dr. M Cotton for your comment. Please accept our apologies for this and other proofread mistakes, as we mentioned in the study population and eligibility criteria “Pediatric patients showed signs of infection and/or symptoms of the infection within the first 48 hours were excluded from the study.” Thus it is corrected as, “…39 pediatric patients showed signs of infection and/or symptoms of the infection within the first 48 hours and were excluded from the study.” It is not asymptomatic but “symptoms” Please see the revised manuscript result section.

Page 10, line 173: Replace 'fourthly' with 'forty'

Response:

Thank our respect reviewer Dr. M Cotton. We corrected accordingly. Please see the revised manuscript method section.

It becomes “Two hundred forty-eight (55.4%) of the study participants were male with an overall male-to-female ratio of 1.24: 1.”

Page 10, line 180: Delete 'An underlying disease condition, which is'

Response:

Thank our respect reviewer Dr. M Cotton. We corrected accordingly. Please see the revised manuscript result section.

It becomes “Severe acute malnutrition (SAM) was reported by 54 (12.1%) participants.”

Page 11, line 172: Change ‘remaining’ to ‘remainder’

Response:

Thank our respect reviewer Dr. M Cotton. Following your recommendation, it is corrected accordingly. Please see the revised manuscript result section.

It becomes “Of the total patients included in the study, 201 (44.9%) were from the neonatal intensive care unit (NICU) and the remainder were from the pediatric ward.”

Table 3: What is a drainage tube? Is it a nasogastric tube?

Response:

Thank our respect reviewer Dr. M Cotton. As per your wise advice, we clarify what a drainage tube signifies in this particular study. Drainage tube indicated: insertion of chest tube, endotracheal and nasogastric (NG) intubation. We put this in a footnote. Please see the revised manuscript table 1.

Table 1: How does a peripheral IV line differ from a peripheral vascular catheter?

Response:

Thank our respect reviewer Dr. M Cotton.

[b]Peripheral intravenous (IV) catheter: A peripheral intravenous (IV) catheter is inserted into small peripheral veins to provide access to administer IV fluids and medications.

Regarding, a peripheral vascular catheter this is inconsistency we mean “urinary catheter” as described in Table 3 instead of “peripheral vascular catheter”. We made the necessary corrections in the revised manuscript. Thank you for your deep insight. Please see the revised manuscript result section.

Page 12, line 204: Was duration of hospitalization correlated with underlying disease? Di any children have avoidable hospitalization? (this was addressed in 1st African pediatric NI study – (PIDJ 1989 [10] 676-83).

Response:

Thank our respect reviewer Dr. M Cotton for your comment. In short, we did not see any correlation between these two variables, however, we observed a positive correlation. For your information; the correlation between duration of hospitalization and underlying disease is 0.0609, which is fairly low, but it's positive.

Regarding the question on “Do any children have avoidable hospitalization?”. To be honest, we do not have any information or this is beyond the scope of the study. We did not have any confidence to answer this specific question. We consider this interesting issue in our next project. Thank you.

Discussion: Were any organisms isolated? Is the antibiotic resistance profile known? This is important information

Response:

Thank our respect reviewer Dr. M Cotton for your comment. Since the study was conducted for 8 months and due to financial constraints and lack logistics we did not use laboratory culture to isolate organisms and perform antimicrobial susceptibility profile. This is one of the limitations of the present study and we indicate this issue in the study limitation section. Please see the revised manuscript limitation section.

Dear Dr. M Cotton we are so glad to have your comments and suggestions. We would also like to appreciate your help to correct our proofread mistakes. As per your advice, we corrected your comments accordingly. If there is anything you can comment we are ready to correct and willing to learn from you. Thank you with all respect.

Reviewer: 3

Reviewer Name: Joanna Merckx
Institution and Country: McGill University, Canada
Competing interests: employee, Medical Affairs bioMérieux Canada - no COI for the review of this paper

Please leave your comments for the authors below
Sahiledengle et al report the results of their prospective study, over a period of 8 months, on the incidence of HAI in a tertiary care pediatric hospital in Ethiopia. The manuscript describes the patient population and provides epidemiologic cumulative incidence and incidence rate data for the composite outcome of HAI in both their NICU and pediatric wards. The group used valuable methods, using a prospective study design and using an individual patient chart investigation approach. In addition, the study aims to determine risk factors associated with HAI in the study population.

While the overall results and the presented data are certainly of high value, mainly given the lack of epidemiologic data in the studied setting, major limitations apply and the manuscript requires major changes prior to be suitable for publication.

Response:

First, we would like to give our sincere gratitude to our respected reviewer Dr. Joanna Merckx for providing advice, suggestions, and comments. This is a prestigious learning opportunity for us; we learned a lot from your comment and we also motivated us to read more. Moreover, we take a lesson for our next project. Thank your Dr. for such detailed, to the point and important comments. Since some of the general comments were well addressed in the detailed comments section please check the detailed comment point by point response. Please follow our point by point response to reviewer comments. We used a yellow text highlighter for all the affected revisions we made in the revised manuscript document.

