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HIV status and the risk of typhoid fever and iNTS: A systematic review and meta-analysis

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SUMMARY

Objectives: The WHO recommends prioritising people living with HIV (PLHIV) for typhoid vaccination, but evidence for increased typhoid fever risk is inconsistent. We aimed to evaluate whether HIV infection alters the risk of blood culture-confirmed typhoid fever.

Methods: We systematically searched four databases from inception to 30 November 2023 for studies reporting Salmonella Typhi bacteraemia with documented HIV status. Where available, we also extracted data on invasive non-typhoidal Salmonella (iNTS) bacteraemia. We used random-effects meta-analysis to pool odds ratios (ORs) and assessed effect modification by ART era, age, and CD4 count.

Results: Seventeen studies met inclusion criteria, comprising 10,117 PLHIV and 53,289 HIV-negative individuals from Africa and Asia. PLHIV had lower odds of typhoid fever (OR 0.53, 95% CI 0.30–0.92), but higher odds of iNTS disease (OR 4.06, 2.23–7.39). Apparent protection against typhoid was most evident in adults with CD4 counts < 200 cells/μl and was not significant after ART rollout.

Conclusions: Advanced HIV infection may reduce the risk of typhoid fever. While altered clinical presentations or healthcare-seeking behaviours could contribute, the contrasting increase in iNTS risk within the same populations suggests a genuine difference in susceptibility. These findings support re-evaluating WHO guidance that prioritises PLHIV for typhoid vaccination.

Introduction

People living with HIV (PLHIV) are at greater risk of community-onset bloodstream infection (BSI) than HIV-negative individuals.[1,2] Typhoid fever is an invasive infection caused by the bacterium *Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella* Typhi). Whilst it might follow that PLHIV would be at increased risk of typhoid fever, several reports suggest the opposite trend.[2–4] By contrast, invasive non-typhoidal *Salmonella* (iNTS) disease – caused by bacteria belonging to the same subspecies as *Salmonella* Typhi – is a well-established opportunistic infection among PLHIV.[5–7]

In 2017, there were an estimated 10.9 million cases of typhoid fever worldwide (95% uncertainty interval (UI) 9.3–12.6 million) accounting for approximately 105,000 Years Lived with Disability.[8] Typhoid fever is most commonly diagnosed by isolating *Salmonella* Typhi from blood culture, though recovery from any usually-sterile body site is diagnostic.[9,10]

Due to their epidemiologic overlap, any interaction between HIV and typhoid fever is clinically and strategically significant. Of the estimated 39.9 million people (95% UI 36.1–44.6 million) living with HIV,[11] most reside in Africa, where typhoid fever incidence is moderate to high.[12] Asia and the Pacific, regions with the world's second-highest HIV burden, experience the highest global typhoid rates.[12]

Typhoid conjugate vaccine (TCV) is a novel and effective intervention prequalified by the World Health Organization (WHO) for use in typhoid-endemic settings.[13] Currently, WHO lists PLHIV among special populations who should be prioritised for typhoid

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vaccination due to a "high risk of acquiring or transmitting [S. Typhi] infection" [sic].[14]

We conducted a systematic review and meta-analysis to determine whether HIV infection alters the likelihood of blood culture-confirmed typhoid fever compared to HIV-negative individuals. We hypothesised that the relationship between HIV and typhoid might differ according to immunosuppression severity and antiretroviral therapy (ART) availability. We also compared the risk of typhoid fever to that of iNTS disease – an invasive salmonellosis syndrome strongly associated with HIV. Clarifying these relationships will inform vaccine policy and enhance understanding of how these globally significant diseases intersect.

Methods

In this systematic review and meta-analysis, we searched MEDLINE, EMBASE, and Web of Science from inception to 29 November 2023, and screened the first 200 abstracts retrieved from Google Scholar on 20 November 2023.[15] We developed the search strategy in collaboration with a librarian (MC), with peer review provided by an information specialist (AS). The strategy included synonyms for HIV AND (Salmonella Typhi OR BSI) (Supplementary Appendix, pp 4–5). We prospectively registered the review protocol on PROSPERO (CRD42021156888, 19 April 2021) and report our findings according to PRISMA guidelines (Supplementary Appendix, pp 29–31).[16]

We included observational studies that reported the HIV status of blood culture recipients, and in which at least one participant - whether HIV-infected or uninfected - had *Salmonella* Typhi BSI. Where data from the same population were presented in two publications, we included the largest or most complete dataset. We excluded duplicate or overlapping data from the same cohort.

We excluded interventional studies, case reports, editorials, and any studies where participants had been selected on the basis of a pre-existing medical condition. We searched the reference lists of systematic reviews identified in the search for potentially relevant articles. Full inclusion and exclusion criteria are reported in Supplementary Appendix pp 5.

We imported references from each database using Endnote v20 (Clarivate Analytics, Boston, MA, United States) and subsequently exported them into Covidence systematic review management software for deduplication, screening, quality assessment, and data extraction.[17]

We assessed studies for risk of bias using a tool adapted from a recent systematic review of iNTS disease incidence, evaluating two domains: selection and recruitment, and measurement and reporting.[18] We evaluated the representativeness of the study population, robustness of HIV status ascertainment, and methods used to identify *Salmonella* Typhi. Methods of *Salmonella* Typhi identification that are recognised (and that we thereby deemed low-risk of bias) include serotyping (according to the Kauffman-White-Le Minor scheme[19]), molecular methods such as PCR for *Salmonella* Typhi-specific targets, and DNA sequencing.[20,21] We deemed as low-risk HIV ascertainment using validated antigen, antibody or PCR-based methods. The complete risk assessment strategy is reproduced in Supplementary Appendix, pp 6–11.

