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DATA DESCRIPTOR

Occurrence of human infection with *Salmonella* Typhi in sub-Saharan Africa

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Typhoid fever, caused by *Salmonella enterica* serovar Typhi, results in over 1.2 million cases and 29 thousand deaths annually from sub-Saharan Africa. Combating this disease requires various intervention approaches, such as typhoid conjugate vaccines and improving water, sanitation, and hygiene. Enhancing the effectiveness of these strategies necessitates a deeper understanding of the variation of the typhoid fever across the target region. Although the magnitude and variation of typhoid fever at the country level have been studied globally, sub-national variation remains underexplored. To address this gap, we collected data from 229 published reports on typhoid fever occurrences in sub-Saharan Africa between January 2000 and December 2020. The dataset includes information on the year and geographical location of observation, diagnostic tests used, and the type of studies in which typhoid fever was reported. By analyzing this dataset, we can gain insights into the sub-national heterogeneity of typhoid fever's burden in the region. This knowledge will be instrumental in designing more effective intervention strategies to combat the disease.

Background & Summary

Typhoid fever is a systemic bacterial infection caused by *Salmonella enterica* serovar Typhi (*Salmonella* Typhi or *S. Typhi*). Patients usually present sustained fever (39–40 °C) and other symptoms include weakness, stomach pain, headache, diarrhea or constipation, cough, and loss of appetite. Severe forms of illness include ileal perforation, which can lead to death. *S. Typhi* is transmitted via fecally-contaminated food and water and the majority of typhoid fever incidence is known to occur in low- and middle-income countries (LMIC)^{1–6}.

Globally, typhoid fever causes estimated 12 million cases and 130 thousand deaths according a recent modelling study in which incidence rate data come from population-based longitudinal surveillance studies conducted at 22 sites in 14 different countries between 1978 and 2017¹. Earlier estimates of the global burden of typhoid fever were based on a relatively simplistic approach of extrapolating the incidence rates observed in one setting to the entire country or to neighbouring countries where data is unavailable^{2–4}. However, the surveillance is often conducted at sites where the disease incidence has already been reported and therefore would not necessarily well represent the country⁵. Later studies used sophisticated modelling techniques to adjust observed values using the distribution of geospatial variables that potentially affect the transmission of typhoid fever rather than simple extrapolation^{1,6}.

While they clearly show variation at the country level, existing studies fail to emphasize that the burden of typhoid fever also shows significant sub-national variation for each country. Outbreaks often show district-level variation of typhoid incidence^{7–9} and country-level surveys show sub-national heterogeneity of incidence^{10–13}. Understanding idiosyncratic behaviour of typhoid transmission between communities will be critical for a country to implement intervention programs such as campaign vaccination against endemic or epidemic typhoid fever more efficiently and effectively. Efficiency and effectiveness of an intervention program can improve, for

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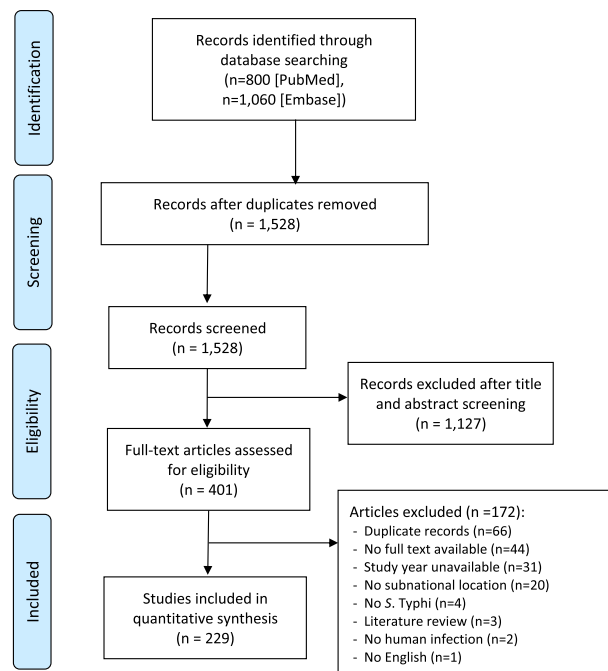


Fig. 1 PRISMA flow diagram.

instance, if the interventions are targeted on high-burden areas. Identifying those high-burden areas will depend on how well we understand the spatial variation of the burden of typhoid fever across the target country.

