Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment

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Summary

Background No access to safe water is an important risk factor for typhoid fever, yet risk-level heterogeneity is unaccounted for in previous global burden estimates. Since WHO has recommended risk-based use of typhoid polysaccharide vaccine, we revisited the burden of typhoid fever in low-income and middle-income countries (LMICs) after adjusting for water-related risk.

Methods We estimated the typhoid disease burden from studies done in LMICs based on blood-culture-confirmed incidence rates applied to the 2010 population, after correcting for operational issues related to surveillance, limitations of diagnostic tests, and water-related risk. We derived incidence estimates, correction factors, and mortality estimates from systematic literature reviews. We did scenario analyses for risk factors, diagnostic sensitivity, and case fatality rates, accounting for the uncertainty in these estimates and we compared them with previous disease burden estimates.

Findings The estimated number of typhoid fever cases in LMICs in 2010 after adjusting for water-related risk was 11·9 million (95% CI 9·9–14·7) cases with 129 000 (75 000–208 000) deaths. By comparison, the estimated risk-unadjusted burden was 20·6 million (17·5–24·2) cases and 223 000 (131 000–344 000) deaths. Scenario analyses indicated that the risk-factor adjustment and updated diagnostic test correction factor derived from systematic literature reviews were the drivers of differences between the current estimate and past estimates.

Interpretation The risk-adjusted typhoid fever burden estimate was more conservative than previous estimates. However, by distinguishing the risk differences, it will allow assessment of the effect at the population level and will facilitate cost-effectiveness calculations for risk-based vaccination strategies for future typhoid conjugate vaccine.

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See **Online** for an audio interview with Vittal Mogasale

Introduction

Access to safe water and sanitation is inadequate in many parts of the world. The scarcity of these basic amenities weighs heavily on public health, and typhoid fever—a severe life-threatening illness caused by *Salmonella* serovar Typhi—is one of the many unfortunate consequences.

Several efforts have been made to estimate the global burden of typhoid fever.[1–5] Crump and colleagues[2] estimated 21·6 million cases (range 10·8–43·3 million) in the year 2000 with the highest incidence in children in south and southeast Asia. Buckle and colleagues[3] later estimated 13·9–26·9 million cases worldwide for 2010. Although, these estimates provide a broad measure of the typhoid burden, approaches that distinguish the risk differences by population groups within countries are necessary. WHO's typhoid position paper[6] suggested targeting of high-risk populations for polysaccharide vaccination.[6,7] Therefore, strategies for typhoid conjugate vaccination need to appraise the consequences of targeting high-risk populations as opposed to universal vaccination.

We aimed to revisit the disease burden of typhoid fever in low-income and middle-income countries (LMICs) where vaccines would most likely be deployed. Hence, we include only LMICs based on World Bank criteria[8] and exclude high-income countries and the European region from our analyses. We use updated longitudinal surveillance data and a revised estimate of the diagnostic sensitivity of blood culture. Additionally, we attempt to estimate separate incidence for high-risk populations and the rest based on water-related risk. The incidence differentiation will provide information to assess the trade-offs in terms of health effect and cost-effectiveness of targeted versus universal vaccination strategies for typhoid conjugate vaccine.

Methods

We estimated the disease burden from typhoid fever in LMICs using adjusted incidences obtained from population-based, longitudinal studies (figure 1).

Incidence of typhoid fever in LMICs

To identify relevant studies, we first did a systematic literature review of population-based, longitudinal studies of blood-culture-confirmed typhoid fever (for

search strategy see panel). For typhoid vaccine trials, we used typhoid incidences from placebo groups only. We omitted from this analysis studies from typhoid fever outbreaks and hospital-based reports.

We adjusted incidences for the underestimation biases resulting from the proportion of patients refusing blood draws for culture and the proportion of the population who did not use study sentinel sites for health care. For the adjustment, we assumed that patients refusing blood draws would have the same incidence as those who did not, and that the population accessing sentinel health facilities would have the same typhoid incidence rate as those who did not.

We then adjusted these incidences by age and applied them to the total population in the countries in the assigned UN region to obtain incidences at a country level. The distribution of typhoid fever cases by age group was based on studies that presented age-specific typhoid fever incidence. Data suggest that the average age of typhoid infection is lower in areas with high incidence.[2,9] Therefore, we estimated the age-group distribution separately for high-incidence populations (>100 cases per 100 000 person-years) and medium-incidence (10–100 cases per 100 000 person-years) populations.