General comments:
-The main objective for the study and the manuscript is stated as: the lack of a prior published manuscript on the topic. Epidemiological data on the incidence of HAI are necessary, because without a valid and precise baseline, the problem remains unnoticed and interventions are not designed nor implemented, and neither can their impact be assessed. Reformulation of the study objective with a sentence on the importance of regional HAI data for improvement of patient care is recommended. A link with AMR can be made.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, we rephrased the abstract and introduction section, particularly the objective of the study. We also used your interesting expression of the problem. Please see the revised manuscript abstract and introduction section last paragraph.

“Epidemiological data on the incidence of hospital-acquired infections (HAIs) are necessary because without a valid and precise baseline, the problem remains unnoticed and interventions are not designed nor implemented, and neither can their impact be assessed. In Ethiopia, data about the

occurrence of hospital-acquired infections among hospitalized pediatric patients are lacking. We aimed to determine the incidence and risk factors of hospital-acquired infections among pediatric patients in Ethiopia."

-The secondary objective to assess risk factors misses rigorous evaluation and interpretation of the results. Alternative statistical methodology and/or recognition of the limitations of current methods and correct interpretation of the results is suggested.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We recognize this as a limitation and we include a statement in the limitation of the study sections

> In this study, we focused on a small number of risk factors for hospital-acquired infections; some important variables were not included.

-The methods are not clearly described and multiple details remain unclear eg. the moments and procedures followed for the data assessment and data collection, the definitions used and the availability of diagnostics for infectious processes (microbiology).

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We revised this issue in detail in the revised manuscript.

"Data collection procedures

"First, consent was sought from each child's parents/guardians before commencing any study procedures. On admission, all children were evaluated clinically to exclude community-acquired infections by a pediatrician. Afterward, socio-demographic and clinical data were collected by a structured questioner using an individual patient chart investigation approach-accordingly-a detailed clinical history of patients were taken and recorded. Patients presenting with no new signs or symptoms of infection after the first 48 hours of admission were included and followed prospectively for the development of HAIs during their stay in the hospital. Data were collected from enrolled patients on a daily bases: children were followed by a pediatrician daily, charts were reviewed and discussions with nurses and physician caring for the patient were held. HAIs were confirmed by senior pediatrician specialists working in the respective NICU and pediatrics ward."

Please see the revised manuscript "Data collection procedures" and limitation of the study section

-Clinical diagnosis of HAI is made. Can the authors describe the methods available for pathogen identification?

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. In this study, data on pathogen identification and AMR were not collected because of financial constraints. And we explain this issue in the study limitation section. Please see the revised manuscript.

"Finally, we did not use laboratory culture to isolate organisms as a guide in addition to the clinical criteria to confirm the results of HAIs because of financial constraint, laboratory facilities, and expertise."

-There is no description on how biases were addressed during the different study phases: protocol development, data analysis and result interpretation. Which are the remaining biases that need to be taken into account interpreting the results? Only a comment is made about possibly missing cases that manifested after discharge.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice and suggestion, we include the data quality control section. Please see the revised manuscript method section.

-The outcome HAI is a composite outcome: better description of the different components of HAI and which where assessed, including the validity of the assessment, would improve the understanding of the HAI. The different HAI are now only reported in the supplemental table, bringing these data to the main paper might be considered.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your advice, we bring the different types of HAIs identified in this study and it is presented by bar-graph for better illustration. Please see the revised manuscript Figure 2 and the data quality control section.

-An important issue is the variable: length of stay (LOS), in the study: “duration of hospitalization”. This variable, being continuous, is used as a binary variable “6 days” or more (chosen based on the median LOS). *It is not completely clear which time contributes and which time does not contribute to the denominator. More detailed reporting on the calculation of the incidence rate is necessary.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment and suggestion. We apologize for not making this very clear in the data analysis section. The variable LOS continues; we dichotomize these days based on the median days since the variable LOS is not normally distributed/ skewed. We calculated the cumulative incidence as the proportion of children who experienced HAIs during the study period (8 months), without taking into account when the study participants developed the HAIs. While we estimated the incidence rate as the number of HAIs cases per unit of time, and the denominator is the total amount of time "at risk" without experiencing HAIs for all children who were being followed for 8 months. We rewrite this information in the revised manuscript for better clarification. Please see the revised manuscript data analysis section.

*In the discussion and conclusion, duration of hospitalization is interpreted as a causal factor, which if avoided and taken out, will lead to a direct decrease of the HAI rate and HAI cumulative incidence. This conclusion is not correct and flawed. *There are multiple issues with the LOS variable: from being a possible collider, outcome (effect of HAI- reversed causation) and being confounded. *The used analysis also does not take any time-varying risk into account.
*With the present analysis methods, an association between duration of admission and HAI incidence can be concluded, but no further causal, nor speculations regarding the impact of decreasing length of stay on HAI can be made using the present data and analysis.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. You are right, we agree with your comment. It is corrected accordingly. Please see the discussion and conclusion section of the revised manuscript.

“In this study, the risks of developing HAIs were three times higher among children who stayed longer than or equal to the median six days than their counterparts. Despite this positive association, this is not proof that decreasing the length of stays neither increasing admission days decreased/increase the occurrence of HAIs. Possible revered causation may be one of the mechanisms why this prolonged length of stay is associated with HAIs. Moreover, there is evidence that HAIs cause a prolonged length of stay [61-64]." Taken from the discussion section

Conclusions: “Length of stay in the hospital and underling severe acute malnutrition were found to be important factors associated with increased risk of hospital-acquired infections.”

