The global burden of enteric fever, 2017–2021: a systematic analysis from the global burden of disease study 2021

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Summary

Background Enteric fever is a major public health challenge in developing countries. We conducted a systematic analysis from the Global Burden of Diseases 2021 Study to provide updated estimates of enteric fever's burden.

Methods We presented estimates for incident cases and deaths, age-standardized incidence and mortality rates, years of life lost (YLLs), and case-fatality rates spanning the study period of 2017–2021, stratified by region, country, socio-demographic index (SDI), and age group. Random-effects Poisson regression for longitudinal data was used to estimate the association between SDI and case-fatality rates, adjusting for antimicrobial resistance patterns.

Findings In 2021, there were 9.3 million global cases of enteric fever (95% uncertainty interval: 7.3–11.9) and 107.5 thousand deaths (56.1–180.8). The age-standardized incidence rate decreased from 152/100,000 person-years (118–195) in 2017 to 128/100,000 person-years (100–163) in 2021, and the mortality rate decreased from 1.87/100,000 person-years (0.95–3.18) to 1.50/100,000 person-years (0.78–2.54). There were wide geographical differences, with South Asia contributing the most cases and deaths. Age-standardized incidence exceeded the threshold for "high burden" of enteric fever (100/100,000 person-years) in 23 countries in 2021.
Children under five accounted for 40% of deaths and 47% of YLLs, with incidence and mortality peaking during the second year. Case-fatality was highest in low SDI countries and showed a global trend toward reduction, except among children aged 1–4 years. After adjusting for the prevalence of multidrug resistance, fluoroquinolone non-susceptibility, and third-generation cephalosporin resistance, a higher SDI was associated with a lower case-fatality rate, with a 1.1% (0.7–1.7) reduction for each percentage point increase in SDI.

Interpretation Despite notable improvements, several countries still showed a high burden of enteric fever, which remains a significant global health concern, especially among children under five. Although enhancing water and sanitation systems is crucial, the most significant reductions in the global disease burden are likely to be achieved through broader vaccine coverage. This includes the use of typhoid conjugate vaccines, which are effective in infants and young children and offer extended protection, along with improved data collection and surveillance to guide vaccine distribution efforts across high-incidence areas.

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Keywords: Typhoid fever; Epidemiology; *Salmonella* typhi; *Salmonella enterica*

Introduction

Typhoid and paratyphoid fevers (hereafter called enteric fever) are serious systemic infections caused by *Salmonella enterica* serovars Typhi and Paratyphi.[1] If untreated, enteric fever can result in cognitive disturbances and may cause severe gastrointestinal complications potentially resulting in septic shock and death.[1] Enteric fever is typically transmitted through contaminated food or water and is more common in low- and middle-income countries with poor sanitation, inadequate access to clean water, and overcrowded living conditions.[2] Endemic countries are primarily in South and Southeast

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Research in context

Evidence before this study

Enteric fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi, remains a major public health concern in developing countries. Despite improvements in water, sanitation, and hygiene, control efforts are complicated by the rise of antimicrobial resistance (AMR), including multidrug resistance and fluoroquinolone non-susceptibility, along with the limited use of typhoid conjugate vaccines. Prior estimates of the disease burden relied largely on regional data, small-scale studies, and earlier versions of the Global Burden of Disease (GBD) Study including data from 1990 to 2017.

Added value of this study

This study provides updated global estimates of enteric fever from 2017 to 2021, integrating recent AMR data from 75 endemic countries. It highlights significant disparities in incidence and mortality, particularly in South Asia, and emphasizes the ongoing burden among children. The findings support broader use of typhoid conjugate vaccines to mitigate the impact of AMR on enteric fever control.

Implications of all the available evidence

The findings underscore the need for enhanced vaccination programs, particularly the deployment of typhoid conjugate vaccines, which are effective in young children and provide long-term protection. While improvements in water and sanitation are still crucial, broader vaccine coverage is essential to significantly reduce the global burden of enteric fever in high-incidence areas. Policymakers, healthcare professionals, and researchers can utilize this updated evidence to advocate for and implement targeted interventions.

Asia (where the monsoon season exacerbates transmission by increasing water contamination), and Sub-Saharan Africa.[2,3] Despite a more than 50% decrease in incidence over the past three decades, largely due to improved hygienic conditions, enteric fever is still associated with significant global morbidity and mortality, especially among children, with about 14 million estimated cases and 130 thousand deaths in 2017.[3] The mainstay treatment is timely antibiotic treatment including chloramphenicol, trimethoprim–sulfamethoxazole, ampicillin or amoxicillin, fluoroquinolones, third-generation cephalosporin and azithromycin.[4] Yet, antibiotic resistance is a major concern in several endemic countries, where access to more expensive antibiotic alternatives is limited.[5]

Alongside continued improvements in sanitation and living conditions, vaccination remains the most effective prevention strategy. Vaccination reduces incidence and hinders the development of antimicrobial-resistant strains.[6] Since 2017–2018, two WHO pre-qualified typhoid conjugate vaccines have been endorsed for use in high-incidence countries.[7,8] Despite their demonstrated efficacy,[9,10] adoption in routine vaccination campaigns has been limited.[11,12] Monitoring global and country-specific data on the burden of enteric fever is crucial for advocating routine adoption of vaccination by all endemic countries.

In the current study, we systematically analyzed data on enteric fever from the latest iteration of the Global Burden of Disease (GBD) Study 2021.[13,14] Our goal was to report updated global, regional and country-specific estimates of incidence, mortality, and case-fatality rates from 2017 to 2021. Additionally, we aimed to assess the role of country-level socio-demographic index (SDI) and drug resistance patterns on these trends in 75 endemic countries.

Methods

Data acquisition

The GBD 2021 study provides a comprehensive evaluation of the burden and health impact of 369 conditions, including diseases, injuries, and disabilities, and 88 risk factors across 204 countries and areas.[13,14] A complete explanation of the methods and data sources used by the GBD 2021 study is beyond the scope of the current publication and can be found in recent landmark publications.[13,14] In brief, by utilizing a Bayesian meta-regression tool, the study incorporates data from systematic literature reviews, hospital discharge records, surveillance systems, survey results, and insurance claims to model and estimate the burden of these conditions from 1990 to 2021.

The GBD analysis is based on 1000 iterations for each model pertaining to each outcome variable by specific cause and the uncertainty interval (UI) is defined by the 2.5th percentile and the 97.5th percentile of these projected outcomes, representing the lower and upper limits, respectively.[15]

Ethics

The current investigation employed GBD 2021 data which have been made available under the Open Data Commons Attribution License through the GBD Collaborative Network website (http://ghdx.healthdata.org).