We classified countries by their respective UN region.[10] And, for every UN region, we calculated the mean incidence from the population-weighted average of nation-specific incidences within the same region. We derived country-specific estimates after weighting for population age distribution (three age groups), proportion of population living in urban slums, and population living in rural areas without access to improved water. We imputed the regional mean incidence estimate for countries without typhoid fever incidence estimates. For regions without regional incidence rate estimates, we assigned values from the average of neighbouring regions.

Adjustment for blood culture sensitivity

Because of the low sensitivity of blood culture, we also adjusted incidences for the diagnostic sensitivity of blood culture. We estimated the diagnostic sensitivity of blood culture on the basis of a second systematic literature review to select studies that reported both blood culture and bone-marrow culture for the same person (see panel for search strategy). Since data suggest that blood culture might be positive in the presence of a negative bone-marrow culture,[11–14] we counted people who tested positive either by bone marrow or blood culture as true positives and, for this analysis, calculated the diagnostic sensitivity as the proportion of blood-culture-positives out of all true positives. We then estimated the case-weighted average of blood-culture sensitivity based on all selected studies.

Adjustment based on risk-factor analysis

Unlike previous burden estimates, we also adjusted the typhoid incidence based on water-related risk. Most typhoid fever studies are undertaken in populations believed to be at increased risk of typhoid fever, often urban slums that do not have access to safe water. Data from these studies might not be applicable to the whole population. To account for this, we used a surrogate indicator for safe water, "access to improved water", as defined by WHO-UNICEF.[15] This variable was selected because of the strong linkage between water and typhoid transmission and the availability of typhoid risk-factor studies that assessed the risk associated with this variable.

To estimate the increased risk of typhoid fever due to poor access to safe water, we did a third systematic literature review to identify typhoid fever case-control studies reporting odds ratio for exposure to improved water versus unimproved water (see panel for search strategy). If a study identified water source as "improved" on the basis of the WHO-UNICEF definition but reported water source as "microbiologically unsafe" (WHO definition, >1 colony-forming unit [CFU]/mL *Escherichia coli*), we deemed the water source as "unimproved" to represent increased risk. The mean value for pooled odds ratio was summarised on the basis of meta-analysis and was used in risk-factor correction as a surrogate for access to improved water. Two methods were deployed in estimating typhoid fever incidence: risk-factor-adjusted and risk-factor-unadjusted. The risk-factor-adjusted approach classifies populations into high-risk and at-risk categories. We defined high risk as a rural population lacking access to improved water and an urban population living in slums. We defined at-risk as a rural population having access to improved water and an urban population not living in slums. In the first approach, for high-risk populations, we directly applied age-group-specific incidences from longitudinal studies. For at-risk populations, we applied age-group-specific incidences after correcting for the risk-factor—ie, the lower risk of infection (figure 1). In the second approach, where risk factors were not adjusted for, we directly applied age-specific incidences from longitudinal studies to the whole population in the country.

Global population data and case-fatality rates

We extracted population estimates for the year 2010 for LMICs from a UN database[16] in three age categories (0–4·9, 5–14·9, ≥15 years). The fraction of the population residing in urban slums and population with poor access to improved water sources was extracted from the UN Millennium Development Goals Indicators database.[17] For the countries without this information, we used the regional population-weighted average estimate.

We estimated the case-fatality rates (CFRs) on the basis of an additional literature review and applied this value to total typhoid fever cases to calculate the total number of typhoid deaths. Typhoid fever CFR is likely to vary with access to health-care services. Although the CFR was greater than 15% in the pre-antibiotic era,[18] a CFR of 1–4% is widely accepted now.[6] A conservative 1% CFR was used in previous disease burden estimates,[2,3] which