We also put “The used analysis also does not take any time-varying risk into account.” as a study limitation in the revised manuscript.

Dr. Joanna Merckx to be honest with you, we did not know such a thing exists in HAIs infection studies “time-varying risk “ and “time-dependent bias” until reading your comments. This is a lesson for our next project. Please accept our apologies for this limitation. Thank you.

-It is clear that events within the first 48h of admission, as is the consensus, are censored. It is unclear if the first 2 days are counted in the denominator of time at risk for the patients that do not get excluded from the study.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. In short, patients who have developed any form of infection within 48 h of admission were excluded and all the rest of the pediatric patients were followed until discharge for the occurrence of HAI. We count those days in the denominator of time at risk for the patients that do not exclude from the study. Commonly, calculation of days at-risk until the first infectious episode or for the entire period of hospitalization was collected.

-The time at risk for the different HAI is not clear. Presenting the device-specific rate for lines, urinary catheter, mechanical ventilation would be informative. It is not clear if these risks are calculated by their time of exposure or the total duration of hospitalization is used.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. As shown in Table 2 we presented the proportion of hospital-acquired infections among pediatric patients. We did not estimate the time at risk for the different HAI. Since the study aimed to estimate the overall incidence of HAIs and the daily total number of patients, a total number of device-specific days and daily counts at the end of the study period were collected to estimate the device-associated HAI incidence rates.

-There is no reflection on the mortality of the patients and if these were patients with diagnosed HAI or not.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment.. We included this information in the revised manuscript result section.

Of the study participants, 24 (5.4%) died. Therefore, the overall incidence density rate of admitted pediatrics mortality was 7.44 per 1000 pediatrics days of follow up

-It is good that also the absolute effect measures are communicated.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice we calculated and include AR in table 4. Please see the revised manuscript table 4.

-Severe malnutrition and infection risk, including HAI, is a separate discussion. Given the lack of microbiology data endogenous infections will be misclassified as HAI. This aspect is not touched upon in the manuscript. For this particular subgroup, data on CLABSI – BSI vs HAP are of interest.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. Please see the study limitation section. We satisfactorily addressed this issue "Several limitations on this prospective study need to be considered. ….. we did not use laboratory culture to isolate organisms as a guide in addition to the clinical criteria to confirm the results of HAIs because of financial constraints. Given the lack of microbiology data endogenous infections may be misclassified as HAIs."

-For neonates: no report on prematurity or (V)LBW status is given. These variables are important baseline characteristics of the study population when describing HAI in a NICU unit.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. We included this information in the revised manuscript table 1 and Figure 2. Please see the revised manuscript table 1.

-The manuscript would benefit from help with the English language. Past and present tense are often mixed. Below in the comments, I refer to some particular sentences or words used.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your support and editing job. We have corrected this inconstancy throughout the document.

Detailed comments:
-Abstract:
-line 20-24 - Objectives: wording "infections among admitted pediatric in Ethiopia. " – to change to admitted children or pediatric patients.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, we corrected accordingly "Therefore, the study aims to determine the incidence and risk factors of hospital-acquired infections among pediatric patients in Ethiopia." Please see the revised manuscript abstract section.

-Design: prospective cohort study.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, it is corrected. Please see the revised manuscript abstract section.

-line 38-39: The 13 in 100 is not a rate but a cumulative incidence or proportion as the authors report correctly in the results, it is misleading to call it a morbidity rate in the abstract.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. You are right and it is corrected as per your advice.

Conclusions: The overall cumulative incidence of hospital-acquired infections was about 13 per 100 admitted children. Length of stay in the hospital and the presence of underlying diseases were found to be important factors associated with increased risk of hospital-acquired infections.

Please see the revised manuscript abstract.

-line 41: " Avoiding unnecessary length of stay could save lives and minimize the occurrence of healthcare-acquired infections. ": there is no proof that this will help, this is not a conclusion you can make from the study. There is only an association found, this is not a proof that decreasing the length of stay in children from 5 to 4 days will do the job, neither from 7 to 6 or 6 to 5. Moreover because it is even written in the introduction that there is evidence that HAI cause prolonged length of stay. Revered causation can thus be one out of the mechanisms why this prolonged LOS is associated with HAI.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. Again, it is a prestigious opportunity for us to learn from your comments. We did not see it in this ways, the other reviewer also raised a similar concern. And we revised the conclusion and we restrict ourselves not to say much about the length of stay as this is not the aim of the study. Please see the revised manuscript conclusion section.

Conclusions: The overall cumulative incidence of hospital-acquired infections was about 13 per 100 admitted children. Length of stay in the hospital and the presence of underlying diseases were found to be important factors associated with increased risk of hospital-acquired infections.

-Attention to English: "Pediatric and neonates inpatients were recruited and followed-up" and "The full burden of healthcare-associated infections could not be captured in this specific study as our study, was limited to in-hospital assessment only and leaving outpatients who may potentially develop an infection after discharge. "

Response:

Thank our respect reviewer Dr. Joanna Merckx for your wise suggestion. We revised this section. Please see the revised manuscript “Strengths and limitations of this study” section.