Although population-based prospective studies serve as the basis for existing estimates of country-level and global burden of typhoid fever, report of sporadic cases and outbreaks provide wider spatial coverage and hold information on sub-national variation of occurrence of typhoid fever¹⁴. In this study, we provide the data set on the occurrence of typhoid fever extracted from peer-reviewed literature. We focus on sub-Saharan Africa, where systematic surveillance has shown that the burden is substantial^{1,2,5,6}. The dataset we report provides information on the occurrence of typhoid fever at the hospital, district, or higher sub-national administrative levels. While these datasets alone may not fully capture sub-national variations in typhoid fever, they can be enhanced by grey literature. Nonetheless, they hold potential to improve our understanding of sub-national heterogeneity in typhoid fever, especially when combined with other methods¹⁵.

Methods

Search and data sources. Data on the occurrence of typhoid fever were extracted from peer-reviewed research articles indexed in PubMed or Embase published between January 1, 2000 and October 31, 2020. Systematic review of the literature followed a standard procedure and the overview of the procedure in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1). The search term used for querying PubMed and Embase was designed to capture different uses of typhoid fever in the literature such as typhoid fever, *Salmonella typhi*, *S. Typhi*, or enteric fever and limit to the countries from sub-Saharan Africa. The exact search terms appear in the Supplement.

Eligibility criteria and study selection. A study, regardless of study types, was eligible for inclusion in this analysis if it clearly reports date and location of occurrence as well as diagnostic method used for confirmation of the occurrence of human typhoid cases. We included reports of polymerase chain reaction (PCR) or culture-confirmed typhoid fever where *S. Typhi* was isolated from normally sterile sites such as blood, urine, bone marrow, or cerebrospinal fluid. We also included studies that confirm typhoid fever through serologic tests (e.g., Widal test or enzyme-linked immunosorbent assay [ELISA]) or suspected clinically (e.g., ileal perforation) while acknowledging that those case definitions are less reliable compared with culture or PCR confirmation. We excluded the studies that are based on the analyses of existing data and do not report novel occurrence of typhoid fever in humans. For instance, some articles report results of experiments using the existing isolates (e.g., susceptibility to antimicrobials or other medicinal plants) and were therefore excluded. Other studies fail to provide serovars while reporting infection *Salmonella*.

Data extraction, study variables, and analytic approach. Two authors (J-HK and PP) reviewed the literature and extracted the data. Where there was discordance among the two reviewers, the first author decided after discussions. Extracted data included year of observation, location (smallest sub-national area possible), diagnostic method, and the number of typhoid cases reported. In reports of typhoid cases from observations that span multiple years without further details broken down by year, we assumed that at least 1 episode of typhoid fever case occurred each year. We defined a typhoid fever occurrence as a report of at least 1 episode of typhoid fever excluding any duplicate reports from the same cohort. For imported cases, we assumed that the typhoid episode occurred in the country in which the infection occurred according to the report. If the imported cases led