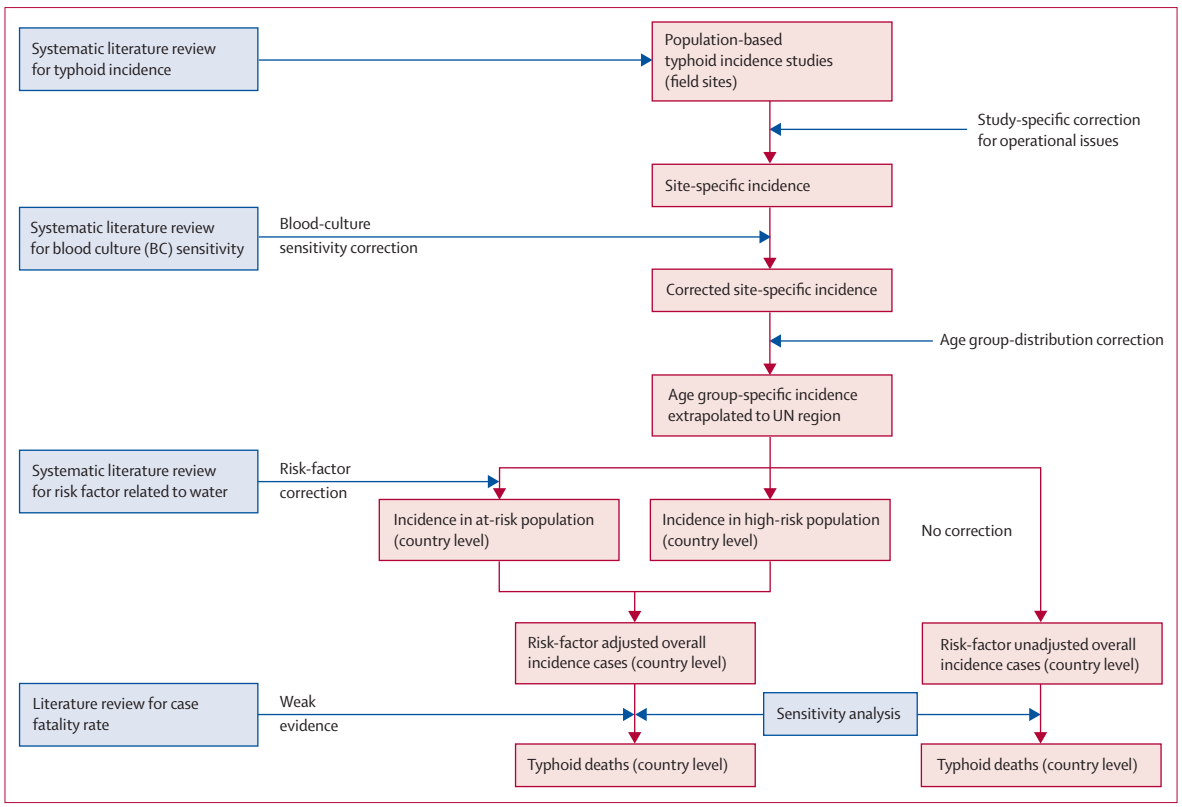

Figure 1: **Flowchart of typhoid disease burden estimation**
*We defined high risk as "rural population lacking access to improved water and urban population living in slums". We defined at-risk as "rural population having access to improved water and urban population not living in slums".

we applied as a baseline rate. Published work indicated a higher CFR associated with various typhoid outcomes in the African region than in other regions.[19] Accordingly, we considered a lower CFR outside Africa in the alternative scenario.

Uncertainty and scenario analyses

The uncertainty associated with every incidence estimate from longitudinal studies was accounted for by creating a probability distribution for each input variable. We applied β-PERT distributions to estimate the blood-culture sensitivity, risk-factor correction, and CFR estimates. We did a Monte Carlo simulation based on 5000 random draws from each of the input distributions to conduct probabilistic multivariate sensitivity analysis and to estimate 95% CIs for cases and deaths using Ersatz (Version 1.31, Epigear International, Brisbane, Australia).[20]

We estimated the typhoid fever disease burden under alternative scenarios for risk-factor, blood-culture sensitivity, and CFR outside Africa. The results were compared with two previous studies[2,3] of the global burden of typhoid fever. Since one[2] of the studies was based on a population from 2000, we extrapolated the incidence to a population from 2010 for comparison.

	Total population	High-risk categories[17]		High-risk populations	
		Urban slum (% of total population)	Rural, with no access to improved water (% of total population)	Fraction (% of total population)	Population size
Africa					
East Africa	326 151 000	15%	43%	58%	187 816 425
Middle Africa	128 209 000	30%	38%	68%	87 276 422
North Africa	212 387 000	16%	9%	25%	53 836 931
West Africa	306 044 000	26%	32%	58%	178 129 405
South Africa	57 967 000	17%	8%	25%	14 472 788
Asia					
East Asia	1 380 837 000	13%	11%	24%	334 633 289
South Asia	1 719 118 000	12%	11%	23%	398 354 439
Central Asia	61 346 000	1%	12%	13%	8 011 657
Southeast Asia	584 372 000	15%	10%	25%	144 837 488
West Asia	180 898 000	17%	9%	25%	45 610 731
Latin America					
Caribbean	44 782 000	29%	11%	40%	17 855 083
Central America	153 118 000	13%	5%	18%	27 219 642
South America	392 985 000	21%	6%	27%	105 339 220
Total	5 557 307 000	15%	14%	29%	1 608 592 886

Table 1: **Total population and high-risk populations of potential typhoid endemic countries**