Strengths and limitations of this study

> To the best of our knowledge, this is the first prospective study to examine the incidence and risk factors of hospital-acquired infection among pediatric patients in Ethiopia.
> We did not use laboratory culture to isolate organisms as a guide in addition to the clinical criteria to confirm the results of HAIs, which could affect our results.
> In this study, we focused on a small number of risk factors for hospital-acquired infections; some important variables were not included.

-Reporting of p-values in the abstract does not add value.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your wise suggestion. As the ARR show both the strength and direction of the association, we removed p-values from the abstract section. Thank you for your suggestion. Please see the revised manuscript abstract.

-Introduction:
-Faster focussing on HAI in the pediatric population and the absence of regional data would make the introduction more concise and to the point. -It remains unclear if in the hospital or the region any surveillance program is set up or will be set up and where we can situate the collection – measurement of HAI in the near future in the region.

Response:

Thank our respect reviewer Dr. Joanna Merckx. Up to date, there is no surveillance program at the regional or national level targeted on HAIs in Ethiopia. The available evidence on HAIs in the country was gendered from primary studies. If you are interested in measurements of HAIs in the region we are more than willing to collaborate with you at any time. Thank you for showing this positive initiative.

-line 75: take out “as well”

Response:

Thank our respect reviewer Dr. Joanna Merckx. It is corrected. Please see the revised manuscript.

-line 78: “the” change to that

Response:

Thank our respect reviewer Dr. Joanna Merckx. It is corrected. Please see the revised manuscript.

-line 80: “correct “highlighted”

Response:

Thank our respect reviewer Dr. Joanna Merckx. We rephrased the statement. Please see the revised manuscript.
-line 83: “in lieu” not correctly used
Response:

Thank our respect reviewer Dr. Joanna Merckx. We rephrased the statement. Please see the revised manuscript.

-line 92: is not a rate if not over patient days

Response:

Thank our respect reviewer Dr. Joanna Merckx. We corrected accordingly. Thank you. Please see the revised manuscript.

-Methods:
-line 107: NICU introduced as abbreviation and only later written full

Response:

Thank our respect reviewer Dr. Joanna Merckx. Sorry for this mistake, we corrected in the revised manuscript. Please see the revised manuscript method section.

-line 108: change were to are

Response:

Thank our respect reviewer Dr. Joanna Merckx. We corrected accordingly. Thank you.. Please see the revised manuscript method section.

-line 112: the word “pediatric” is often used for pediatric patients or children – please correct

Response:

Thank our respect reviewer Dr. Joanna Merckx. We corrected this issue throughout the manuscript. Thank you. Please see the revised manuscript method section.

-line 112: can you explain what is meant with the patients “becoming asymptomatic within the first 48h” means – are those not already excluded?

Response:

Thank our respect reviewer Dr. Joanna Merckx for this comment. Please accept our apologies for this proofread mistake, as we mentioned in the study population and eligibility criteria “ We enrolled patients presenting with no new signs or symptoms of infection after the first 48 hours of admission in the study. Children have shown signs of infection or symptoms of the infection within the first 48 hours

were excluded from the study. Thus, it is not " it is asymptomatic" rather "symptoms". Sorry for this and other proofread errors.

"Study population and eligibility criteria: All patients (age less than 18 years) admitted to the pediatric ward and neonatal intensive care unit (NICU) were enrolled and those who at least stayed for 48 hours were eligible for the study. Enrolled patients showed signs of infection and/or symptoms of infection within the first 48 hours were excluded from the study." Please see the revised manuscript method section.

-line 115: it is unclear when consent was sought and when data collection was precisely performed. It is unclear when HAI were "diagnosed": at the moment of presentation or after discharge – was there daily chart review? Were the study nurses – clinicians contacted to review the charts daily?
-line 118: is this clinical history or what was collected? It is unclear if there were data collected through interview with the parents or all data come from patient chart review.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment and suggestions. To clarify the procedures in brief "Consent was sought from each child's parents/guardians before commencing any study procedures. First, on admission, all children were evaluated clinically to exclude community-acquired infection by a senior pediatrician. Afterward, socio-demographic and clinical data were collected by a structured questioner from an individual patient medical record folder-a detailed clinical history of patients was taken and recorded. Patients presenting with no new signs or symptoms of infection after the first 48 hours of admission were included and followed prospectively for the development of HAIs during their stay in the hospital. Data were collected from enrolled patients on a daily bases: patients were followed by a pediatrician daily, charts were reviewed and discussions with nurses caring for the patient were held." Following your comments, we clarified these very important issues in the revised manuscript. Please see the revised manuscript "Data collection procedures" section.

-Was the data collection piloted? Is the CDC tool in use outside this study?

Response:

Thank our respect reviewer Dr. Joanna Merckx. The CDC tool was used in previous studies conducted in Ethiopia. (Ali et al from West Ethiopia in 2018 https://doi.org/10.1186/s13756-017-0298-5 and (Yallew etal North Ethiopia 2017) https://doi.org/10.1371/journal.pone.0181145. In this particular study, the data collection tool was pre-tested before the data collection period.