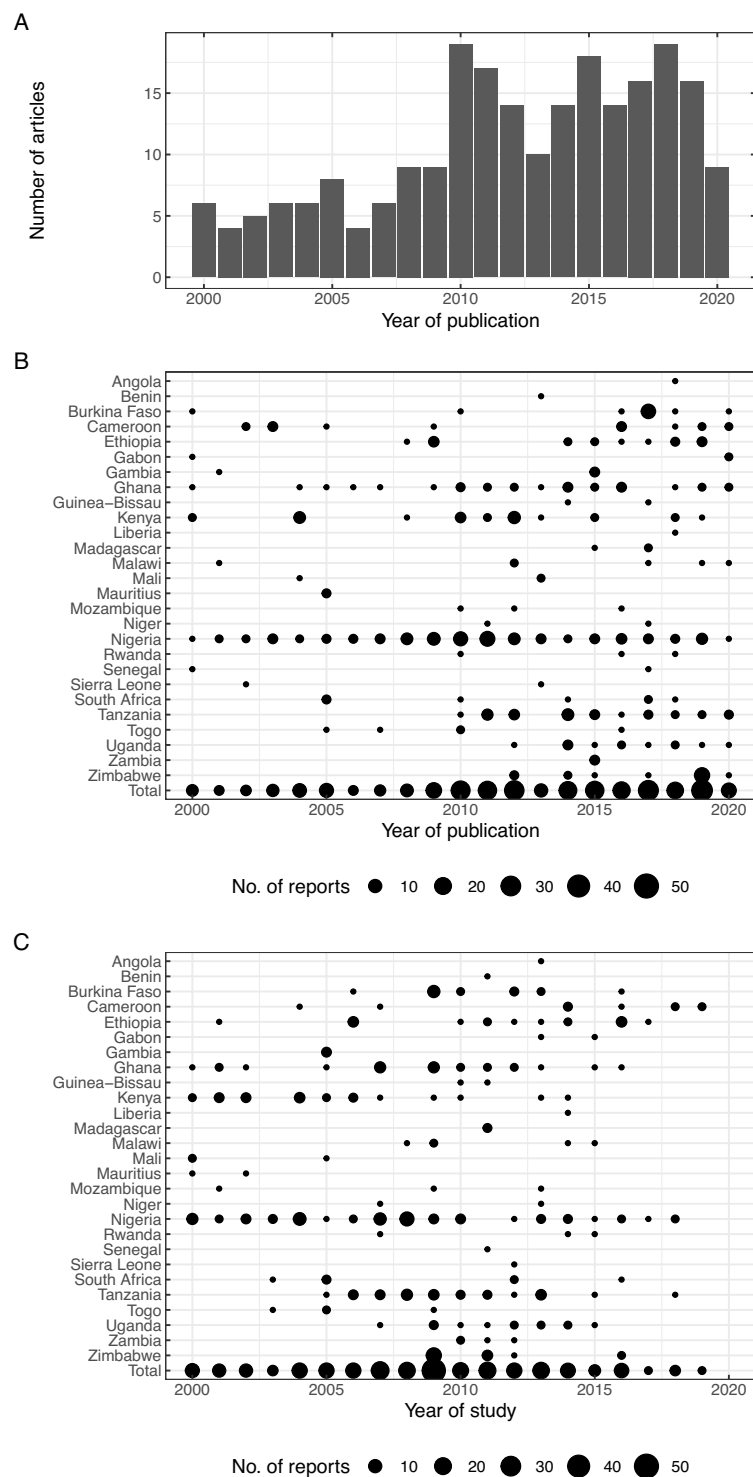


Fig. 2 Number of included reports by year and country. The overall number of reports of typhoid occurrence in sub-Saharan Africa increases over time with considerable variation by year of publication (A) and country (B). The number of studies showed substantial variation also by country and the year in which the study began (C).

to local transmission, we assumed that typhoid occurred in both the country of infection origin and the country of report. An outbreak was defined based on the definition used in the report.

Data Records

Occurrence data were stored in an Excel spreadsheet where each row indicates an occurrence event of typhoid fever for specific year and location. Some occurrence events reported from a larger region may overlap those from smaller sub-regions within a region. Columns indicate data source (e.g., title of the article), years of observation and report, diagnostic method, number of cases reported, sub-national region (up to the smallest units