Statistics

We extracted and reported age-standardized incidence and mortality rates attributed to enteric fever, accompanied by the respective 95% UI, as drawn from the GBD 2021 database for the period 2017 to 2021. Data from the period 1990 to 2017 were not included, as this timeframe has been addressed in a previous publication.[3] We considered the Years of life lost (YLLs), a health metric calculated by multiplying the number of deaths due to enteric fever by the standard life expectancy at age of death in years. We computed the case-fatality rate by dividing the number of deaths by the incident cases, expressed as a percentage.

We conducted a comprehensive assessment to quantify the regional (i.e. as defined by GBD super-regions) and country-specific burden of enteric fever in 75 endemic countries, which were previously identified by a recent study performed by the GRAM Typhoid Collaborators.[5] Regional age-adjusted incidence rates over 100/100,000 person-years were considered as "high incidence".[16] We conducted stratified analyses by age group (<1, 1, 2–4, 5–14, 15–49, 50–69, and ≥70 years old).

We considered the socio-demographic index (SDI), a population-level metric developed by the GBD group, measuring the level of development of a country on a scale from 0 to 1. This index is calculated as the composite average of rankings in income per capita, average educational attainment, and fertility rates.[17] By stratifying the global burden of enteric fever by SDI quintiles (2021) we provided a perspective on its impact across different development levels. We obtained annual prevalence estimates of multidrug resistance (i.e. simultaneous resistance to trimethoprim–sulfamethoxazole, chloramphenicol, ampicillin or amoxicillin), fluoroquinolone non-susceptibility, and third-generation cephalosporin resistance in *Salmonella* Typhi infections from a seminal modeling study.[5] These estimates covered 75 endemic countries for the years 2017–2019, allowing us to integrate critical resistance data into our analysis.

We employed multivariable random-effects Poisson regression for longitudinal data to assess the association between SDI and case-fatality rate in these endemic countries in the 2017–2019 period. As antimicrobial resistance patterns are likely associated with case-fatality rates, the analysis considered the country-level annual prevalence of multidrug resistance, fluoroquinolone non-susceptibility, and third-generation cephalosporin resistance as relevant covariates. The outcome variable comprised annual death counts recorded during the 2017–2019 period in each country. Death counts were assumed to follow a Poisson distribution. The natural logarithm of incident cases was included as an offset in the regression equation to standardize the population at risk of death across countries and years. In our model specification, we considered country-level clustering and applied Huber-White standard error estimators.[18] These estimators are resilient to misspecification of within-country correlation structures and assumptions regarding covariance among countries. The results are presented in terms of incidence rate ratios as derived from the exponentiated β-coefficients and accompanied by 95% confidence intervals.

Choropleth maps of age-standardized incidence and mortality rates for the 75 endemic countries of interest were plotted by using the online tool datawrapper.de (https://www.datawrapper.de/). Data processing, analysis and visualization were performed with the Stata software (STATA 18.0, College Station, Texas, USA).

Role of funding source
The funder of the study had no involvement in the study's design, data collection, data analysis, data interpretation, or the writing of the report. The first authors had full access to the study data, and the corresponding authors held the final responsibility for the decision to submit the manuscript for publication.

Results
Incidence
The latest iteration of the GBDs 2021 estimated a total of 10.9 million global cases (95% UI: 8.5–14.0) in 2017 declining to 9.3 million (95% UI: 7.3–11.9) in 2021, representing a 15% decrease. The global age-adjusted incidence rate declined by about 16% in the same period (from 152/100,000 person-years [95% UI: 118–195] to 128/100,000 person years [95% UI: 100–163]).

Among the four endemic GBD super-regions, South Asia showed the highest number of incident cases (6.7 million; 95% UI: 5.2–8.6) accounting for approximately 62% of global cases, followed by Sub-Saharan Africa (1.3 million; 95% UI: 1.0–1.7; 14% of global cases) and Southeast Asia, East Asia, and Oceania (1.1 million; 95% UI: 0.9–1.4, 12% of global cases). The highest age-standardized incidence rate in 2021 was observed in South Asia (379.6/100,000 person-years; 95% UI: 295.9–484.0; Table 1, Fig. 1). All super-regions showed improvements in age-standardized incidence rates, ranging from a reduction of approximately 11% in Southeast Asia, East Asia, and Oceania to a reduction of 17% in South Asia.

In 2021, India contributed the highest number of incident cases, totaling 5.4 million (95% UI: 4.1–6.9), which represented approximately 58% of global cases. This was followed by Pakistan (8%) and Bangladesh (5%). India also exhibited the highest age-standardized incidence rate at 411.5/100,000 person-years (95% UI: 318.4–529.6), followed by Papua New Guinea at 351.0/100,000 person-years (95% UI: 266.7–469.6) and Burkina Faso at 343.3/100,000 person-years (95% UI: 283.3–427.5, Table 2).

Age-standardized incidence rates decreased in all endemic countries from 2017 to 2021 (Table 2). Initially, 43 countries exceeded the threshold for a "high burden" of enteric fever (i.e. >100/100,000 person-years); this number decreased to 23 countries by 2021. The largest reductions were observed in Côte d'Ivoire (17.5%),