Two reviewers independently screened abstracts and full-texts (PJ, AH, WC, NJ, CM); we reconciled disagreements via a casting vote from an independent third member of the review team. We emailed the corresponding authors of papers to clarify whether relevant data were incompletely reported; the study was excluded if no response was received after two emails. PJ and CM / NJ independently extracted the data and performed quality assessments. The primary outcome data were the number of *Salmonella* Typhi-positive blood cultures (n) from the total number of blood cultures performed (N) for both HIV-positive and HIV-negative participants during the study ascertainment period. Where available, this data was additionally obtained for BSI with any NTS serovar. We sought to extract data on participant characteristics that might influence the risk of typhoid fever, including demographics, CD4 cell count, and use of trimethoprim-sulphamethoxazole preventive therapy. Our data extraction tool used is reproduced in Supplementary Appendix, pp 12–13.

Data analysis

Our primary outcome was the relative incidence of *Salmonella* Typhi BSI in participants with and without HIV. Our secondary outcome was the relative incidence of non-typhoidal *Salmonella* (NTS) BSI in the same study populations, also stratified by HIV status.

We calculated pooled odds ratios from combined study estimates using a random-effects model. Between-study variance was estimated using the DerSimonian–Laird method, and inverse-variance weighting was applied to give more weight to studies with greater precision. Heterogeneity was assessed using the I^2 statistic. To assess the robustness of our findings against potential small-sample bias, we additionally applied the Hartung–Knapp method to the primary analysis for typhoid fever (Supplementary Figure 8).

We performed subgroup analyses based on the following characteristics: (i) risk of bias (low vs. moderate vs. high); (ii) age group (paediatric [≤15 years] vs. adult [> 15 years]). One study presented data for adolescents aged ≥13 years alongside adults, which could not be disaggregated; we therefore included these participants in the adult category.[3] iii) timing relative to ART availability ("pre-ART" vs. "post-ART," using the year 2004 as the delineator)[22] iv) studies where average CD4 cell count of PLHIV was known. We conducted meta-regression based on the midpoint of study data collection (the date halfway between the start and end of recruitment). We assessed the risk of publication bias using funnel plots and Egger's regression.

We used the "meta" (v8.0.1) package in the R statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria) (v4.3.3) for primary and subgroup meta-analyses and the "metafor" (v4.6.0) package for meta-regression.[23–25]

The analytic code and extracted data used in this systematic review are archived at Zenodo:
https://doi.org/10.5281/zenodo.15463296.

Results

Study selection

Our electronic searches retrieved 12,687 records, of which 5047 were duplicates (Fig. 1). We screened 7640 titles and abstracts, which yielded 105 articles that met the criteria for full-text review. 17 studies contributed data to the meta-analysis that formed our primary outcome; 13 of these studies had data available for the iNTS disease pooled analysis.[3,26–37] Characteristics of included studies are shown in Table 1.

Study characteristics

Included studies enrolled 10,117 PLHIV and 53,289 HIV-negative individuals, among whom 209 episodes of *Salmonella* Typhi BSI occurred: 21 episodes in PLHIV and 188 in HIV-negative individuals.

Fifteen studies took place in Africa, and two in South-East Asia (both Cambodia).[36,38] Tanzania was the most frequently represented country, contributing eight studies to the analysis (Table 1 & Supplementary Figure 1).[3,26,28–30,33,34,39] Kenya contributed three studies,[27,40,41] Côte d'Ivoire contributed two,[31,37] and Nigeria contributed one.[35]