	Year	Incidence by age group	Overall incidence
North Africa			
Sharkia, Egypt[21]	2001	6 (all age groups)	6
Fayoum, Egypt[22]	2002	29 (all age groups)	29
Regional	..	11 (0–4 years); 47 (5–14 years); 10 (≥15 years)	18
West Africa			
Ashanti region, Ghana[23,24]	2007–09	196 (0–1 year); 424 (2–4 years); 117 (5–14 years); NA (≥15 years)	NA
Regional	..	328 (0–4 years); 117 (5–14 years); 78 (≥15 years)	123
East Africa			
Kibera, Kenya[25]	2007–09	821 (0–1 year); 2243 (2–4 years); 1788 (5–9 years); 870 (10–14 years); 231 (≥15 years)	822
Lwak, Kenya[25]	2007–09	345 (0–1 years); 742 (2–4 years); 215 (5–9 years); 260 (10–14 years); 608 (≥15 years)	444
Pemba, Zanzibar, Tanzania[26]	2009–10	42 (0–4 years); 51 (5–14 years); 64 (≥15 years)	55
Regional	..	719 (0–4 years); 662 (5–14 years); 296 (≥15 years)	465
South Africa			
Eastern Transvaal, South Africa[27]	1985–88	387 (5–14 years)	
Regional	..	395 (0–4 years); 387 (5–14 years); 111 (≥15 years)	195
East Asia			
Quan county, Guangxi, China[28]	1995–96	NA (0–4 years); 14 (5–9 years); 25 (10–14 years); 32 (15–19 years); 13 (≥20 years)	NA
Hechi, Guangxi, China[8]	2001–02	NA (0–4 years); 29 (5–14 years); 12 (≥15 years)	NA
Regional	..	57 (0–4 years); 24 (5–14 years); 14 (≥15 years)	18
South Asia			
New Delhi, India[29]	1995–96	1623 (0–1 year); 4170 (2–4 years); 1664 (5–9 years); 1424 (10–14 years); 1026 (15–19 years); 134 (≥20 years)	1166
Kolkata, India[9]	2003–04	90 (0–1 year); 343 (2–4 years); 498 (5–14 years); 121 (≥15 years)	216
Kolkata, India[30]	2005–06	1233 (2–4 years); 589 (5–14 years); 57 (≥15 years)	NA
Dhaka, Bangladesh[31]	2000–01	1869 (0–4 years); 209 (≥5 years)	395
Dhaka, Bangladesh[32]	2003–04	1456 (0–4 years); 120 (≥5 years)	282
Karachi, Pakistan[33]	1999–01	375 (2–4 years); 945 (5–9 years); 751 (10–14 years); NA (≥15 years)	NA
Karachi, Pakistan[9]	2002–04	598 (2–4 years); 431 (5–14 years); NA (≥15 years)	NA
Periurban Karachi, Pakistan[34]	2007–08	443 (0–1 year); 380 (2–4 years); NA (5–14 years); NA (≥15 years)	NA
Karachi, Pakistan[35]	2002–07	265 (2–4 years); 228 (5–14 years)	NA
Regional	..	1319 (0–4 years); 773 (5–14 years); 148 (≥15 years)	405
Southeast Asia			
Jakarta, Indonesia[8,36]	2002–03	17 (0–1 year); 283 (2–4 years); 285 (5–9 years); 327 (10–14 years); 327 (15–19 years); 84 (≥20 years)	160
Sumatra, Indonesia[37]	1986–89	1307 (2–4 years); 1352 (5–9 years); 1150 (10–14 years); 987 (15–19 years)	NA
Dong Thap Province, Vietnam[38]	1995–96	NA (0–4 years); NA (5–14 years); NA (≥15 years)	288
Dong Thap Province, Vietnam[39]	1998–00	414 (2–4 years); NA (5–14 years); NA (≥15 years)	NA
Hue, Vietnam[9]	2002–03	25 (5–14 years); 11 (≥15 years)	NA
Regional	..	619 (0–4 years); 630 (5–14 years); 160 (≥15 years)	282
South America			
Santiago, Chile[40]	1986–89	NA (0–4 years); 83 (5–9 years); 100 (10–14 years); NA (≥15 years)	NA
Santiago, Chile[41]	1982–87	NA (0–4 years); 120 (5–14 years); NA (≥15 years)	NA
Regional	..	28 (0–4 years); 106 (5–14 years); 15 (≥15 years)	29

(Table 2 continues in next column)

(Continued from previous column)

NA=not available.