-line 122: word pediatrics

Response:

Thank our respect reviewer Dr. Joanna Merckx. We corrected this inconsistency throughout the manuscript. Please see the revised manuscript.

-line 137: “underline” - underlying disease – however: be specific if co-morbidity is meant or admission diagnosis or discharge diagnosis.

Response:

Thank our respect reviewer Dr. Joanna Merckx. As we mentioned in table 1 this underling condition refers to severe acute malnutrition. We diagnosed this at the time of admission. Severe Acute Malnutrition is a disease that is an underlying condition in many admissions, particularly among under-five children in Ethiopia (please check this article conducted in Ethiopia: https://doi.org/10.1016/j.clnesp.2019.07.001). As per your recommendation, we clarified this in table 1 (footnote) and the study variables section. Please see the revised manuscript.

-HIV status: measured for every patient on admission?

Response:

Thank our respect reviewer Dr. Joanna Merckx. In short, No (n=53) children not tested as we described in table 1.

HIV status	Positive	2	0.4
	Negative	393	87.7
	Not tested	53	11.8

-The operational definitions can maybe be introduced earlier.

Thank our respect reviewer Dr. Joanna Merckx. Following your recommendation we put the operational definition immediately after “Data collection procedures” and before “Study variables”. Please see the revised manuscript.

-line 151: what is “an adverse reaction to the presence of an infectious agent”

Response

Thank our respect reviewer Dr. Joanna Merckx. This is not our definition of HAIs we adopted from the CDC and multiple studies also used this standard definition of HAIs. As you know infection that is neither present nor incubating at the time the patient came to the hospital was considered as hospital-acquired infections. And the invasion of an organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to the infectious agents and the toxins they produce an infection. Many HAIs are antimicrobial-resistant and can result in severe complications, and cause outward unfavorable effects.

-line 156: where does the definition of late-onset neonatal sepsis comes from: this is related to time since birth – age of the patient – not time since admission. Unclear. Are children on the pediatrics ward at risk for early onset or late onset neonatal sepsis? Are they admitted to the ward?

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. It is a learning opportunity for us; since the study was conducted in a referral hospital those premature neonates were referred and admitted to the hospital for further management from nearby district hospitals and primary healthcare facilities. Also, on various occasions neonates were admitted to the referral hospital because of complications due to home delivery (home delivery is customary in the study area and many parts of Ethiopia). As you know neonatal sepsis is the single most common cause of neonatal death in hospitals as well as the community in many developing countries, including Ethiopia. In this study, we just enrolled neonates presenting with no new signs or symptoms of infection after the first 48 hours

of admission, and we identified 6 late-onset neonatal sepsis cases after 48 hours of admission in NICU (2 cases after 7 days of admission and 4 cases were identified after 72 hours of admission). That is why we put late-onset sepsis referring to the presentation of sepsis after 72 hours (7 days). In did, early-onset or late-onset neonatal sepsis were related to time since birth not the time since admission. Furthermore, in Ethiopia, nosocomial infection in newborns defined as " Infection occurring after birth but excluding those infections known to have been transmitted across the placenta such as congenital syphilis, cytomegalovirus, rubella, varicella (chicken pox) and the protozoan parasite, *Toxoplasmosis gondii*." Dear Dr. Joanna Merckx if you have any suggestion please show us the way how to report these findings. With all respect thank you.

-patient involvement can be summarized in 1 sentence

Response:

Thank our respect reviewer Dr. Joanna Merckx. We rephrased the statement as

"Patients and the public were not involved in the planning, designing, and interpreting this data analysis. However, consent was sought from all patients involved in this study. "

-Results:-There are little social determinant variables measured – all described variables, except origin from a rural or urban site, are rather general demographics.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. Since there is limited information on the patient medical record folder we are unable to collect more social determinant variables. We will consider this in our next project. Thank you.

-A flow chart would be informative.

Response:

Thank our respect reviewer Dr. Joanna Merckx. We included Figure 1 to illustrate study participants. Please see Figure 1.

-line 181: unclear if the diagnosis of SAM is made by a questionnaire of medically assessed – re-write "reported by"

Response:

Thank our respect reviewer Dr. Joanna Merckx. The diagnosis of SAM is made medically and we re-write the sentence as "Fifty-four, (12.1%) of children were diagnosed with severe acute malnutrition (SAM) at the time of admission" please see the revised manuscript.

-The use of antimicrobials is an important variable. Is there more granular data on: antimicrobials before admission – during total admission – treatment for HAI – po versus IV versus IM. The description "at the time of the study" is unclear

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. We wish to have such kind of important information before the commencement of the present study. Dr. we thank you for bringing this interesting question. We will learn more from your comments. Unfortunately, we only collected

data on antimicrobials use before admission (please see table 1 foot note) and antimicrobial use before surgery.

-line 186: time of onset of HAI – time of diagnosis?

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. It should be “time of diagnosis”. We also correct this in the revised manuscript. Thank you for your comment.

-line 192-193: wording - pediatrics

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. We corrected this wording issues throughout the manuscript. Please see the revised manuscript.

-line 200: “statistically associated”: does not make sense.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We re-write this statement as “Bivariate analysis of risk ratio has indicated that hospital duration (> 6 days), the patient received antimicrobial medications, presence of drainage tube, and children diagnosed for SAM were predispose for HAIs.” Please see the revised manuscript.