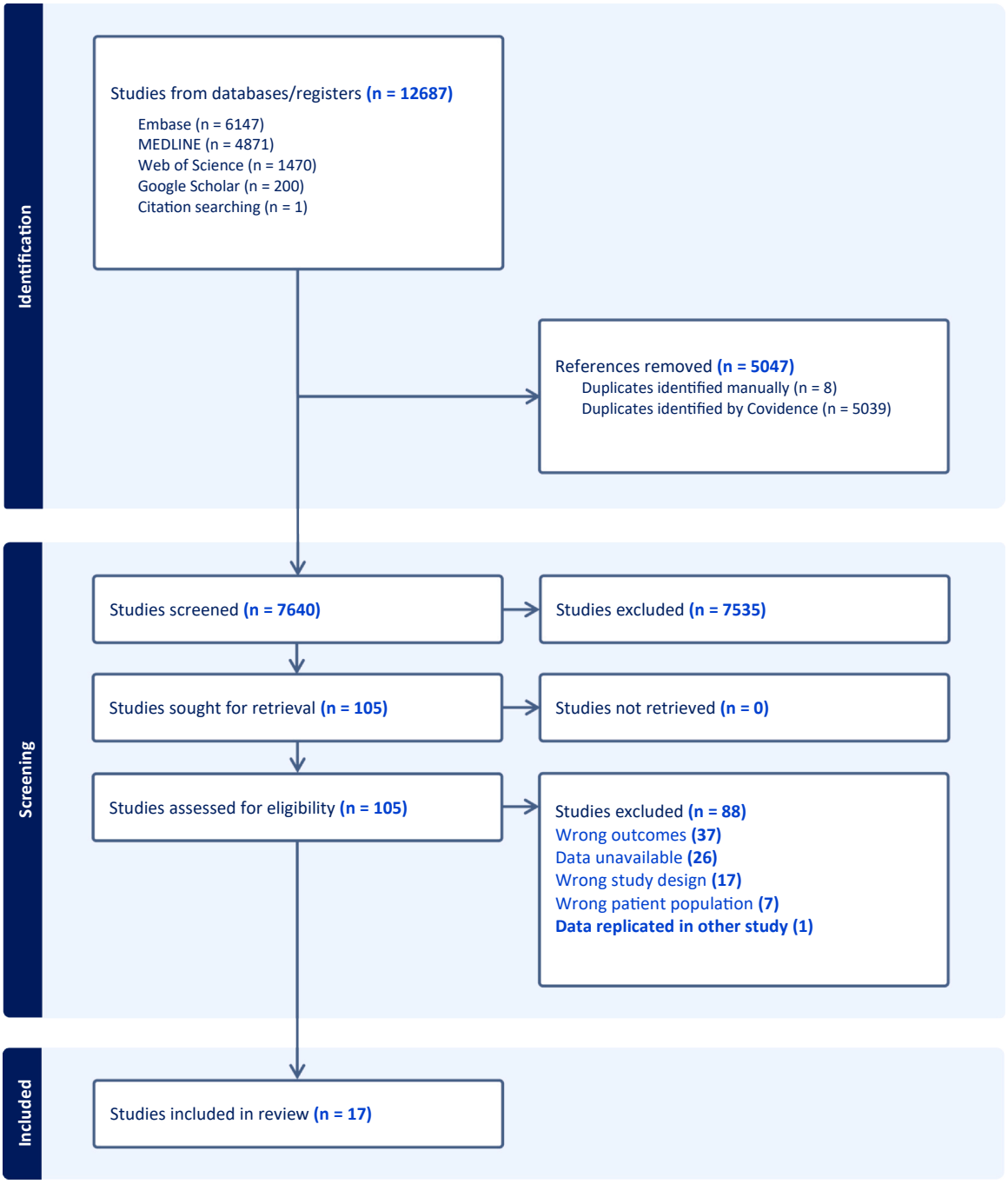

Fig. 1. PRISMA flow diagram showing identification, screening, eligibility, and inclusion of studies in this systematic review and meta-analysis of *Salmonella* Typhi bloodstream infection incidence in PLHIV compared to HIV-negative individuals.

Eight studies included adult populations only (including one where adolescents (≥ 13 years) where aggregated with adults).[3,26,27,31–33,36,37,39] Seven studies focused on paediatric populations.[28–30,34,35,38,41] These included children up to five years in two studies,[35,41] up to seven years in one study,[29] up to 13 years in three studies [28,30,40] and up to 15 years in one study.[38] Muthumbi and colleagues included participants of all ages; however, because recruitment periods and criteria for blood culture collection differed between paediatric and adult populations, we pooled data for adults and children separately.[40]

All included studies were observational studies conducted at healthcare facilities, although one study additionally drew from three community cohorts.[27] Fourteen studies collected data prospectively[3,26,28–33,37–39,41]; three retrospectively.[27,36,40]

Risk of bias

We rated six studies low-risk for bias[3,29,30,33,34,40]; seven moderate-risk,[26,28,32,35,36,38,39,41] and three high-risk.[27,31,37] Bias was most commonly introduced by methods used for typing *Salmonella* recovered from blood cultures. Two of seventeen studies described methods that do not differentiate between *Salmonella* serovars[26,41]; seven studies did not provide sufficient detail to judge whether their methods for identifying *Salmonella* Typhi were robust (Supplementary Table 1).[28,29,31,32,36–39] The second most frequent study characteristics associated with potential bias were the method of selection of participants for blood culture. Two studies selected admissions to an infectious disease unit, regardless of

Table 1
Baseline characteristics of included studies.

Author and Year	Year of publication	Years of data collection	Country	Study Design	Participants	Paediatric or Adult?	iNTS bacteraemia among PLHIV	iNTS bacteraemia among HIV uninfected	Typhoid bacteraemia among PLHIV	Typhoid bacteraemia among HIV uninfected	Quality Assessment
Archibald et al.[26]	1998	February 1995 to April 1995	Tanzania	Prospective cohort	≥ 15 years attending hospital with temperature ≥ 37.5 °C	Adult	23/282	6/235	0/282	1/235	Moderate
Batchelor et al.[27]	1996	November 1988-October 1992	Kenya	Retrospective cohort, data from several cohorts	≥ 15 years	Adult	60/2623	7/2006	6/2623	8/2006	High
Biggs et al.[28]	2014	June 2006-August 2008	Tanzania	Prospective cohort at two sites: high and low malaria endemicity	2 months to 13 years, attending hospital	Paediatric	9/202	154/4102	0/202	17/4102	Moderate
Blomberg et al.[29]	2007	August 2001 to August 2002	Tanzania	Prospective cohort	0 to 7 years with signs of systemic infection admitted to hospital	Paediatric	7/155	10/756	0/155	2/756	Low
Boillat-Blanco et al.[39]	2021	July 2013 to July 2014	Tanzania	Prospective cohort	≥ 18 years with fever (≥ 38 °C) attending outpatient clinics / health centres	Adult			3/128	8/391	Moderate
Chheng et al.[38]	2013	October 2009 and October 2010	Cambodia	Prospective cohort	< 16 years admitted to hospital if axillary temperature ≥ 38 °C within 48 h of admission.	Paediatric			0/58	22/1167	Moderate
Crump et al. (paediatric)[30]	2011	September 2007 to August 2008	Tanzania	Prospective cohort	Hospital inpatients ≥ 2months to < 13 years. History of fever in previous 48 h or rectal temperature ≥ 38 °C or axillary temperature ≥ 37.5 °C	Paediatric	1/57	0/341	0/57	6/341	Low
Crump et al. (adults)[3]	2011	September 2007 to August 2008	Tanzania	Prospective cohort	Inpatients with oral temperatures ≥ 38 °C	Adolescents and adults	2/161	0/244	2/161	24/244	Low
Grant et al.[31]	1997	March to July 1995	Côte d'Ivoire	Prospective cohort	Admissions to hospital ≥ 15 years	Adults	23/199	1/51	1/199	3/51	High
Kassa-Kelembho et al.[32]	2003	April to July 1999	Central African Republic	Prospective cohort	Admissions to hospital medical department with fever and lack of response to quinine therapy for malaria	Adults	22/116	0/15	2/116	0/15	Moderate
Meremo et al.[33]	2012	June to December 2011	Tanzania	Prospective cohort	Patients admitted to the medical wards with an axillary temperature > 37.5 °C	Adults	12/156	1/190	0/156	1/190	Low
Mtove et al.[34]	2010	March 2008 to Feb 2009	Tanzania	Prospective cohort	Children aged 2 months to 14 years admitted to hospital with fever (axillary ≥ 37.5 °C or care-giver reporting rise in body temperature) for three or more days or fever of less than three days with one of several physiologic markers of severity.	Paediatric	2/67	43/787	1/67	13/787	Low