	Incidence				Deaths				Case-fatality rate (%)
	Number (thousands)	(95% UI)	Age-standardized rate (per 100,000 py)	(95% UI)	Number (thousands)	(95% UI)	Age-standardized rate (per 100,000 py)	(95% UI)	
Global									
2017	10,920.3	(8481.8–13985.6)	152.0	(118.1–194.5)	133.5	(67.2–226.0)	1.87	(0.95–3.18)	1.22
2021	9320.6	(7274.4–11903.4)	127.8	(99.5–163.2)	107.5	(56.1–180.8)	1.50	(0.78–2.54)	1.15
Regions by SDI quintiles									
Low SDI									
2017	2529.6	(1945.2–3252.0)	208.9	(163.3–268.5)	35.1	(17.0–62.6)	2.74	(1.35–4.74)	1.39
2021	2220.7	(1708.0–2863.0)	171.0	(133.6–219.7)	29.3	(14.6–52.8)	2.15	(1.07–3.77)	1.32
Low-middle SDI									
2017	5990.1	(4665.9–7680.5)	312.6	(244.9–399.2)	72.1	(36.4–120.5)	3.74	(1.88–6.22)	1.20
2021	5033.8	(3928.0–6404.7)	258.1	(203.1–327.5)	57.6	(30.4–95.1)	2.96	(1.55–4.88)	1.14
Middle SDI									
2017	2149.5	(1686.3–2728.6)	99.9	(78.0–127.5)	23.9	(12.0–38.9)	1.13	(0.57–1.85)	1.11
2021	1849.2	(1444.7–2345.6)	85.4	(66.9–108.8)	18.8	(9.5–31.2)	0.89	(0.46–1.48)	1.02
High-middle SDI									
2017	231.4	(181.3–293.0)	23.7	(18.4–30.2)	2.3	(1.2–3.7)	0.24	(0.12–0.40)	0.97
2021	199.2	(155.3–252.4)	20.5	(16.0–26.1)	1.6	(0.8–2.7)	0.17	(0.09–0.28)	0.81
High SDI									
2017	14.8	(12.3–17.9)	1.7	(1.4–2.1)	0.1	(0.0−0.2)	0.01	(0.00−0.02)	0.52
2021	13.5	(11.2–16.2)	1.5	(1.3–1.9)	0.1	(0.0−0.1)	0.01	(0.00−0.02)	0.48
Endemic regions									
North Africa and Middle East									
2017	137.9	(108.8–180.1)	22.6	(17.8–29.6)	1.6	(0.8–2.9)	0.26	(0.12–0.47)	1.15
2021	120.0	(93.0–157.2)	19.2	(14.9–25.1)	1.3	(0.6–2.3)	0.20	(0.10–0.37)	1.07
South Asia									
2017	8043.6	(6234.9–10334.6)	456.7	(354.6–584.5)	93.5	(47.2–155.2)	5.32	(2.69–8.84)	1.16
2021	6723.1	(5215.2–8579.0)	379.6	(295.9–484.0)	72.1	(38.2–119.5)	4.15	(2.18–6.87)	1.07
Southeast Asia, East Asia, and Oceania									
2017	1282.4	(1002.7–1623.9)	72.5	(56.7–92.2)	15.1	(7.5–25.7)	0.88	(0.44–1.51)	1.18
2021	1138.8	(888.6–1447.7)	64.7	(50.4–82.9)	13.3	(6.5–22.1)	0.78	(0.38–1.33)	1.17
Sub-Saharan Africa									
2017	1408.8	(1088.0–1799.5)	112.0	(87.4–143.5)	23.1	(11.0–43.3)	1.73	(0.81–3.16)	1.64
2021	1291.1	(991.6–1656.0)	94.8	(73.8–121.6)	20.6	(9.9–39.2)	1.44	(0.69–2.66)	1.60

Abbreviations: py, person-year; SDI, socio-demographic index; UI, uncertainty interval.

Table 1: **Incident cases and deaths attributable to enteric fever in 2017 and 2021, including age-standardized rates and case-fatality rates, by socio-demographic index quintiles and endemic regions.**

Guinea-Bissau (17.3%), and Zambia (17.2%). Among countries contributing most cases, India reported a decrease of 16.9%, Pakistan 14.2%, and Bangladesh 15.2%.

The incidence rate was dramatically higher among children, peaking from 12 to 23 months of age with a global average of 659.1/100,000 person-years (95% UI: 388.1–899.2) and steadily decreasing thereafter, reaching a low of 39.6/100,000 person-years (95% UI: 23.1–61.2) over 70 years old in 2021 (Fig. 2). The age distribution of cases varied across endemic super-regions. In Sub-Saharan Africa, approximately 68% of cases occurred in children under 14 years of age, whereas in Southeast Asia, East Asia, and Oceania, about 53% of cases were in this age group.

Deaths, case-fatality, YLLs

In 2017, an estimated 133.5 thousand global deaths (95% UI: 67.2–226.0) were attributed to enteric fever. This number declined to 107.5 thousand (95% UI: 56.1–180.8) in 2021, marking a decrease of about 19%. The global age-adjusted mortality rate also saw a decline of approximately 20%, from 1.87 (95% UI: 0.95–3.18) to 1.50/100,000 person-years (95% UI: 0.78–2.54) during the same period. We estimated a drop in mean global case-fatality rate from approximately 1.22% in 2017 to 1.15% in 2021.

In 2021, South Asia showed the highest number of deaths (72.1 thousand; 95% UI: 38.2–119.5) among endemic super-regions, accounting for approximately 67% of global deaths. This was followed by Sub-Saharan

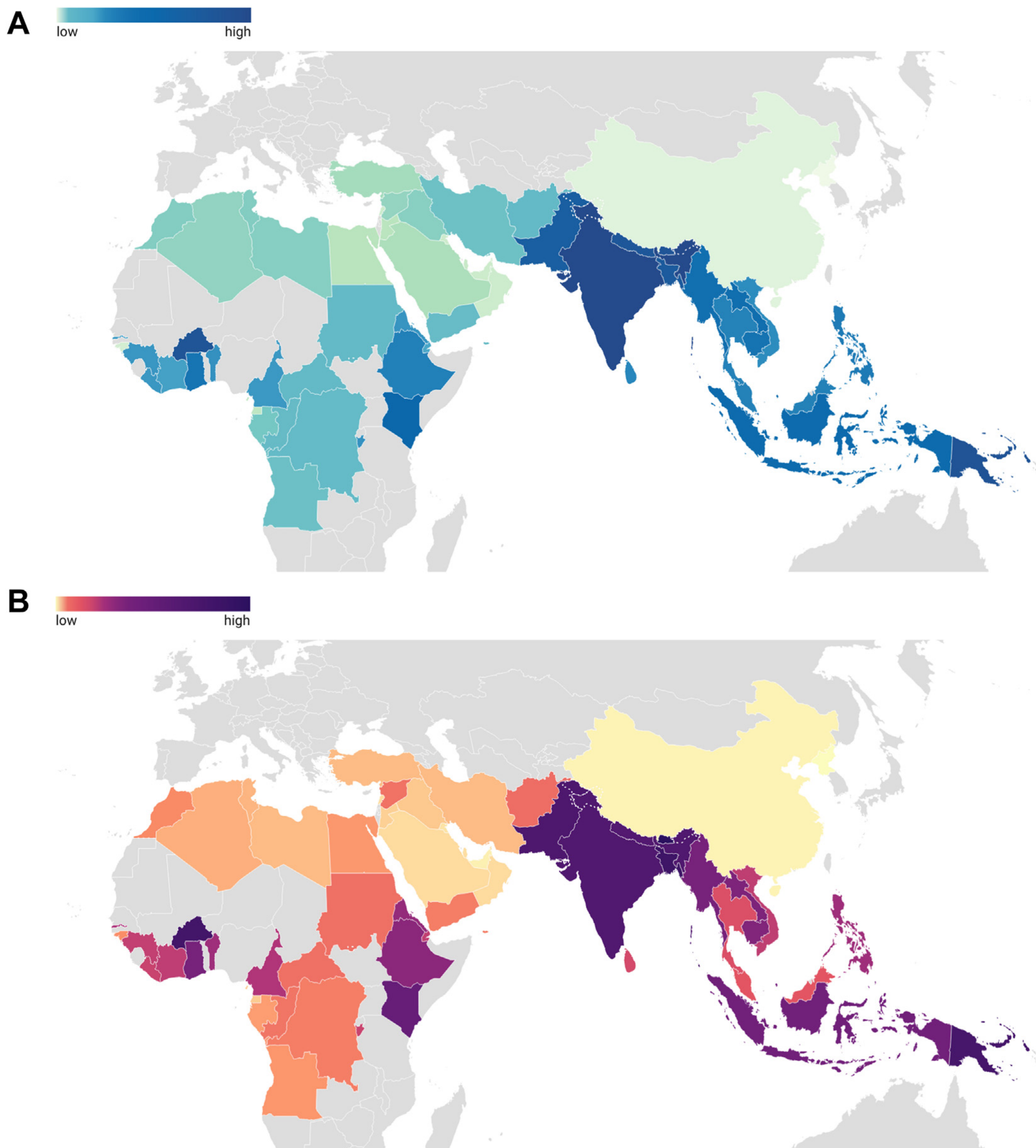

Fig. 1: Age-standardized incidence (panel A) and mortality (panel B) of enteric fever in 75 endemic countries, 2021.