-line 204: it is important to write out what was adjusted for.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We included what was adjusted in the final multivariable model (table 4 footnote). Thank you. Please see the revised manuscript table 4.

-The only underlying condition included in the analysis is SAM – please name as such. Regarding SAM: type of HAI? Their time at risk – more time with IV?

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We corrected accordingly as per your wise advice. “Patients with SAM conditions had 2.83 times higher risk of developing HAIs compared to their counterparts [adjusted RR: 2.83, 95% CI (1.61-4.97)].” Please see the revised manuscript result section.

- There are 54 SAM cases in this study, of these 13 develop HAIs (Please table 1)
- 12 diagnosis for pneumonia and 1 measles
- Of 54 SAM patients, 51 with IV line, and 21 SAM patients longer hospital stay

-line 208: It is stated that clinical related confounders were not statistically significantly associated with the presence of HAI. Which of the variables are defined as confounders – is there certainty that the confounders are not mediaters nor colliders? A DAG can be of value. Or:
Are the variables “assumed” confounders dependent of their “statistical significant” result in the bivariate analysis? Thanks for clarification.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. To be honest we did not have any idea what you mean? We are not even familiar with this terminology of “…mediaters nor colliders.”. Please accept our apologies for this limitation. We may not adequately satisfy your question. However, in this study, we include variables that were assumed confounders based on their statistical significant result in the bivariate analysis. That is all we have done. Thank you for giving us the insight to read more and learn from your comments.

-Where there patients with more than 1 episode of HAI?

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. In short no, we identified 57 HAIs and none of the study participants were identified with more than one episode of HAIs.

-Discussion:
-line 220: word pediatrics and incorrect reporting of the 18 per 1000 as a proportion.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. we corrected as per your wise advice. “In this study, the overall incidence rate of HAIs was 17.7 per 1000 pediatrics days of follow up.” Please see the revised manuscript.

-line 222: point?

Response

Thank our respect reviewer Dr. Joanna Merckx. We corrected accordingly. Thank you.

-When comparing data can it be made clear if the comparator are pediatric data only or combined pediatric and adult data. In addition: NICU and pediatrics have difference incidence and incidence rate – there is little discussion and direct comparison. What is also unclear is if the studies used for comparison are all cohort studies or include point-prevalence surveys or are part of structured infection prevention and control structures. Some more detail and grouping of comparisons is more informative compared to the many different data that are now written out in the paragraph.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment and suggestion. While we discussed our finding we carefully observe these differences and explains the difference accordingly in the revised manuscript. We try our best to make the discussion and comparisons more informative. Please see the revised manuscript.

-Differences by sex: this is compared with a study on surgical site infections – how does this pediatric and neonatal population directly relate to this study? Is in the neonatal population this difference important?

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We feel your concern and we accept your comment. Since, the previous study "Luksamijarulkul P, Parikumsil P, Oomsuwan VN. Nosocomial surgical site infection among Photharam hospital patients with surgery: Incidence, risk factors, and development of risk screening form. J Med Assoc Thai. 2006; 89(1): 81-9." was direct to surgical site infection it is difficult for us to compare our finding on gender difference. As a result, we replaced the citation with other repeated cross-sectional studies, with prospective follow-up of 19,468 hospitalized patients; which reported study that "males present higher overall HAIs prevalence ..." please see the revised manuscript.

-little attention goes to how many of the HAP are VAP.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. While we report HAP we put a footnote in table 2 that describes ventilator-associated pneumonia. Overall, among mechanically ventilated patients we identified 7 VAP during their hospital stay. VAP developed in 9.21% [7/76] of children undergoing mechanical ventilation. As per your wise advice, we discuss this VAP in detail. Please see the revised manuscript discussion section.

-For the discussion on the association between length of hospitalization and HAI incidence I refer to the major comments. The discussion, acknowledging biases is warranted.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We revised this discussion section following your suggestion and advice.

In this study, the risks of developing HAIs were three times higher among children who stayed longer than or equal to the median six days than their counterparts. Despite this association is found, this is not proof that decreasing the length of stay in admitted children, neither increasing length of stay decreased/increase the occurrence of HAIs. Moreover, there is evidence that HAIs cause the prolonged length of stay [61-63]. Possible revered causation may be one of the mechanisms why this prolonged length of stay is associated with HAIs.

Thank you for this learning opportunity, please see the revised manuscript.

-line 257: typo: thru

Thank our respect reviewer Dr. Joanna Merckx for your comment. It is corrected.

-Conclusions:
-line 271: the word community is oddly used, given these are nosocomial infections – but of course, our hospitalized patients always originally come from and within a community.

-line: 273: incorrect conclusion as discussed prior

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, we revised the conclusion section accordingly. Please see the revised manuscript.

"Conclusions

The present study revealed that the cumulative incidence of hospital-acquired infections (HAIs) was about 13 per 100 admitted children. And the overall incidence rate of HAIs was 17.75 per 1000 pediatrics days. Length of stay in the hospital and patients with severe acute malnutrition (SAM) conditions were associated with increased risk of hospital-acquired infections. Further studies are strongly recommended to identify other important factors including isolating the bacterial, fungal, and viral agents responsible for HAIs in the region. "

Thank you for your valuable comment.