Table 2: **Region and site specific typhoid fever incidence (per 100 000 people) from systematic literature review (adjusted for study specific operational issues; not adjusted for blood-culture sensitivity)**

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The endemic population in LMICs was about 5·6 billion in 2010 (table 1). The population at high risk of typhoid infection was about 1·6 billion (29%) whereas the remainder 4·0 billion were at risk.

The first systematic literature review identified 22 papers presenting population-based, longitudinal studies of incidence estimates for blood-culture-confirmed typhoid fever from 20 distinct sites in LMICs (table 2).[9,21–41] Although studies were published from 1990 to 2013, the incidence estimates ranged from 1982 to 2010.

On the basis of four studies in countries with high incidence of typhoid fever, the estimated proportion of typhoid cases was 21% for the age group of 0–4·9 years, 40% for that of 5–14·9 years, and 39% for those aged 15 years or older.[9,25,29,36] The corresponding proportion in medium-incidence countries was 7% for the age group of 0–4·9 years, 54% for that of 5·0–14·9 years, and 39% those aged 15 years or older, based on three studies.[22,26,28]

The second systematic literature review identified ten papers that presented results of both blood culture and bone-marrow culture on the same patient.[11–14, 42–47] Of the 529 patients who tested positive by either blood culture or bone marrow culture, 327 (62%) were reported positive by blood culture. We estimated a case-weighted average diagnostic sensitivity of blood culture of 61·1% (95% CI 51·9–70·3; table 3).

The third systematic literature review identified 12 case-control studies[48–59] that presented odds of typhoid fever for exposure to unimproved water versus improved water from ten different countries (panel). Of the 915 cases of typhoid fever and 1609 controls, 576 (63%) cases and 745 (46%) controls were exposed to unimproved water. Based on a random-effects model that accounted for heterogeneity between the studies, the pooled odds of exposure to unimproved water was 2·4 (95% CI 1·7–3·6) in typhoid fever cases compared with the controls, which was used for risk-factor correction (table 3).

The risk-adjusted overall incidence of typhoid fever for 2010 was 214 per 100 000 individuals and the risk-unadjusted overall incidence was 371 per 100 000 individuals, which we compared with the incidences reported by Crump and colleagues[2] extrapolated to the 2010 population (figure 2). On the basis of risk-factor-corrected and diagnostic sensitivity-corrected incidence, 23 Asian countries and 45 African countries had high incidence of typhoid fever (figure 3).

Data for the CFRs of typhoid fever from longitudinal studies were scarce. We identified two studies: one in our review from Ghana[23] that reported a CFR of 2·7% and another from Nepal[60] which had reported a CFR of 1·8% in the past.

As a conservative approach, we multiplied estimates of CFRs in people with typhoid fever admitted to hospital and rate of hospital admission in people with typhoid fever in scenario analysis, assuming zero deaths outside hospitals. On the basis of a review,[61] we estimated a case-weighted mean CFR of 2·8% (95% CI 2·0–3·6) using a random-effects model that accounted for heterogeneity between the studies. The review had reported 7415 cases of patients with typhoid fever admitted to hospital and 259 deaths in 28 studies from 15 countries during 1984–2005 (appendix). We identified weighted mean rates of hospital admission of 7·7% (4·3–11·1) from eight studies[9,21,22,25,29,31,32,34] presenting hospital admission rates in 13 sites in our longitudinal incidence review. Finally, we multiplied a randomly selected hospitalised CFR estimate (from 28 studies) to a randomly selected rate estimate of hospital admission (from 13 sites) for 1000 times using a bootstrap method to estimate an overall CFR of 0·5% (0·4–0·6) for the alternative scenario. Since this is a conservative estimate of overall CFR, we took the upper bound of this value (0·6%) as the lower bound for CFR (1%) in base-case uncertainty analysis. Because more severe typhoid cases tend to be admitted to hospital, the CFR in admitted patients is likely to overestimate overall typhoid CFR, therefore we used the lower bound of 2·0% as the upper bound in base-case uncertainty analysis (table 3).

See Online for appendix

The revisited risk-adjusted estimate of typhoid fever in LMICs in 2010 was 11·9 million (95% CI 9·9–14·8) cases and 128 775 (75 233–208 146) deaths (table 4). Most cases and deaths (72·5%) were projected to occur in Asia, with 59% in south Asia alone.

The probabilistic multivariate sensitivity analysis showed that assumptions on risk-factor correction, blood-culture sensitivity, and the CFR were the drivers of greatest uncertainty, for which we present scenario analyses.