Africa (20.6 thousand; 95% UI: 9.9–39.2; 19% of global deaths) and Southeast Asia, East Asia, and Oceania (13.3 thousand; 95% UI: 6.5–22.1, 12% of global deaths). South Asia showed the highest age-standardized mortality rates (4.15/100,000 person-years; 95% UI: 2.18–6.87; Table 1, Fig. 1) in 2021. This region also demonstrated the largest improvement since 2017, representing an approximate 22% reduction.

In 2021, the case-fatality rate ranged from approximately 1.07% in North Africa and Middle East to 1.60% in Sub-Saharan Africa. South Asia showed the largest improvement from 2017 to 2021, decreasing from 1.16% to 1.07%. Conversely, there was no apparent improvement in Southeast Asia, East Asia, and Oceania during the same period (Fig. 3).

India accounted for approximately 48% of global deaths (51.5 thousand; 95% UI 27.0–84.8), followed by Pakistan (11%) and Bangladesh (7%). The highest age-standardized mortality rates were observed in Bhutan (6.01/100,000 person-years; 95% UI: 3.08–10.1), Bangladesh (5.09/100,000 person-years; 95% UI: 2.58–8.39) and Burkina Faso (4.77/100,000 person-years; 95% UI: 2.31–8.84; Fig. 1, Table 2). Age-standardized mortality rates decreased in all endemic countries during the 2017–2021 period, except for Zimbabwe (approximately +6%). The largest decreases

	Age-standardized incidence rate (× 100,000 py)		Age-standardized mortality rate (× 100,000 py)	
	2017 (95% UI)	2021 (95% UI)	2017 (95% UI)	2021 (95% UI)
North Africa and Middle East				
Afghanistan	31.6 (24.6–41.7)	26.9 (20.4–35.7)	0.51 (0.24–0.95)	0.43 (0.80–0.20)
Algeria	20.2 (15.7–27.0)	17.1 (13.3–23.0)	0.19 (0.09–0.36)	0.16 (0.07–0.30)
Egypt	19.4 (15.6–24.1)	16.4 (12.6–20.4)	0.24 (0.12–0.42)	0.20 (0.09–0.35)
Iran (Islamic Republic of)	25.1 (19.5–33.1)	21.0 (16.4–27.5)	0.22 (0.10–0.41)	0.14 (0.07–0.26)
Iraq	20.8 (16.1–27.2)	17.3 (13.1–22.8)	0.16 (0.07–0.32)	0.13 (0.06–0.24)
Jordan	19.0 (14.6–24.7)	16.4 (12.7–21.4)	0.16 (0.07–0.30)	0.12 (0.06–0.23)
Kuwait	18.7 (14.8–24.4)	16.1 (12.3–21.0)	0.12 (0.04–0.28)	0.10 (0.03–0.24)
Lebanon	18.8 (14.4–25.3)	16.2 (12.3–21.8)	0.14 (0.06–0.27)	0.11 (0.05–0.20)
Libya	20.3 (15.8–26.8)	17.3 (13.4–22.5)	0.18 (0.08–0.35)	0.14 (0.06–0.28)
Morocco	20.6 (16.0–27.0)	17.5 (13.4–23.1)	0.29 (0.13–0.52)	0.23 (0.10–0.42)
Oman	19.0 (14.8–25.5)	16.2 (12.3–21.4)	0.16 (0.05–0.37)	0.11 (0.03–0.28)
Qatar	18.9 (14.5–25.3)	16.2 (12.3–22.0)	0.15 (0.05–0.34)	0.10 (0.03–0.25)
Saudi Arabia	19.0 (15.1–24.6)	16.5 (12.8–21.3)	0.14 (0.04–0.33)	0.11 (0.04–0.27)
Sudan	33.3 (25.8–43.8)	27.9 (20.5–37.3)	0.50 (0.23–0.96)	0.40 (0.17–0.75)
Syrian Arab Republic	20.1 (15.7–26.7)	17.0 (13.0–22.5)	0.42 (0.19–0.77)	0.36 (0.16–0.63)
Tunisia	20.9 (16.4–27.8)	17.4 (13.6–23.1)	0.19 (0.09–0.37)	0.15 (0.07–0.29)
Turkey	19.8 (15.4–26.1)	16.6 (12.3–21.9)	0.17 (0.08–0.32)	0.14 (0.06–0.27)
United Arab Emirates	18.6 (14.6–24.3)	16.2 (12.5–20.9)	0.11 (0.03–0.27)	0.07 (0.02–0.18)
Yemen	26.5 (20.7–34.4)	22.9 (17.8–29.8)	0.31 (0.14–0.61)	0.26 (0.12–0.50)
South Asia				
Bangladesh	363.1 (294.3–460.3)	307.2 (247.8–390.4)	6.02 (3.09–9.98)	5.09 (2.58–8.38)
Bhutan	400.9 (307.5–523.4)	340.3 (258.6–440.1)	6.90 (3.52–11.57)	6.01 (3.08–10.1)
India	495.2 (380.3–640.3)	411.5 (318.4–529.6)	5.30 (2.65–8.87)	4.04 (2.13–6.68)
Nepal	393.4 (298.0–509.7)	327.9 (255.9–425.1)	4.80 (2.35–8.60)	3.90 (1.92–6.79)
Pakistan	332.5 (257.6–426.4)	285.2 (221.0–365.4)	4.89 (2.48–8.69)	4.13 (1.95–7.23)
Southeast Asia, East Asia, and Oceania				
Cambodia	177.4 (133.7–228.7)	153.0 (114.4–196.5)	2.28 (1.09–4.18)	2.03 (0.97–3.73)
China	10.6 (8.6–13.2)	9.5 (7.6–11.9)	0.09 (0.04–0.16)	0.07 (0.03–0.13)
Democratic People's Republic of Korea	4.7 (3.5–6.1)	4.0 (3.0–5.2)	0.06 (0.03–0.11)	0.05 (0.02–0.10)
Indonesia	218.7 (167.8–281.4)	188.5 (143.8–243.5)	2.79 (1.34–4.68)	2.45 (1.18–4.22)
Lao People's Democratic Republic	200.9 (155.8–256.0)	172.0 (130.0–225.6)	2.38 (1.14–4.35)	2.09 (0.98–4.02)
Malaysia	132.3 (100.1–170.7)	117.3 (89.6–155.1)	1.01 (0.48–1.79)	0.79 (0.38–1.41)
Myanmar	188.0 (143.2–243.4)	164.4 (126.0–214.0)	2.59 (1.23–4.67)	2.25 (1.08–4.30)
Papua New Guinea	414.4 (323.9–540.0)	351.0 (266.7–469.6)	5.33 (2.56–9.95)	4.60 (2.19–8.42)
Philippines	143.0 (110.8–185.5)	133.6 (103.2–173.5)	1.73 (0.82–2.96)	1.56 (0.74–2.70)
Sri Lanka	125.4 (85.8–173.5)	109.2 (74.5–152.1)	1.27 (0.60–2.44)	1.04 (0.48–1.90)
Thailand	131.5 (101.7–168.6)	114.8 (88.0–151.5)	1.06 (0.50–1.86)	0.93 (0.44–1.69)
Timor-Leste	217.8 (163.7–279.1)	189.0 (140.0–240.5)	2.52 (1.18–4.48)	2.20 (1.04–3.96)
Viet Nam	121.5 (96.0–153.6)	102.0 (79.2–133.1)	1.60 (0.74–2.80)	1.32 (0.64–2.28)
Sub-Saharan Africa				
Angola	25.3 (19.5–32.8)	21.3 (16.2–27.4)	0.25 (0.11–0.49)	0.20 (0.09–0.41)
Benin	114.7 (88.6–149.8)	96.3 (70.8–129.2)	1.85 (0.85–3.67)	1.56 (0.70–3.08)
Burkina Faso	402.9 (331.7–499.8)	343.3 (283.3–427.5)	6.06 (2.97–10.88)	4.77 (2.31–8.84)
Burundi	110.4 (83.2–144.2)	94.8 (70.5–123.8)	1.51 (0.69–2.78)	1.20 (0.54–2.27)
Cameroon	106.5 (80.6–137.9)	89.3 (68.7–114.5)	1.82 (0.84–3.47)	1.44 (0.64–2.67)
Central African Republic	31.4 (24.8–41.2)	27.8 (21.9–36.4)	0.42 (0.19–0.79)	0.38 (0.17–0.71)
Chad	122.5 (95.3–159.2)	103.5 (76.4–139.0)	1.73 (0.79–3.16)	1.45 (0.67–2.59)
Congo	27.5 (21.3–35.9)	23.6 (18.4–31.0)	0.37 (0.16–0.68)	0.30 (0.14–0.56)
Cote d'Ivoire	103.4 (80.6–133.2)	85.3 (66.2–111.5)	1.70 (0.80–3.23)	1.33 (0.60–2.46)
Democratic Republic of the Congo	28.3 (21.4–36.8)	24.3 (18.4–31.5)	0.32 (0.15–0.64)	0.26 (0.12–0.52)
Djibouti	98.5 (76.1–127.7)	82.1 (62.2–106.2)	1.67 (0.77–3.01)	1.30 (0.58–2.34)