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Year of publication	Years of data collection	Country	Study Design	Participants	Paediatric or Adult?	iNTS bacteraemia among PLHIV	iNTS bacteraemia among HIV uninfected	Typhoid bacteraemia among PLHIV	Typhoid bacteraemia among HIV uninfected	Quality Assessment
Muthumbi et al. (paediatric)[40]	2015	August 1998 to December 2014	Kenya	Retrospective cohort	Children ≤ 14 years admitted to hospital had routine blood cultures taken	Paediatric			0/2059	14/29275	Low
Muthumbi et al. (adults)[40]	2015	January 2007 to December 2014	Kenya	Retrospective cohort	Adults (> 14 years) admitted to hospital with history of fever, axillary temperature of < 36 °C or > 37.4 °C, or signs of focal sepsis	Adults			1/2604	3/6776	Low
Obaro et al.[35]	2011	September 2008 to November 2009	Nigeria	Prospective cohort	Children with fever or hypothermia attending outpatient clinics or emergency units aged 2 months to 5 years before admission to tertiary and district hospitals.	Paediatric	0/32	8/937	0/32	22/937	Moderate
Onchiri et al.[41]	2016	April 2012 to March 2014	Kenya	Prospective cohort	Children with axillary temperature ≥ 37.5 °C aged between 6 months and five years presenting to outpatient clinics at study sites	Paediatric			2/40	19/1418	Moderate
Phe et al.[36]	2013	January 2009 to December 2011	Cambodia	Retrospective cohort	All adults with a community acquired episode of systemic inflammatory response syndrome: defined as the presence of at least two of the following signs: fever/ hypothermia (temperature < 35 or > 38 °C), tachycardia (heart rate > 90 beats/min), tachypnea (respiratory rate > 20/min) and hypo- or hyperleukocytosis (white cells count < 4 000 or > 12 000/ll). between the periods of study	Adults	16/976	8/4481	2/976	21/4481	Moderate
Vugia et al.[37]	1993	May to June 1991	Côte d'Ivoire	Prospective cohort	Adult patients admitted to the adult infectious disease service		16/202	0/117	1/202	4/117	High

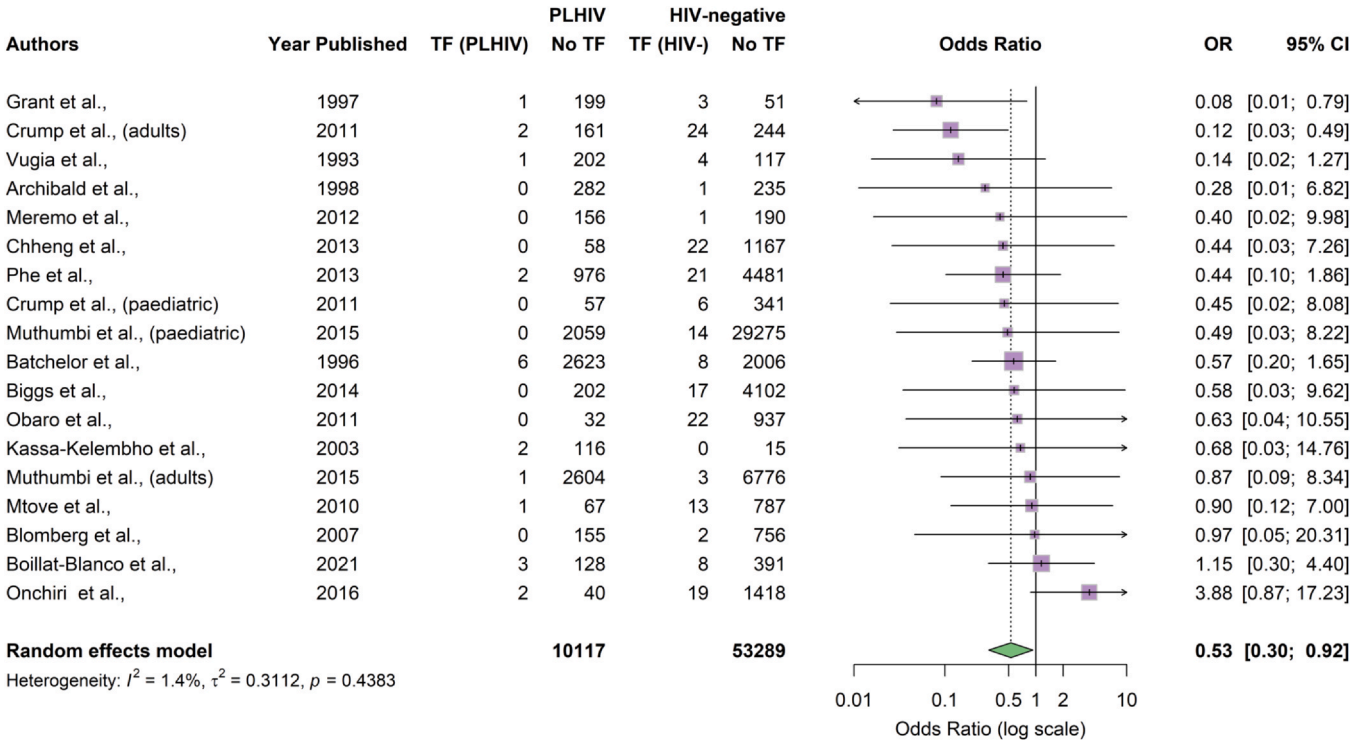

Fig. 2. Forest plot from a random-effects meta-analysis of 17 studies comparing the odds of blood culture-confirmed *Salmonella* Typhi infection in PLHIV versus HIV-negative individuals. Study-specific odds ratios and 95% confidence intervals are shown alongside pooled estimates. Absolute case numbers are displayed to the left of the plot. We calculated heterogeneity using the I^2 statistic. This figure was generated using the meta package in R (v8.0.1)[23].