The risk-factor-unadjusted typhoid burden was 20·6 million cases (95% CI 17·5–24·2) and about

	Mean (95% CI)	Estimation method
Odds of exposure to unimproved water in typhoid fever cases *vs* controls[48–59]*	2·4 (1·7–3·6)	Systematic literature review and meta-analysis
Percentage of blood-culture sensitivity —base case[11–14,42–47]	61·1% (51·9–70·3)	Systematic literature review and weighted average
Percentage of blood-culture sensitivity —alternate case[2,3]	50·0% (40·0–60·0)	Reference from past studies
Percentage of case-fatality rate in hospitalised aptients with typhoid [61]	2·87% (2·0–3·6)	Weighted average
Percentage of hospital admission rate among cases with typhoid fever[9,21,22,25,29,31,32,34]	7·7% (4·3–11·1)	Systematic literature review and weighted average
Percentage of overall case-fatality rate: Asia and Africa—base case[2,3]	1·0% (0·6–2·1)	Monte-Carlo simulation of weighted average
Percentage of overall case fatality rate: Asia—alternate case[2,3]	0·5% (0·4–0·6)	Monte-Carlo simulation of weighted average

*Used as a surrogate indicator for water related risk of typhoid fever.

Table 3: **Assumptions used in base case and sensitivity analysis for estimation of typhoid cases and deaths**

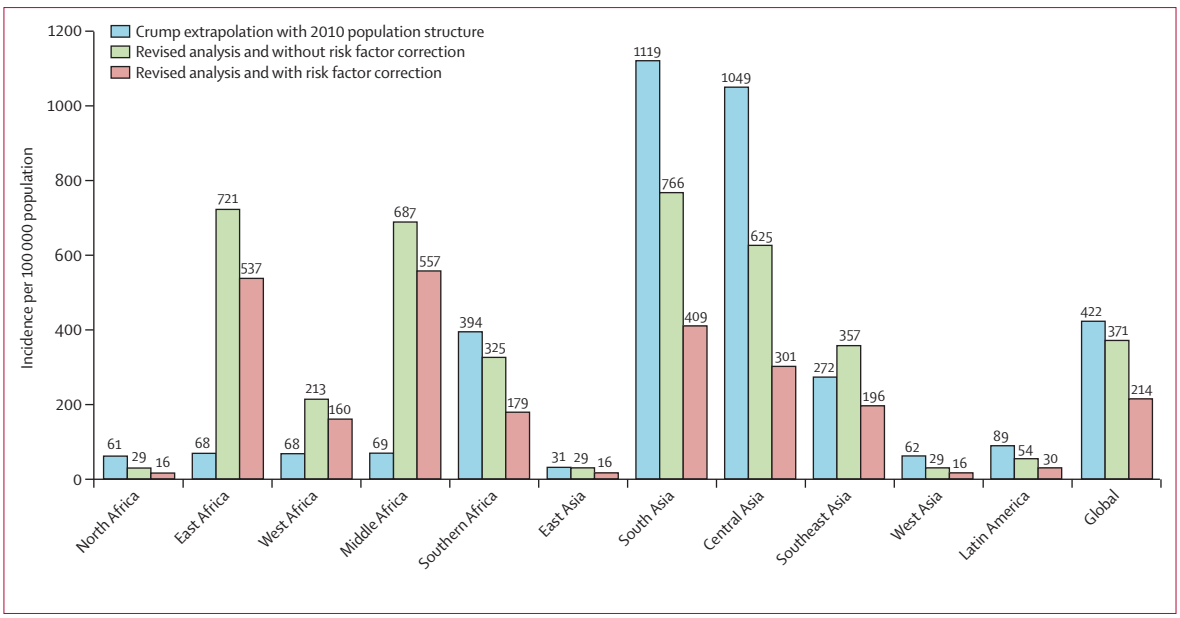

Figure 2: **Typhoid incidence in low-income and middle-income countries using three methods (unadjusted for blood-culture sensitivity)**