(Table 2 continues on next page)

	Age-standardized incidence rate (× 100,000 py)		Age-standardized mortality rate (× 100,000 py)	
	2017 (95% UI)	2021 (95% UI)	2017 (95% UI)	2021 (95% UI)
(Continued from previous page)				
Equatorial Guinea	18.9 (14.5–24.5)	16.3 (12.2–21.5)	0.15 (0.04–0.36)	0.13 (0.03–0.31)
Eritrea	108.8 (82.8–138.9)	91.4 (68.5–118.0)	1.97 (0.89–3.46)	1.73 (0.76–3.11)
Ethiopia	141.0 (110.4–181.8)	121 (92.3–156.0)	2.13 (0.99–3.76)	1.88 (0.87–3.34)
Gabon	22.7 (17.4–29.1)	19.2 (14.6–25.1)	0.24 (0.09–0.46)	0.19 (0.08–0.36)
Gambia	101.7 (77.3–130.0)	86.3 (65.4–109.9)	1.75 (0.86–3.25)	1.47 (0.70–2.69)
Ghana	179.4 (143.7–225.6)	150.5 (116.5–189.7)	2.74 (1.32–4.92)	2.23 (1.06–4.18)
Guinea	108.0 (83.7–140.4)	90.5 (69.1–118.4)	1.63 (0.76–3.14)	1.29 (0.58–2.47)
Guinea-Bissau	17.0 (13.2–22.0)	14.1 (11.0–18.4)	0.30 (0.14–0.55)	0.22 (0.10–0.40)
Kenya	258.8 (199.9–332.3)	217.3 (167.5–278.8)	3.45 (1.66–5.69)	3.02 (1.49–5.19)
Liberia	106.6 (80.3–139.0)	89.7 (67.5–116.1)	1.43 (0.63–2.70)	1.20 (0.53–2.34)
Madagascar	105.0 (81.3–131.5)	87.8 (67.9–112.3)	1.33 (0.61–2.40)	1.13 (0.53–2.02)
Malawi	26.8 (22.5–31.6)	24.6 (20.1–29.4)	0.40 (0.19–0.70)	0.36 (0.18–0.66)
Mali	114.5 (87.5–147.4)	97.1 (73.6–126.5)	1.80 (0.88–3.27)	1.41 (0.66–2.60)
Mauritania	106.6 (81.4–137.1)	89.2 (67.6–116.5)	1.50 (0.67–2.65)	1.36 (0.64–2.42)
Mozambique	110.5 (84.8–142.1)	93.1 (68.5–121.2)	1.84 (0.81–3.44)	1.58 (0.71–3.05)
Niger	122.1 (94.1–159.6)	104.0 (79.4–136.5)	1.66 (0.73–3.10)	1.32 (0.60–2.53)
Nigeria	112.5 (87.4–145.2)	94.1 (73.0–122.0)	1.72 (0.79–3.33)	1.43 (0.62–2.91)
Rwanda	104.0 (79.0–134.0)	88.4 (66.4–114.4)	1.74 (0.80–3.27)	1.49 (0.72–2.79)
Senegal	100.3 (77.0–130.2)	84.8 (64.9–109.7)	1.97 (0.97–3.60)	1.52 (0.75–2.65)
Sierra Leone	114.0 (86.6–149.8)	96.7 (73.0–125.9)	1.66 (0.78–3.27)	1.43 (0.64–2.92)
Somalia	109.4 (82.6–141.9)	95.3 (70.9–124.1)	1.43 (0.61–2.65)	1.20 (0.51–2.28)
South Sudan	115.9 (87.1–150.6)	99.1 (75.1–127.8)	1.97 (0.85–3.61)	1.71 (0.76–3.19)
Togo	107.5 (82.1–141.1)	89.7 (66.0–117.7)	1.52 (0.68–2.80)	1.24 (0.54–2.29)
Uganda	105.8 (80.2–136.8)	89.5 (66.1–118.2)	1.54 (0.70–2.86)	1.31 (0.62–2.47)
United Republic of Tanzania	178.7 (140.1–221.3)	150.8 (120.0–188.6)	3.21 (1.55–5.76)	2.61 (1.28–4.95)
Zambia	96.1 (73.5–122.5)	79.6 (60.3–101.9)	2.72 (1.24–4.76)	2.18 (1.01–3.86)
Zimbabwe	1.7 (1.3–2.1)	1.5 (1.2–1.9)	0.02 (0.01–0.04)	0.02 (0.01–0.04)