-Table 1:
-the age categories vary widely in the number of months. A figure might be more informative for this variable – presentation of the mean and median can make more sense.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, we included a bar graph for the presentation of age category by sex. Please see the revised manuscript Figure 1.

-antimicrobials: needs to be clear in the legend if this is IV or po or all – prior – ever (for those who only look at the table) – antibiotics – etc.

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We include a footnote on the use of antimicrobials. Please see the revised manuscript Table 1 footnote.

-reformulate: with drainage

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. We reformulated accordingly. Thank you for your advice. Please see the revised manuscript Table 1.

-Because only severe malnutrition is used for the underlying pathologies, just write it as such in the table

Response

Thank our respect reviewer Dr. Joanna Merckx for your suggestion. It is corrected as you suggested. Please see the revised manuscript Table 1-3 and other parts of the manuscript.

-HIV status: were all the children tested on admission? Is this part of the admission tests?

Response

Thank our respect reviewer Dr. Joanna Merckx for your comment. In short, yes this is the admission test and this is a standard procedure for many admissions (through provider initiative counseling and testing (PICT) service).

-One column can present both the total number (here called frequency- often presented as n=; and the % (percent).

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. We presented the table as per you suggestion [one column for both n(%)].Please see the revised manuscript Table 1.

-Table 2: The table represents the Type of HAI; add in the legend: CI: Confidence Interval; “a including ventilator-associated pneumonia in pediatrics patients”: what is meant by adding in pediatric patients? Not in neonates?

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. We add CI in the legends; we apologize for this wording “…in pediatric patients”. In the revised manuscript we corrected accordingly. Please see the revised manuscript Table 2 foot notes. Thank you.

-Table 3: the column with p-values does not add any value, neither “starring” of statistical significant results; it needs to be added if these RR are from bivariate (crude estimates) or multivariate analysis – if adjusted: add in variables (it is clear to me that it is crude, because there is an additional table 4 – however this needs to be more clear in the legend or with the title of the table; also in this table write directly severe malnutrition as the investigated underlying illness.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, we removed p-values from crude estimates table 3 and we clearly described this in the title of table 3. We also describe SAM as you suggested in this other part of the manuscript. Thank you. Please see the revised manuscript Table 3.

-Table 4:
-Add in the legend the variables adjusted for – and if different models were used or not.
-Not necessary or additional value of reporting the p-value.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment and suggestion. Following your recommendation, we included a footnote of variables we adjusted for in the final multivariable model. We also removed p-values from table 4. Thank you for this and multiple suggestions you the improvement of the current manuscript. Please see the revised manuscript Table 4.

-eTable 3: The Chi-square test does not add much value to the table.

Response:

Thank our respect reviewer Dr. Joanna Merckx for your comment. As per your wise advice, we removed p-values (Chi-square test) from table 3. Please see the revised manuscript Table 3.

Dr. Joanna Merckx we are so privileged to gain knowledge from your comments. All your comments and suggestion are to the point and essential for the improvement of our manuscript. We learn a lot from you, sometimes we are ashamed of our mistakes; sometimes we are encouraged to reading more; we discover new knowledge, and we see our limitations when we encounter some of your interesting questions. Dr. we try our best to address your comments and concerns. If there is anything you can comment on or correct we are ready and willing to learn from you. Thank you again.

VERSION 2 – REVIEW

REVIEWER	Cotton, Mark Stellenbosch University, Paediatrics & Child Health
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	The paper is useful but requires more editing for grammar and readability.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3 previously commented "There is no description on how biases were addressed during the different study phases: protocol development, data analysis and result interpretation. Which are the remaining biases that need to be taken into account interpreting the results? Only a comment is made about possibly missing cases that manifested after discharge". We do not feel that this comment has been addressed by the added data quality control section. Please discuss any potential bias from the study design, and how these potential biases were controlled. Any potential bias which you were unable to control should be discussed as a limitation of the study.

Response:

Thank you for your wise advice. As per your suggestion we include a statement on any potential bias from the study design, and how these potential biases were controlled in data quality control section and study limitation section.
We include the following statement in the data quality control section of the revised manuscript. “In order to minimize the potential effects of confounder variables, multivariable logistic regression model was used, and analyses were adjusted to known confounder, such as age. In addition, the researchers try to reduce selection bias by including all admitted patients in our follow ups. Moreover, to reduce the effect of observer bias the data collectors have no preconceived expectations of what they should find in an examination” Further, we discussed the remaining potential bias as a limitation of the study section. Please see the revised manuscript data quality and limitation of the study section.

- The following comment from reviewer 3 does not appear to have been addressed by the revisions to your Introduction: "Faster focussing on HAI in the pediatric population and the absence of regional data would make the introduction more concise and to the point".
- Reviewer 3 previously stated that "It remains unclear if in the hospital or the region any surveillance program is set up or will be set up and where we can situate the collection
– measurement of HAI in the near future in the region". You have clarified in your response that "to date, there is no surveillance program at the regional or national level targeted on HAIs in Ethiopia. The available evidence on HAIs in the country was gendered from primary studies". Please add this information to the manuscript.