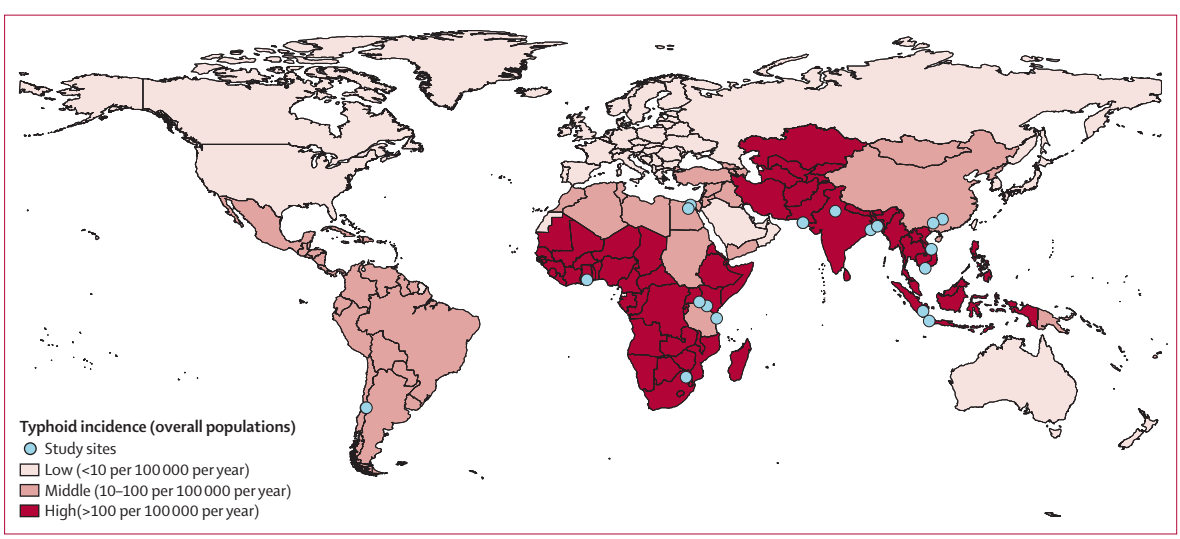

Figure 3: **Typhoid incidence in low-income and middle-income countries (risk-adjusted and corrected for blood culture sensitivity)**

222 000 deaths (95% CI 131 000–344 000; table 5). We compared the previous disease burden estimates with our estimates, applying 50% blood-culture sensitivity and risk-factor correction (mean=25·3 million; 95% CI 20·9–30·5).

Discussion

Our data suggest that the global burden of typhoid fever remains high in LMICs, especially in south Asia. Compared with the previous two global burden estimates,[2,3] both the number of cases and deaths are lower in our analysis. However, when we made the same assumptions as did these previous approaches, our results were similar, with gross overlapping of CIs. This similarity shows that our disease burden approach is coherent with previous estimates apart from the addition of systematic literature-based updates and risk-factor adjustments. This finding also indicates that global disease burden estimates that do not account for risk factors might overestimate the disease burden compared with studies that account for risk from poor access to improved water.

The disease burden method used here has a clear advantage over past estimates in evidence-based decision making, particularly for WHO policy guidance for typhoid conjugate vaccine. WHO has recommended targeting of