Abbreviations: py, person-year; UI, uncertainty interval.

Table 2: **Age-standardized incidence and mortality rates of enteric fever in 75 endemic countries in 2017 and 2021.**

were observed in Islamic Republic of Iran (37%), United Arab Emirates (36%) and Oman (31%).

The case-fatality rate varied widely among endemic countries. Highest rates were observed in Zambia (2.68%), Eritrea (1.97%), and Senegal (1.89%), while the lowest were in United Arab Emirates (0.37%), Kuwait (0.55%), and Qatar (0.63%; Appendix Table 1). Notable improvements were seen in the Islamic Republic of Iran (from 0.88% in 2017 to 0.68% in 2021), United Arab Emirates (from 0.47% to 0.37%), and Oman (from 0.83% to 0.65%). Conversely, the largest increases occurred in Zimbabwe (from 1.30% to 1.52%), Mauritania (from 1.50% to 1.61%), and Eritrea (from 1.90% to 1.97%). Among countries with the highest death tolls, India reduced its case-fatality rate from 1.06% in 2017 to 0.96% in 2021, while Pakistan saw a slight decrease from 1.56% to 1.52%. Bangladesh and Indonesia showed no apparent improvements.

The mortality rate was disproportionately higher among children, peaking from 12 to 23 months of age with a global average of 9.7/100,000 person-years (95% UI: 4.7–17.9) and reaching a low of 0.4/100,000 person-years (95% UI: 0.2–0.7) among individuals over 70 years old (Fig. 2). Children under five accounted for approximately 40% of all fatalities. Regional variations in age distribution were notable, with Sub-Saharan Africa recording about 74% of deaths in children under 14, compared to approximately 57% in Southeast Asia, East Asia, and Oceania.

In 2021, the highest global case-fatality rate was observed among children under one year (1.77%), while individuals aged 50–69 years had the lowest rate (0.91%). Over the 2017–2021 period, there was a decrease in case-fatality rates for the 5–14 years (from 1.24% to 1.04%) and the 15–49 years age groups (from 1.06% to 1.00%). However, rates increased among children aged 12–23 months (from 1.36% to 1.48%) and those aged 2–4 years (from 1.32% to 1.38%). We observed large apparent geographical heterogeneity in case-fatality rates and trends across age groups. South

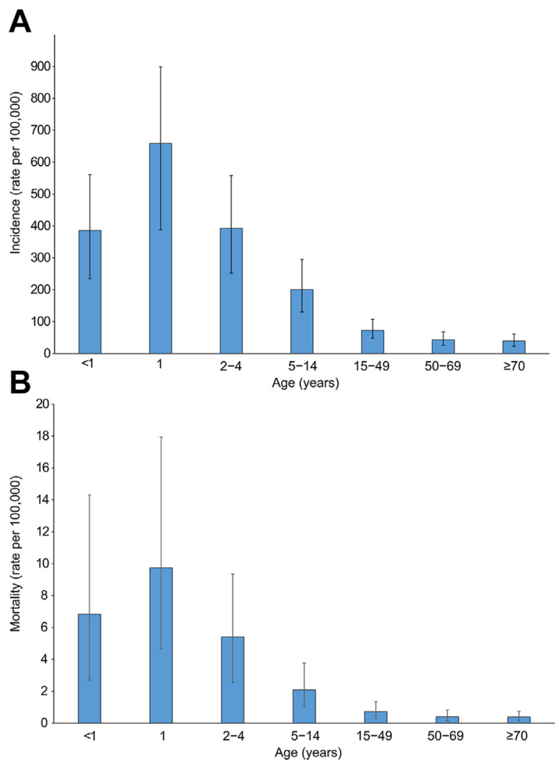

Fig. 2: Global age-specific incidence (panel A) and mortality (panel B) rates of enteric fever, 2021. Error bars represent 95% uncertainty intervals.

Asia, in particular, experienced notable increases in case-fatality rates among children aged 1–4 years from 2017 to 2021. In contrast, North Africa, the Middle East, and Sub-Saharan Africa demonstrated apparent improvements in the same age group (Fig. 3).

In 2021, enteric fever was responsible for 8.0 million YLLs (95% UI: 4.1–13.8), representing a decrease of about 21% from 10.1 million YLLs (95% UI: 5.0–17.3) in 2017. Age-standardized YLL rates declined from 143/100,000 person-years (95% UI: 71.8–246) in 2017 to 114/100,000 person-years (95% UI: 58.3–197) in 2021, a reduction of approximately 20%. In 2021, more than 75% of the global YLLs occurred in children aged 14 years or younger, with about 47% occurring in children under five.

Associations with socio-demographic index

There was an association between increasing SDI quintiles and lower incidence, mortality, and case-fatality rate (Table 1). In 2021, low-middle SDI countries had the highest age-standardized incidence rate at 258.1/100,000 person-years (95% UI: 203.1–327.5) and a mortality rate of 2.96/100,000 person-years (95% UI: 1.55–4.88). Low SDI countries also exhibited high rates, with an incidence of 171.0/100,000 person-years (95% UI: 133.6–219.7) and a mortality rate of 2.15/100,000 person-years (95% UI: 1.07–3.77). Case-fatality rates ranged from about 0.48% in high SDI countries to 1.32% in low SDI countries.