Response:
Thank you for your suggestion. As per your wise advice we include the above statement in the last paragraph of the introduction section. Please see the revised manuscript introduction section. Thank you.

Up to date, there is no surveillance program at the regional or national level targeted on HAIs in Ethiopia. The available evidence on HAIs in the country was gendered from primary studies. Moreover, to the best of our knowledge, there is no single published report on the incidence and risk factors of HAIs among pediatric patients in Ethiopia. In order to maximize the prevention of hospital-acquired infections (HAIs) and antimicrobial resistance in Ethiopia, epidemiological data on the incidence of HAIs are crucial because without a valid and precise assessment of HAIs, the problem remains unnoticed. Therefore, this study was designed to determine the incidence and risk factors of HAIs among pediatric patients in Goba Referral Hospital, Southeast Ethiopia. The current study helps policymakers to improve their decision making and input for healthcare professionals for the improvement of patient care.

In addition, the above previously stated comment from Reviewer 3“ -Introduction: -Faster focussing on HAI in the pediatric population and the absence of regional data would make the introduction more concise and to the point. It remains unclear if in the hospital or the region any surveillance program is set up or will be set up and where we can situate the collection – measurement of HAI in the near future in the region.” We believe this comments are addressed in the revised manuscript. Thank you.

- On line 235 please correct "... HAIs in hospitalized pediatric in Sub-Saharan African ..." to "... HAIs in hospitalized pediatric patients in Sub-Saharan Africa ..."

Response:
Thank you for your correction. We corrected accordingly. Please see the revised manuscript discussion section. Thank you.

- You have clarified in your response to reviewer 3 that the definition of HAIs used in the manuscript was adopted from the CDC and other multiple studies. In that case, please provide a reference for the definition in the manuscript.

Response:
Thank you for your suggestion. As per your wise advice we provide a reference for the definition in the manuscript. Thank you.

- You have provided a definition of late-onset neonatal sepsis in your response to reviewer 3. Please ensure this is also defined in the manuscript.

Response:
Thank you for your suggestion. As per your wise advice we provide a definition of late-onset neonatal sepsis in the operational definition section.

- Reviewer 3 previously stated that "A flow chart would be informative". You have stated in the response that a flow chart has been provided as figure 1. Figure 1 appears to be a bar chart, please check and revise.

Response:
Thank you for your suggestion. As per your wise advice we provide a flow chart that showed the study procedures. Please see the included Figure 1 in the revised manuscript document.

- The Patient and Public Involvement statement should not include information on participant consent - this information should be provided elsewhere in the manuscript. Thus, please remove the following sentence from the Patient and Public Involvement statement "However, consent was sought from all patients involved in this study".

Response:
Thank you for your suggestion. As per your wise advice we remove the following sentence from the Patient and Public Involvement statement "However, consent was sought from all patients involved in this study". Please see the revised manuscript Patient and Public Involvement statement section.

- You have stated in the response to reviewer 3 that "since there is limited information on the patient medical record folder we are unable to collect more social determinant variables". Please state this in the manuscript.

Response:

Thank you for your suggestion. As per your wise advice we included the stated information that "since there is limited information on the patient medical record folder we are unable to collect more social determinant variables" in the limitation section of the revised manuscript. We included this statement “Sixth, since there were limited information on the patients’ medical record folders more social determinant variables were not collected. In addition, this study is not free from the effects of information bias as we are not utilized ‘blinding’. Another limitation of the study is that we could not adjust the results for the effect of social determinant variables on HAIs because the information on these social determinant variables was not collected in our study.” Please see the revised manuscript “limitation of the study section”

- You have stated in the response to reviewer 3 that "none of the study participants were identified with more than one episode of HAI". Please state this in the manuscript.

Response:
Thank you for your suggestion. As per your wise advice we state this information the reslt section of the revised manuscript. “A total of 57 patients experienced HAIs and none of the study participants were identified with more than one episode of HAIs.” please see the revised manuscript result section- Incidence and type of hospital-acquired infection

- You have stated in the response to reviewer 3 that "in this study we include variables that were assumed confounders based on their statistical significant result in the bivariate analysis". Please include this information in your manuscript.

Response:
Thank you for your wise advice. as per your suggestion we included the following statement “Variables that were assumed confounders based on their statistical significant result in the bivariate analysis were included in multivariable model.” Please see the Data processing and analysis section of the revised manuscript.

- Reviewer 3 previously commented "What is also unclear is if the studies used for comparison are all cohort studies or include point-prevalence surveys or are part of structured infection prevention and control structures". This comment does not appear to have been addressed in the discussion section.

Response
Thank you for your advice. Our respected editor’s we apologized for not making this clear in our previous manuscript. As reviewer 3 previously commented "What is also unclear is if the studies used for comparison are all cohort studies or include point-prevalence surveys or are part of structured infection prevention and control structures". We addressed this issue in the revised manuscript discussion section (please see paragraph 2 and 3). While we compare our finding with studies conducted elsewhere, we limited our self to the pediatric population, include a more detail and grouping of comparisons as “prospective/cohort study or point-prevalence study”.

Reviewer: 2

The paper is useful but requires more editing for grammar and readability.

Response:
Thank you Reviewer: 2 for your comment. As per your wise advice we improve the revised manuscript to improve readability of the paper.