symptoms.[31,37] One study varied eligibility criteria across several cohorts (Supplementary Table 1).[27] We identified issues with potential ascertainment bias for HIV infection in one study, where the authors relied upon previously established HIV diagnoses, rather than testing participants for HIV directly.[35]

Results of syntheses

In our primary pooled analysis, PLHIV had significantly lower odds of *Salmonella* Typhi BSI compared with HIV-negative individuals (OR 0.53, 95% CI 0.30–0.92; heterogeneity I^2=1.4%; Fig. 2). The Hartung–Knapp method produced an identical point estimate with a slightly narrower confidence interval (OR 0.53, 95% CI 0.32–0.87; Supplementary Figure 8).

Pooled analysis of 13 studies showed that PLHIV had markedly increased odds of NTS bacteraemia compared with HIV-negative participants (OR 4.06, 95% CI 2.23–7.39), though heterogeneity across studies was substantial (I^2=58.4%; Fig. 3).

Sensitivity analyses and meta-regression

Among studies conducted prior to 2004,[26,27,29,31,32,37] PLHIV had significantly lower odds of *Salmonella* Typhi BSI than HIV-negative participants (OR 0.38, 95% CI 0.17–0.84; 6 studies; low heterogeneity, I^2=0%; Fig. 4).

In studies conducted from 2004 onwards,[3,30,33,34,36,38–41] the odds of typhoid BSI in PLHIV were not significantly different compared with HIV-negative participants (OR 0.65, 95% CI 0.34–1.25; 11 studies; low heterogeneity, I^2=18%).

Meta-regression indicated a non-significant trend towards increased odds of *Salmonella* Typhi BSI among PLHIV for every successive median date of participant recruitment (coefficient 38%, 95% CI −18% to 120%; Supplementary Figure 7).

In studies enrolling paediatric participants, the odds of *Salmonella* Typhi BSI were similar between PLHIV and HIV-negative individuals (OR 1.12, 95% CI 0.48–2.59; low heterogeneity, I^2=0%). In contrast, studies of adult populations showed significantly lower odds of typhoid fever among PLHIV compared with HIV-negative participants consistent with the primary outcome finding (OR 0.40, 95% CI 0.23–0.70; Fig. 5).

Quality assessment

Of six studies rated low-risk of bias, PLHIV had significantly lower odds of *Salmonella* Typhi BSI compared with HIV-negative individuals (OR 0.37, 95% CI 0.16–0.87). Among three studies rated high-risk of bias, PLHIV similarly showed lower odds of typhoid fever (OR 0.27, 95% CI 0.08–0.92). However, in eight studies with moderate bias, no significant difference was observed (OR 0.95, 95% CI 0.47–1.91). Heterogeneity was moderate among studies with high-risk of bias but low among studies with low or moderate-risk of bias (Supplementary Figure 2).

CD4 cell count

Four studies reported mean CD4 cell counts among adult PLHIV participants, each indicating advanced immunosuppression (range 78–159 cells / µl).[3,31,33,36] One study reported CD4 percentages and counts, as befitted their paediatric population – these were similarly reflective of advanced HIV disease.[30] For the four adult studies reporting quantitative CD4 cell counts, the pooled odds of *Salmonella* Typhi BSI remained significantly lower among PLHIV compared with HIV-negative participants (OR 0.20, 95% CI 0.08–0.49). Meta-regression suggested a trend towards decreasing odds of typhoid fever with increasing CD4 cell count, though this was not statistically significant (Supplementary Figure 3).