From 2017 to 2021, age-standardized incidence rates decreased by approximately 18% in low SDI countries and 17% in low-middle SDI countries. Conversely, age-standardized mortality rates showed the largest decline in high-middle SDI countries, with a reduction of about 29%. Consequently, the case-fatality rate improved most significantly in high-middle SDI countries, while the improvement was less pronounced in low and low-middle SDI countries (Table 1). In multivariable random-effect Poisson regression for longitudinal data, SDI was confirmed as an important predictor of case-fatality rate after controlling for estimates of the annual prevalence of multidrug resistance, fluoroquinolone non-susceptibility, and third-generation cephalosporin resistance (Appendices 2 and 3). An increase of 1 percentage point in SDI was associated with an estimated 1.1% relative reduction in case-fatality rate (95% CI: 0.7–1.7) and a 1 percentage point increase in prevalence of third-generation cephalosporin resistance was associated with 3.7% relative increase in case-fatality rate (95% CI: 0.2–7.3).

Discussion

In this systematic analysis of the GBD 2021 data, we present recent estimates and trends in the burden of enteric fever from 2017 to 2021, stratified by region, country, and age. The findings confirm that enteric fever is still a significant global health concern with over 9 million annual cases and 100 thousand deaths in 2021. South Asia contributed the majority of cases, deaths, and YLLs, with India alone contributing over half of the global cases and nearly half of the deaths.

The current study shows estimates of incidence derived from Bayesian modelling that are comparable to what were reported by previously published prominent population-based studies performed in various endemic areas.[19–22] The systematic review of Mogasale et al. estimated 11.9 million (95% CI: 9.9–14.7) incident cases and 129 thousand (75–208) deaths among low and middle-income countries in 2010 after adjusting for water-related risk.[19] Recent population-based studies from urban areas of Malawi, Bangladesh and Nepal showed estimates of incidence rates occasionally surpassing 1000/100,000 person years.[20] Other longitudinal studies from different areas of Bangladesh, Nepal and Pakistan reported lower estimates of cultured confirmed *Salmonella* Typhi, spanning from below 100 to approximately 900/100,000 in the 2016–2019 period.[21] Data from the SETA project collected in the 2016–2020 period in six Sub-Saharan countries showed estimates ranging from approximately 20 to over 300/100,000 person-years.[22] Besides these examples of coordinated efforts, rigorously collected population-based data regarding infections by *Salmonella* Typhi and Paratyphi

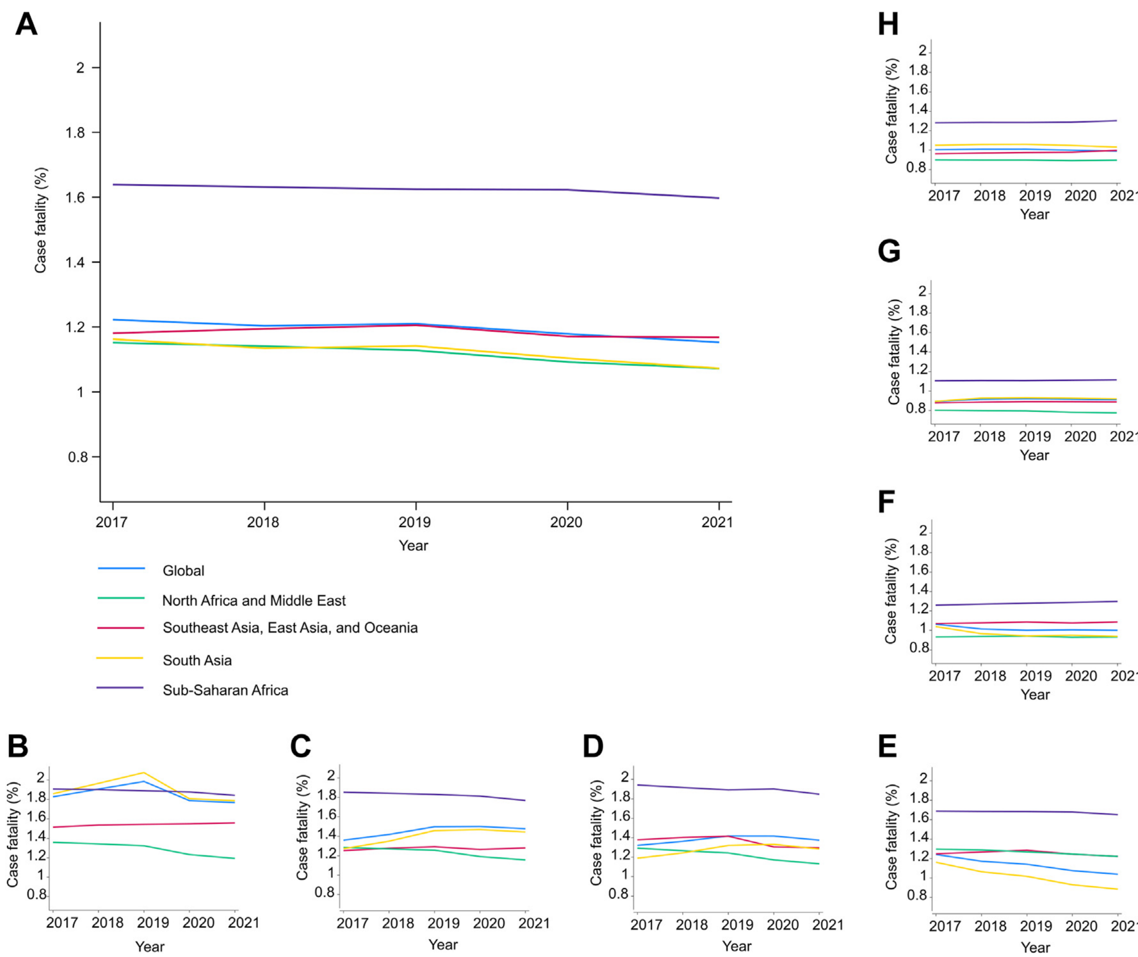

Fig. 3: Global and regional estimates of case-fatality rates of enteric fever from 2017 to 2021, shown for all ages (A), and by age-group: <1 year (B), 12–23 months (C), 2–4 years (D), 5–14 years (E), 15–49 years (F), 50–69 years (G), ≥70 (H) years of age.

are rare, with several endemic countries of the Sub-Saharan area and Oceania lacking this data.[3] In the context of limited data availability, the GBD 2021 data provide a valuable contribution to our understanding of the spatial distribution, morbidity, and mortality trends associated with enteric fever. This comprehensive dataset integrates multiple data sources, offering critical insights into regional variations and temporal patterns.