Diagnostic method	Frequency [n (%)]	Samples of actual terms used in the literature
Culture of blood samples	91 (39.7)	"urine, blood, or stool culture", "blood or stool culture, or Widal-Felix", "blood/urine/stool culture", etc.
Clinical symptoms	66 (28.8)	"typhoid perforation", "intestinal perforation", "clinical diagnosis", "digestive perforation", "typhoid gall bladder perforation", "cholecystitis", "clinical", "hospital record", "ileal perforation", "multiple jejunal perforations", "perforated enteritis", "peritonitis", "small bowel perforation", "enterocutaneous fistula", "septicaemia", "case files", "cases reported", "death records", "typhoid fever", etc.
Widal test	24 (10.5)	"Widal test", "agglutination and titration (>4-fold)", "Widal-Felix", "Widal and Weiffelix direct card agglutination tests (DCAT)", "Tube agglutination test", etc.
Culture of stool samples	14 (6.1)	"stool culture", etc.
Culture	12 (5.2)	"Isolation of Salmonella typhi", "culture", "isolated", "bacterial isolation", "microbiologically confirmed", "laboratory confirmed", "confirmed", etc.
Unclear	9 (3.9)	"Survey questionnaire", "surveillance data", "National Health Laboratory Services data", "standard methods with blood samples", "travel or tropical medicine clinics record", "history based on self report", "questionnaire", "report at medical record", "self reported"
Culture of CSF samples	3 (1.3)	"cerebrospinal fluid culture", "spinal fluid culture", "isolation from CSF, blood, or stool", etc.
Autopsy	3 (1.3)	"post mortem report", "autopsy", "coroner's autopsies"
Culture of bone marrow samples	2 (0.9)	"blood, stool or bone marrow culture", "blood and bone marrow cultures", etc.
Rapid test	2 (0.9)	"rapid typhoid test", "Blood-RDT", "rapid diagnostic test", "RDT", etc.
Culture of other body fluids	1 (0.4)	"aspirates culture", "culture of pus", "wound culture", "wound swab culture", "Ear and throat culture", "Sputum culture", "rectal swab specimens examined bacteriologically", etc.
Biochemical test	1 (0.4)	"biochemical", "biochemical testing of urine sample", "biochemical tests of environmental samples", etc.
Culture of urine samples	1 (0.4)	"urine culture"

Table 1. Frequency of studies by diagnostic methods. CSF = Cerebrospinal fluid.

Country	Sub-national region	Surveillance period	Ref
Burkina Faso	Nanoro, Boulkiemde	2013–2014	¹⁸
Burkina Faso	Nioko II, Polesgo	2012–2013	⁵
Ethiopia	Butajira	2012–2014	⁵
Ghana	Asante Akim North	2007–2009	¹⁹
Ghana	Asante Akim North	2010–2012	⁵
Guinea-Bissau	Bandim	2011–2013	⁵
Kenya	Lwak, Kibera	2006–2009	¹³
Kenya	Kibera	2012–2013	⁵
Madagascar	Imerintiasotika, Isotry	2011–2013	⁵
Senegal	Pikine	2011–2013	⁵
South Africa	Pietermaritzburg	2012–2014	⁵
Sudan	East Wad Medani	2012–2013	⁵
Tanzania	Pemba Island	2010–2012	²⁰
Tanzania	Moshi urban, Moshi rural	2011–2013	⁵

Table 2. Population-based longitudinal surveillance of typhoid fever in sub-Saharan Africa since 2000.

available), study type, longitude and latitude which were acquired through Google Map. Locations may refer to the arbitrary central point of the region (e.g., neighbourhoods, village) or the location of a healthcare facility. Study types were categorized into review of hospital records, case report, outbreak reports, and longitudinal studies. The dataset is available at the Open Science Framework¹⁶.

Technical Validation

To ensure the overall quality of the data, a thorough review process was implemented. Two independent reviewers meticulously examined the data. The reported locations of typhoid occurrences were verified by cross-referencing information from the organization's website and other reliable sources, including Wikipedia. Additionally, the dates of occurrence were confirmed by carefully reviewing the texts and tables provided in the original articles. This multi-step validation process was crucial to ensure the accuracy and reliability of the data used in this study. We provide an overview of the included studies by country and year of publication. Also, we provide more details on the diagnostic methods used to confirm the infection, types of studies in which typhoid fever were reported, year, and sub-national location of occurrence of typhoid fever.

Frequency of studies by year and country. Occurrence of confirmed typhoid fever were reported in 31 countries from Jan 2000 to Dec 2020 with overall reporting frequency increasing over time (Fig. 2A). The number of reports varies by study and year of publication (Fig. 2B) and by year in which the study began (Fig. 2C) considerably. Nigeria consistently reported the highest number of reports on the occurrence of typhoid fever over the period. For countries like Angola, Benin, Burundi, Guinea-Bissau, Liberia, Madagascar, Niger, Uganda, Zambia and Zimbabwe, typhoid fever has been reported after 2010 considering the period from 2000 to 2020.