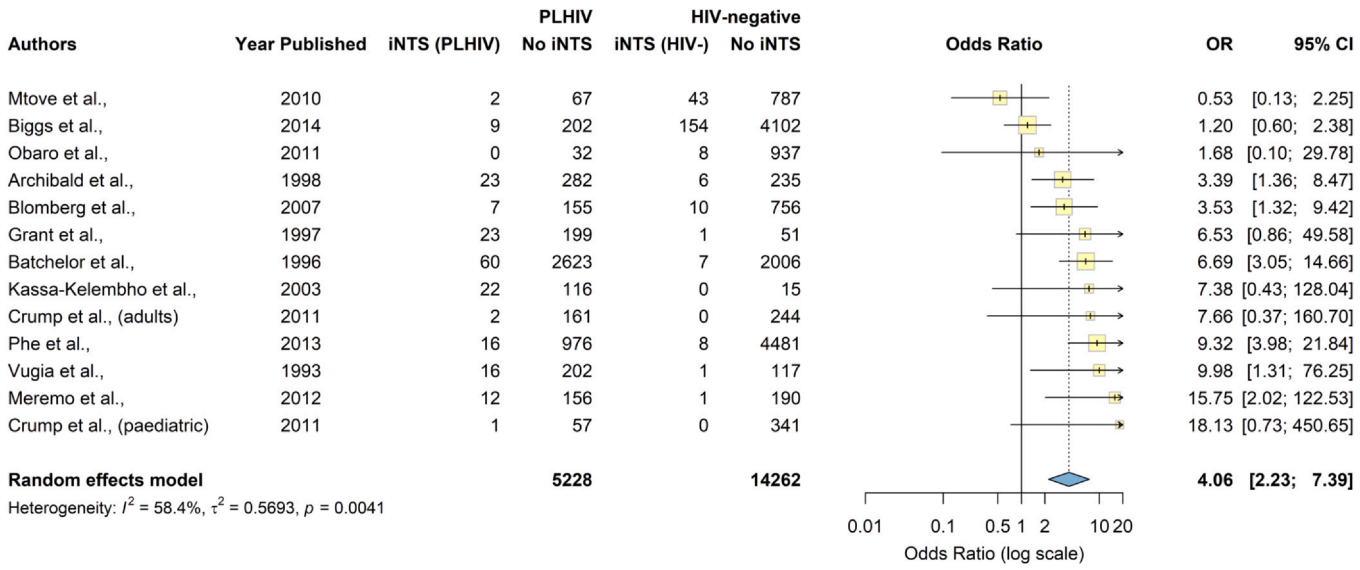

Fig. 3. Forest plot from a random-effects meta-analysis of 13 studies comparing the odds of non-typhoidal *Salmonella* (NTS) bloodstream infection in PLHIV versus HIV-negative individuals. Study-specific odds ratios with 95% confidence intervals are shown alongside pooled estimates. Heterogeneity was assessed using the I^2 statistic. This figure was generated using the meta package in R (v8.0.1).[23].

Trimethoprim-sulphamethoxazole use

Only one study reported the proportion of PLHIV taking trimethoprim-sulphamethoxazole prophylaxis, at 29/161 (18%) – we were therefore unable to assess the influence of this on our primary outcome.[3]

Resistance in Salmonella *Typhi bloodstream isolates*

Four studies reported antimicrobial resistance profiles of *Salmonella* Typhi isolates,[36–38,40] and in three of these trimethoprim-sulphamethoxazole resistance was common.[33,36,37] A pooled analysis of these three studies showed a non-significant point estimate

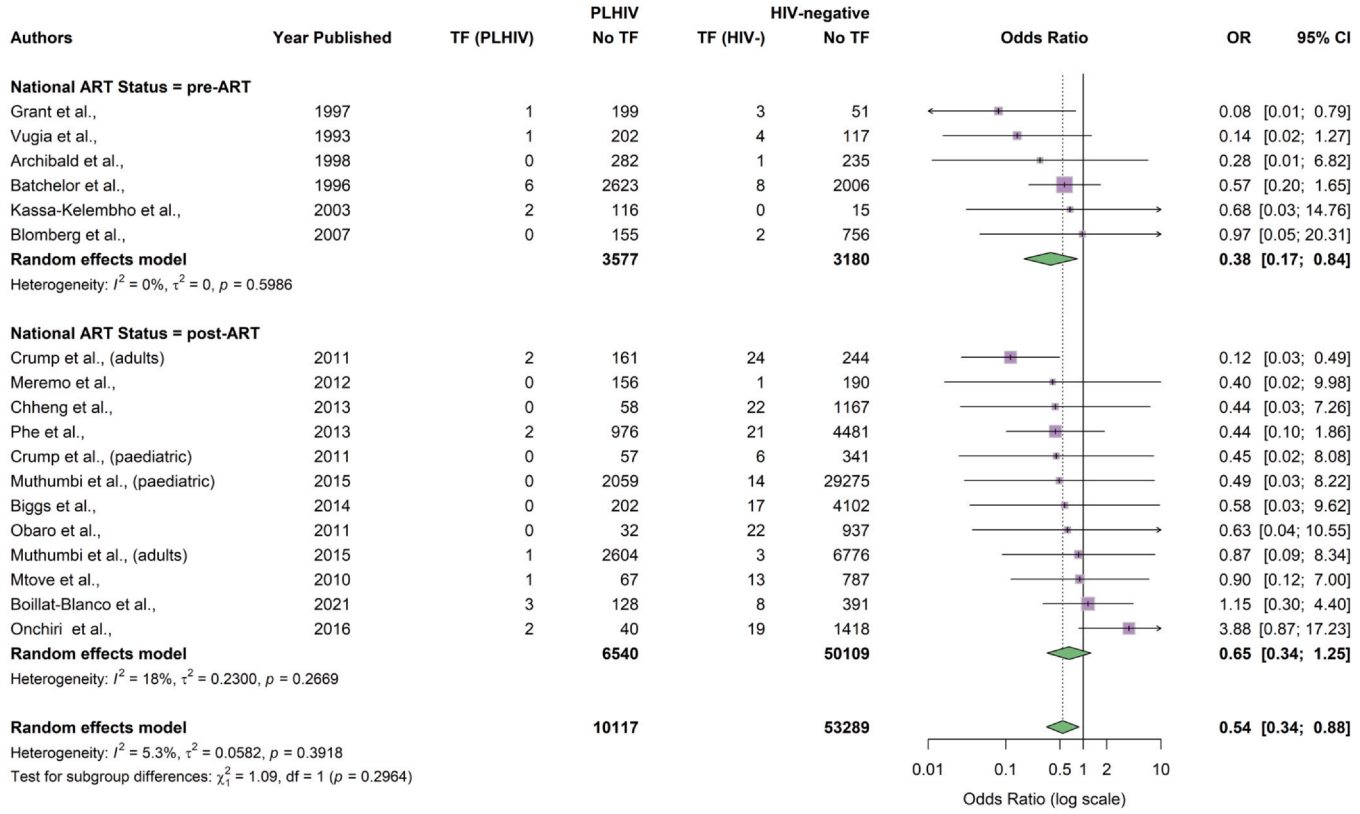

Fig. 4. Forest plot from a random-effects meta-analysis comparing the odds of *Salmonella* Typhi bloodstream infection in PLHIV versus HIV-negative individuals, stratified by ART era. We analysed six studies conducted before 2004 (pre-ART rollout) and 11 studies conducted after. Study-specific and pooled odds ratios with 95% confidence intervals are shown. We assessed heterogeneity using the I^2 statistic. The figure was generated using the meta package in R (v8.0.1).[23].