The current study estimated a global case-fatality rate of approximately 1.2%, reflecting a modest but encouraging improvement over the 2017–2021 period. Although this estimate is lower than the 2.5% reported by the most recent meta-analysis of population-based studies,[23] it is important to note that most of the primary studies synthesized in the meta-analysis were conducted several decades ago, when healthcare assistance levels and antibiotics availability were considerably different in most endemic areas.[23]

The results confirmed the continuing decrease in incidence, and mortality observed in the previously published iteration of the GBD study on enteric fever which provided data until 2017.[3] Although this is encouraging, 23 countries still exceeded the threshold for a "high burden" of enteric fever in 2021, with notable examples outside of South Asia being Papua Nuova Guinea, Burkina Faso and Kenya. Practically all regions and countries showed improvements in age-standardized incidence and mortality during the period considered, though the magnitude of these improvements varied. Since the introduction of the typhoid conjugate vaccine has been limited to a few countries, such as the gradual introduction in Pakistan after 2019, and Liberia and Zimbabwe in 2021,[24] the observed decrease in incidence may be attributed to improvements in sanitation, infrastructure, food handling practices, and access to antibiotics.[25,26] Additionally, public health measures related to the COVID-19 pandemic, including enhanced hand hygiene and social distancing, may have indirectly contributed to the decline in enteric fever cases.

We integrated recently provided country-level estimates of the prevalence of multidrug resistance, third-generation cephalosporin resistance, and fluoroquinolone non-susceptibility into some of our analyses.[5] Antimicrobial resistance, which reflects patterns of antibiotic use (i.e. selective pressure),[27] is likely to influence the spatial distribution of enteric fever deaths. A detailed mapping of these estimates is beyond the scope of this study and is reported elsewhere.[5] However, it is important to note that concomitant resistance to trimethoprim-sulfamethoxazole, chloramphenicol, ampicillin, or amoxicillin is a major concern in most Sub-Saharan countries and Pakistan. Fluoroquinolone non-susceptibility is substantial in Asian countries and the Middle East, while third-generation cephalosporin resistance is prevalent in Pakistan and beginning to appear in other South Asian countries. After accounting for antimicrobial resistance, SDI remained significantly associated with case-fatality, emphasizing the importance of a country's development level in determining the burden of enteric fever.

Analyses by age suggested that children, particularly those five and below, are the most affected by enteric fever in terms of both incidence and mortality. Although previous studies often report a higher burden in children aged five and above,[28] the peak in this study around 1–2 years of age may reflect improvements in healthcare access or diagnostic practices, which could lead to earlier detection and reporting in younger children. About half of the global YLLs due to enteric fever were attributable to children under five. The particular susceptibility of young children to enteric fever stems from several contributing factors such as a higher exposure risk compared to adults, increased chances of dehydration and malnutrition raising the likelihood of hospital admission and severe complications, and more limited effective therapeutic options.[28–30] Moreover, young children often exhibit non-specific symptoms, primarily fever, which can delay accurate diagnosis and timely antibiotic treatment, potentially exacerbating antimicrobial resistance and increasing mortality rates.[31–33] The apparent increase in global case-fatality rate among children aged one to four years, especially in South Asia, is alarming and potentially connected with the emergent third-generation cephalosporin resistance. In this context, the routine adoption of effective vaccination campaigns is paramount. Since 2017–2018, the WHO has endorsed typhoid conjugate vaccines for use in high-incidence countries among infants at least 6 months old.[7,8] Unlike live attenuated vaccines, the conjugate Vi-TT vaccine has proven highly effective in infants, providing 70–80% protection up to 12 years of age and offering durable protection for at least 4 years.[10] It has been estimated that establishing typhoid conjugate vaccination at 9 months of age in endemic countries would reduce typhoid fever cases by 46–74%.[6] These significant results have led some authors to view this as a significant step toward the future eradication of enteric fever.[11,34] However, as already noted, implementation of routine typhoid conjugate vaccination campaigns has been very limited.[11] This is attributable to several challenges, such as difficulties in large-scale deployment in countries with limited healthcare infrastructure, which are frequently affected by socio-political breakdowns and other major public health threats, alongside significant issues like vaccine hesitancy.[35,36]

Among the key strengths of this study are the updated estimates of the global burden of enteric fever, which build on previous GBD data by incorporating recent trends from 2017 to 2021 across 75 endemic countries.[3] Additionally, the integration of antimicrobial resistance data from the GRAM study provides new insights into how resistance patterns may interact with socio-economic factors, offering a deeper understanding of the factors driving case-fatality rates.

We have to acknowledge some limitations of the current study. The GBD estimates are derived from Bayesian modeling, integrating multiple data sources, which inevitably carry the limitations of the primary data sources. The scarcity of population-based data on enteric fever in many endemic regions can significantly skew perceived disparities across geographical areas. Given the virtual absence of routine adoption of conjugate vaccines in endemic countries during this period, except for Pakistan post-2019, vaccination data were not included in our regression model. Moreover, the GBD data do not consider the burden associated with chronic carriage of *Salmonella* Typhi and Paratyphi, such as the increased risk of cholelithiasis and gallbladder cancer.[37]

In summary, despite recent reductions in incidence and mortality, enteric fever remains a significant global health concern, especially in developing countries. Our findings reaffirm that socio-economic inequalities continue to drive enteric fever mortality, and highlight the concerning and expanding role of antimicrobial resistance in driving case-fatality rates. SDI was consistently associated with lower case-fatality rates, even after accounting for antimicrobial resistance patterns, highlighting the importance of socio-economic conditions, clean water supply, sanitation, healthcare infrastructure, and health education. Enteric fever places a particularly heavy burden on children, with high case-fatality rates in those under 5-years old due to challenges in timely diagnosis, treatment, and other peculiar vulnerabilities. Antimicrobial resistance and under-vaccination are critical factors exacerbating this issue. Although the typhoid conjugate vaccine has demonstrated efficacy in reducing incidence, mortality, and resistance,[6] its routine implementation remains limited, with only a few endemic countries starting to introduce it.[11,35] Despite challenges, vaccination is an essential component of the comprehensive approach needed to combat typhoid fever.[24] Strengthening multi-partner initiatives to support vaccine implementation, including strategies to fight vaccination hesitancy,[36] and enhancing typhoid fever surveillance are crucial steps toward better control of enteric fever.

Contributors
Daniele Piovani (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Validation: Lead; Writing—original draft: Lead), Gisella Figlioli (Conceptualization: Equal; Data curation: Supporting; Formal analysis: Supporting; Methodology: Equal; Validation: Equal; Writing—review & editing: Equal), Georgios K. Nikolopoulos (Conceptualization: Equal; Data curation: Supporting; Formal analysis: Supporting; Methodology: Equal; Validation: Equal; Writing—review & editing: Equal), Stefanos Bonovas (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Equal; Investigation: Supporting; Methodology: Equal; Supervision: Lead; Validation: Equal; Writing—review & editing: Lead). All authors have read and approved the final manuscript. Daniele Piovani and Stefanos Bonovas accessed and verified the data. All listed authors meet authorship criteria and no others meeting the criteria have been omitted.

Data sharing statement
The data from this study can be accessed openly through the GBD 2021 online database (see Methods section).

Editor note
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Declaration of interests
All authors hereby attest that they do not have any relevant conflict of interest related to this article.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102883.

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