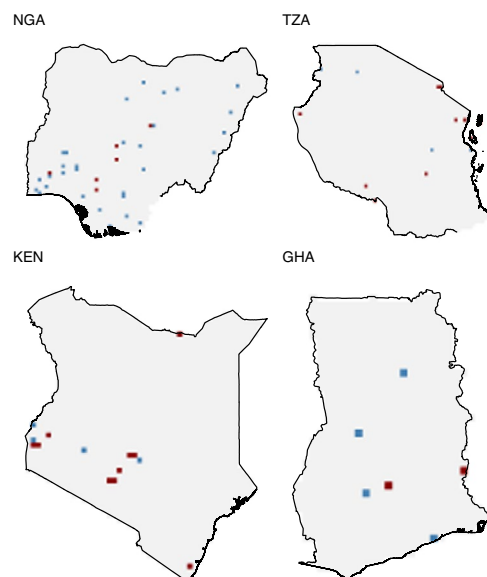


Fig. 3 Geographical locations of occurrence of typhoid fever for four countries where the number of reports of typhoid fever is highest. The map has 20 km by 20 km resolution. Red and blue grids represent locations of typhoid fever confirmed through culture and other methods, respectively. NGA = Nigeria; TZA = United Republic of Tanzania; KEN = Kenya; GHA = Ghana.

Diagnostic methods. We categorized the studies based on the diagnostic method employed to identify typhoid fever (Table 1). In instances where a single study utilized multiple diagnostic methods (e.g., clinical criteria, blood culture, and bone marrow sample culture), we prioritized the method with the higher performance. Specifically, if the study included the method such as the culture of bone marrow or cerebrospinal fluid samples, which is recognized as the highest sensitivity, we selected this method as the representative method of the study. Similarly, a study incorporated blood culture but did not include methods like the bone marrow culture, we chose the blood culture as the representative diagnostic method. If the methods included other culture methods, we chose the methods in the order of culture of urine samples, culture of stool samples, and culture of other body fluids. Other studies did not specifically mention the samples used to culture but implied the culturing method (e.g., “bacterial isolation” or “microbiologically confirmed”). In this case, we created a category called “Culture”. For studies whose diagnostic methods do not include culturing method, we chose the method in an order of Rapid tests, Widal, biochemical tests, and clinical symptoms. While we sought to categorize by the precision of the tests, this category may be somewhat arbitrary. The reader can access the original terms that indicated multiple methods used for each study.

According to this categorization, studies based on culturing blood samples were most frequent ($n = 91$, 39.7%). (Table 1) while still numerous studies relied on less reliable methods, which include clinical signs (e.g., illeal perforation) ($n = 66$, 26.8%) or Widal test (or agglutination) ($n = 24$, 10.5%).

Study types. Study design was diverse and included case reports, outbreak investigation, cross-sectional studies, retrospective studies (i.e., review of hospital records), and prospective studies including multi-year longitudinal surveillance studies. While population-based longitudinal surveillance studies can provide incidence rates of typhoid fever, they are few ($n = 5$) and were conducted around 15 sub-national areas of 10 countries (Table 2). On the other hand, there are other studies that report occurrence of typhoid fever and wider spatial coverage in the dataset. Prospective studies including clinical trials were most common ($n = 93$), followed by retrospective ($n = 74$), cross-sectional ($n = 33$), outbreak investigation ($n = 13$), case-control ($n = 8$), and case report ($n = 8$) studies.

Geographical locations. Occurrence data cover entire continent although occurrences are more frequent in East and West Africa. Top three countries in terms of the number of unique 20 km by 20 km grids where the occurrence was reported were Nigeria ($n = 65$), Kenya ($n = 24$), and United Republic of Tanzania ($n = 23$), and Ghana ($n = 19$) (Fig. 3). Sub-national locations in the dataset includes household, primary clinic, tertiary hospitals, district, or provinces. Occurrence of typhoid fever has been reported in small number of large hospitals and cities with substantial variation across countries. In Angola, National Institute of Public Health of Angola located in the Capital city, Luanda is the only place in which blood culture-confirmed typhoid fever was reported. On the other hand, more than 55 health centers and hospitals spread out through the country.