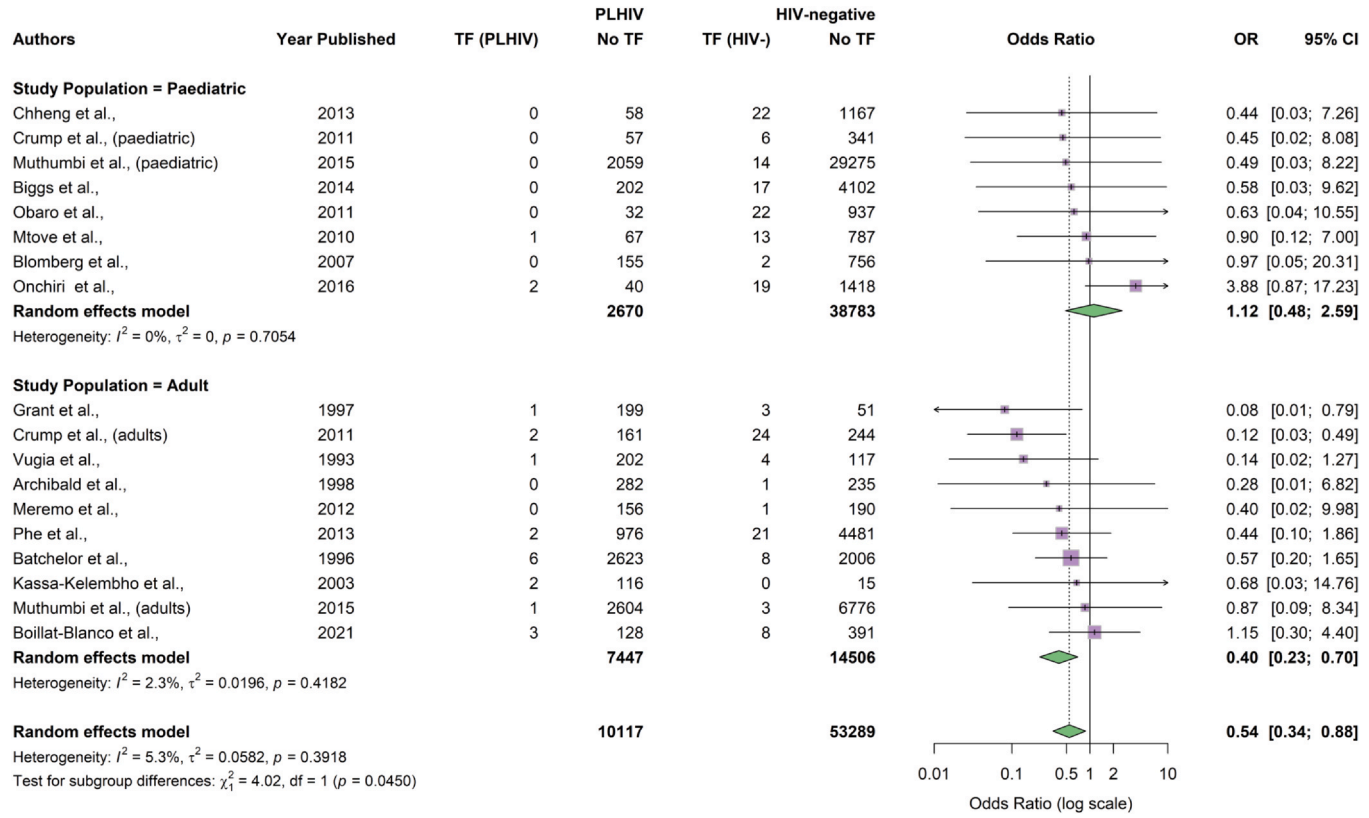

Fig. 5. Forest plot from a random-effects meta-analysis comparing the odds of *Salmonella Typhi* bloodstream infection in PLHIV versus HIV-negative individuals, stratified by population age group. The upper panel includes paediatric studies; the lower panel includes adult studies. We present study-specific and pooled odds ratios with 95% confidence intervals. We assessed heterogeneity using the I^2 statistic. The figure was generated using the meta package in R (v8.0.1).[23].

of reduced *Salmonella* Typhi BSI (OR 0.51, 95% CI 0.18–1.51; Supplementary Figure 4).

Reporting biases

We found no evidence of publication bias or small-study effects using funnel plot asymmetry tests for our typhoid meta-analysis (t=0.88, p=0.40; Supplementary Figure 5) or for our NTS pooled analysis (t=0.88, p=0.40; Supplementary Figure 6).

Discussion

In this systematic review and meta-analysis we found that PLHIV have reduced likelihood of blood-culture confirmed typhoid fever, compared with HIV-negative participants drawn from the same study populations. In contrast, we found that PLHIV have a greater risk of bacteraemia due to non-typhoidal *Salmonella*, in keeping with its well-characterised role as an opportunistic infection. The opposing directions of association for typhoid fever and iNTS, despite similar diagnostic pathways, suggest that differential healthcare-seeking behaviour alone is unlikely to explain our findings.

The strongest negative relationship between HIV and typhoid fever was observed in earlier studies conducted before widespread roll-out of national ART programmes, whereas later studies did not replicate this finding. Furthermore, an analysis of four studies in which PLHIV were known to have severe immunosuppression (CD4 ≤ 200 cells/μl) demonstrated markedly lower odds of *Salmonella* Typhi bloodstream infection. This implies a connection between advanced HIV infection and reduced likelihood of presenting to healthcare facilities with a positive blood culture for *Salmonella* Typhi. This pattern contrasts with findings for iNTS disease, where the odds of infection dramatically increase with lower CD4 counts.[5]

In sensitivity analyses, we demonstrated that the relationship between HIV and reduced *Salmonella* Typhi BSI was confined to adults and not observed among children. It remains unclear why HIV might impact typhoid BSI risk in adults but not in children. Given our small sample size, there is ongoing uncertainty regarding this association in paediatric populations. All but one of the paediatric studies collected data after 2004, potentially reflecting increased ART availability. We are unable to formally assess the relative immunocompromise of these participants, however, since only one paediatric study provided CD4% counts.[30] Age-stratified prospective epidemiological studies are needed to clarify any association between children living with HIV and typhoid fever.

Reassuringly, the pooled odds of *Salmonella* Typhi BSI among PLHIV were significantly reduced in studies assessed as low-risk for bias, suggesting that our primary outcome finding is not a consequence of methodological bias. Notably, the three high-risk studies were also the oldest in our dataset, raising the possibility of confounding between risk of bias and study age, with correspondingly lower ART coverage.

Our meta-analysis included 17 studies, representing the subset of blood culture surveillance studies reporting both *Salmonella* Typhi bloodstream infection and HIV status. We found that HIV status was not commonly reported for participants with typhoid fever (which perhaps reflects the previous uncertainty surrounding any positive or negative association). As a result, our data was limited due to studies lacking relevant denominators.

We used the year 2004 as a surrogate indicator of increased ART. Although we collected data on ART coverage, this information was limited to one study and did not include blood culture outcomes stratified by ART use. Our inference linking the reduced HIV-associated protection against typhoid over time to ART rollout therefore remains cautious. The shift in typhoid epidemiology following the

introduction of multidrug-resistant (MDR) H58 lineage *Salmonella Typhi* to Africa in 2010 may also be a contributing factor.[42] H58 *Salmonella* Typhi is resistant to antibiotics commonly used in the community in resource-limited settings, including chloramphenicol, trimethoprim-sulphamethoxazole, and amoxicillin: it is possible that antibiotic prophylaxis provided to PLHIV offered some protective effect prior to the emergence of H58, after which typhoid rates in PLHIV started to rise.

Nine of 17 studies did not fully describe their microbiological methods for distinguishing *Salmonella* Typhi from other *Salmonella* species. However, since both PLHIV and HIV-uninfected individuals were drawn from the same study populations, suboptimal diagnostic ascertainment should have affected both groups equally.

The inverse association between HIV and blood culture-confirmed typhoid fever has been remarked upon before, though never by a study that was explicitly designed to investigate it. In their 2010 review of community-acquired BSIs in Africa, Reddy and colleagues estimate reduced typhoid odds of 0.07 in PLHIV (no confidence intervals provided).[2] In a 2014 review of community-acquired BSI among PLHIV in Africa, Huson and colleagues estimate odds of 0.11 (95% CI 0.05–0.22).[4] Due to their non-purposive design, these studies based their observations on only three and four studies, respectively. By systematically searching the literature, we have been able to synthesise 17 studies, strengthening confidence in our findings. Despite not having been definitively investigated, the possibility of a negative association between HIV and typhoid fever has permeated through to published literature. Crump and colleagues made note of this observation in the study included in this synthesis, prompting an editorial commentary.[43]

In this commentary, Levine suggests three mechanisms by which PLHIV might be presenting with fewer *Salmonella* Typhi BSI: first, that a greater risk of disability or death reduces presentation to hospitals; second, that trimethoprim-sulphamethoxazole prophylaxis prevents *Salmonella* Typhi from gaining a foothold; and third, that a host-specific mechanism limits clinical manifestations after exposure. We further speculate that *Salmonella* Typhi itself might interact differently with the HIV-infected host, influencing either pathogenicity or clinical presentation distinctively from HIV-negative individuals.

While disability or death could reduce hospital presentation among people living with HIV (PLHIV), typhoid fever typically causes less severe disease than iNTS.[44–47] Given that we observed the expected positive association between HIV and iNTS within the same study populations, it seems unlikely that PLHIV would systematically fail to seek care for typhoid but not for iNTS.

Trimethoprim-sulphamethoxazole has activity against *Staphylococcus aureus* (including methicillin-resistant strains, MRSA) and other Enterobacterales. If prophylaxis were responsible for the reduced incidence of *Salmonella* Typhi BSI, it follows that other susceptible organisms would be similarly impacted. As we demonstrate here, iNTS disease was positively associated with HIV in the included studies.

The host response and symptom manifestations to typhoid may also be altered by HIV. The onset of symptoms in typhoid fever has been shown to coincide with cell-mediated immune responses, which would be attenuated in late-stage HIV.[43,48] If symptoms of clinical typhoid are not manifest, those infected may not present to healthcare facilities.

Though speculative, there are plausible mechanisms by which HIV might alter the pathogenesis of *Salmonella* Typhi infection. In her doctoral thesis, NJ reported that HIV is associated with an increased frequency of TNF-alpha and Interferon-gamma producing mucosal-associated invariant T (MAIT) cells in the blood and duodenum when the cells are stimulated with *Salmonella* Typhi.[49] *Salmonella* Typhi typically elicits a weak inflammatory response in the intestinal mucosa, which may facilitate its invasion.[50,51] PLHIV have dysregulated innate immunity within the gut – the uptake of the pathogen into antigen-presenting cells and consequent dissemination across the gut epithelial barrier may therefore be impaired.[52] Further mechanistic studies to explore these pathways are warranted and may yield insights into HIV-associated immune responses, host susceptibility, and potential therapeutic or preventive strategies.

We present evidence from all available studies and thereby confirm a negative association between HIV infection and blood culture-confirmed typhoid fever in adult populations. Clinicians working in regions where HIV and typhoid fever are co-endemic should be aware of this interaction. Future studies should systematically ascertain and report HIV status in blood culture surveillance, particularly among paediatric populations, to further clarify these associations. Importantly, these findings should not diminish enthusiasm for the typhoid conjugate vaccine, which remains a safe and highly effective public health intervention for children and targeted adult populations in endemic areas. However, our data suggest that adults living with HIV do not constitute a group at increased risk of typhoid fever, which may warrant reconsideration of current vaccination guidelines.

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Appendix A. Supporting information

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