Code availability

All the codes used to generate the figures and tables are available in the GitHub repository¹⁷

Received: 13 November 2023; Accepted: 23 September 2024;

Published online: 05 October 2024

References

1. Antillón, M. *et al.* The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. *PLOS Neglected Tropical Diseases* **11**, e0005376 (2017).
2. Kim, J.-H., Mogasale, V., Im, J., Ramani, E. & Marks, F. Updated estimates of typhoid fever burden in sub-Saharan Africa. *The Lancet Global Health* **5**, e969 (2017).
3. Mogasale, V. *et al.* Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *The Lancet Global Health* **2**, e570–e580 (2014).
4. Crump, J. A., Luby, S. P. & Mintz, E. D. The global burden of typhoid fever. *Bull World Health Organ* **82**, 346–353 (2004).
5. Marks, F. *et al.* Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. *The Lancet Global Health* **5**, e310–e323 (2017).
6. Stanaway, J. D. *et al.* The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Infectious Diseases* **19**, 369–381 (2019).
7. Ali, E. *et al.* Localised transmission hotspots of a typhoid fever outbreak in the Democratic Republic of Congo. *Pan Afr Med J* **28**, 179 (2017).
8. Polonsky, J. A. *et al.* Descriptive epidemiology of typhoid fever during an epidemic in Harare, Zimbabwe, 2012. *PLoS One* **9**, e114702 (2014).
9. Cruz Espinoza, L. M. *et al.* Variations of Invasive Salmonella Infections by Population Size in Asante Akim North Municipal, Ghana. *Clin Infect Dis* **62**(Suppl 1), S17–22 (2016).
10. Ismail, K., Maiga, G., Ssebuggwawo, D., Nabende, P. & Mansourian, A. Spatio-temporal trends and distribution patterns of typhoid disease in Uganda from 2012 to 2017. *Geospatial Health* **15**, (2020).
11. Tamrakar, D. *et al.* Spatial Heterogeneity of Enteric Fever in 2 Diverse Communities in Nepal. *Clinical Infectious Diseases* **71**, S205–S213 (2020).
12. Osei, F. B., Stein, A. & Nyadanu, S. D. Spatial and temporal heterogeneities of district-level typhoid morbidities in Ghana: A requisite insight for informed public health response. *PLoS One* **13**, e0208006 (2018).
13. Breiman, R. F. *et al.* Population-Based Incidence of Typhoid Fever in an Urban Informal Settlement and a Rural Area in Kenya: Implications for Typhoid Vaccine Use in Africa. *PLoS ONE* **7**, e29119 (2012).
14. Kim, J.-H. *et al.* A Systematic Review of Typhoid Fever Occurrence in Africa. *Clin Infect Dis* **69**, S492–S498 (2019).
15. Kim, J.-H. *et al.* Mapping the incidence rate of typhoid fever in sub-Saharan Africa. *PLoS Negl Trop Dis* **18**, e0011902 (2024).
16. Kim, J.-H. Occurrence of human infection with *Salmonella Typhi* in sub-Saharan Africa. <https://doi.org/10.17605/OSF.IO/4HA7P> (2024).
17. Kim, J.-H. Occurrence of human infection with *Salmonella Typhi* in sub-Saharan Africa. https://github.com/kimfinale/typhoid_occurrence (2023).
18. Guiraud, I. *et al.* Population-based incidence, seasonality and serotype distribution of invasive salmonellosis among children in Nanoro, rural Burkina Faso. *PLOS ONE* **12**, e0178577 (2017).
19. Nielsen, M. V. *et al.* Incidence and Characteristics of Bacteremia among Children in Rural Ghana. *PLOS ONE* **7**, e44063 (2012).
20. Thriemer, K. *et al.* The Burden of Invasive Bacterial Infections in Pemba, Zanzibar. *PLOS ONE* **7**, e30350 (2012).

Acknowledgements

This work was supported, in whole or in part, by Gavi, the Vaccine Alliance, and the Bill & Melinda Gates Foundation, via the Vaccine Impact Modelling Consortium (Grant Number OPP1157270/INV-009125) and the Severe Typhoid Fever in Africa Program (Grant Number OPP1127988). The funders were not involved in the study design, data analysis, data interpretation, and writing of the manuscript. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of their affiliated organizations.

Author contributions

J.-H.K. designed the study, performed the literature search, reviewed the articles, extracted the data, and wrote the manuscript. P.P. reviewed the articles, extracted data, and reviewed the manuscript. All authors reviewed the final version of the manuscript and approved its submission.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41597-024-03912-x>.

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