	All ages, mean (95% CI)	0–4 years, mean (95% CI)	5–14 years, mean (95% CI)	≥15 years, mean (95% CI)
Africa				
North Africa				
Cases	33 807 (25 809–44 185)	2317 (1773–3021)	18 413 (14 093–24 009)	13 076 (9959–17 179)
Deaths	366 (206–600)	25 (14–41)	200 (113–326)	142 (80–232)
East Africa				
Cases	1 749 861 (1 386 537–2 203 996)	450 196 (299 564–658 362)	669 576 (493 574–891 592)	630 089 (413 788–911 776)
Deaths	18 963 (10 780–30 428)	4879 (2483–8536)	7256 (3982–11 949)	6828 (3494–11 960)
West Africa				
Cases	489 669 (309 531–729 282)	204 741 (117 920–321 939)	115 256 (45 730–219 951)	169 672 (107 089–253 018)
Deaths	5306 (2660–9271)	2219 (1043–4046)	1249 (452–2687)	1839 (920–3213)
Middle Africa				
Cases	713 517 (568 060–887 805)	196 082 (133 870–280 749)	273 784 (203 597–360 950)	243 651 (163 037–347 637)
Deaths	7732 (4420–12 373)	2125 (1105–3654)	2967 (1637–4874)	2640 (1373–4576)
Southern Africa				
Cases	103 542 (76 359–140 868)	21 805 (16 084–29 661)	41 784 (30 821–56 838)	39 952 (29 454–54 368)
Deaths	1122 (619–1886)	236 (130–397)	453 (250–761)	433 (239–728)
Area total				
Cases	3 090 395 (2 504 427–3 829 277)	875 141 (627 432–1 203 706)	1 118 813 (848 217–1 462 011)	1 096 440 (781 729–1 501 172)
Deaths	33 490 (19 294–53 147)	9484 (5119–15 951)	12 124 (6802–19 712)	11 882 (6454–20 101)
Asia				
East Asia				
Cases	221 417 (115 678–446 715)	45 797 (23 918–92 402)	40 756 (21 614–69 338)	134 864 (56 191–310 268)
Deaths	2399 (1028–5212)	496 (213–1078)	442 (197–880)	1462 (518–3487)
South Asia				
Cases	7 036 692 (5 468 128–9 175 363)	2 416 881 (1 725 304–3 403 270)	2 754 171 (1 978 194–3 804 861)	1 865 640 (1 256 302–2 790 371)
Deaths	76 256 (43 212–125 905)	26 191 (14 199–44 083)	29 847 (16 265–50 263)	20 218 (10 497–36 204)
Central Asia				
Cases	184 835 (143 273–243 803)	63 753 (46 220–88 554)	70 085 (51 250–96 085)	50 997 (35 442–75 322)
Deaths	2003 (1130–3335)	691 (379–1160)	760 (418–1287)	553 (293–978)
Southeast Asia				
Cases	1 144 236 (938 721–1 432 281)	203 652 (158 079–265 970)	449 100 (361 251–569 225)	491 484 (400 357–621 305)
Deaths	12 400 (7211–20 080)	2207 (1242–3619)	4867 (2799–7909)	5326 (3082–8627)
West Asia				
Cases	29 415 (22 513–38 354)	2040 (1567–2645)	16 306 (12 517–21 178)	11 069 (8432–14 538)
Deaths	319 (180–521)	13 (13–36)	177 (100–289)	120 (68–197)
Area total				
Cases	8 616 595 (6 886 651–11 161 349)	2 732 123 (2 016 670–3 802 454)	3 330 418 (2 497 938–4 521 940)	2 554 054 (1 882 029–3 636 465)
Deaths	93 377 (53 650–154 591)	29 608 (16 422–49 925)	36 091 (20 137–60 883)	27 678 (15 186–47 848)
Latin America				
Cases	176 057 (136 071–229 933)	13 436 (10 389–17 540)	106 585 (82 413–139 142)	56 037 (43 269–73 250)
Deaths	1908 (1085–3128)	146 (83–239)	1155 (657–1893)	607 (345–997)
Overall				
Cases	11 883 047 (9 925 551–14 751 214)	3 620 700 (2 823 518–4 777 421)	4 555 816 (3 643 744–5 856 989)	3 706 531 (2 915 024–4 901 677)
Deaths	128 775 (75 233–208 146)	39 237 (22 349–64 597)	49 371 (28 341–80 787)	40 167 (22 671–66 719)

Table 4: **Typhoid fever disease burden in low-income and middle-income countries (adjusted for risk-factor and blood-culture sensitivity)**

high-risk populations with existing polysaccharide vaccine for typhoid control,[6,7] but has not issued a recommendation for typhoid conjugate vaccine. However, the proportion of cases of typhoid fever that occur in high-risk and at-risk areas has not been well defined until now. Our study presents differential incidence of typhoid fever for high-risk versus at-risk populations, which will help with the estimation at a population level impact and cost-effectiveness of targeted vaccination strategies compared with vaccination strategies covering whole populations. Such analysis will help to make informed decision on vaccination strategies for the use of typhoid conjugate vaccine. As we assemble our disease burden estimates at country level and by target population, the

	Base case blood-culture (61% sensitivity)		Alternate case scenario* (risk-factor unadjusted)	Extrapolation Crump et al (2004)[2] incidence to 2010 population*	Buckle et al (2013)[32]†
	Risk-factor adjusted	Risk-factor unadjusted			
Cases					
Asia	8 616 595	16 099 831	19 798 213	27 070 632	13 869 372
Africa	3 090 395	4 137 260	5 087 653	1 078 579	12 836 934
Others	176 057	321 089	394 848	645 594	242 432
Total	11 883 047	20 558 180	25 280 715	28 794 805	26 948 738
Base case—deaths (1·0% CFR)					
Asia	93 377	174 472	214 551	270 706	NA
Africa	33 490	44 835	55 134	10 786	NA
Others	1908	3480	4279	6456	NA
Total	128 775	222 787	273 964	287 948	269 487
Scenario analysis—deaths (0·5% CFR in Asia and other regions)					
Asia	42 236	78 917	NA	NA	NA
Africa	33 490	44 835	NA	NA	NA
Others	863	1574	NA	NA	NA
Total	76 589	125 326	NA	NA	NA

CFR=case-fatality rate. NA=not available. *Estimations assumed 50% blood-culture sensitivity. †Regional classification are slightly different from other estimates; Africa includes middle east; other regions include all regions apart from Asia and Africa including developed countries; number of deaths was calculated on the basis of a 1% CFR.

Table 5: **Scenario analysis for typhoid fever disease burden based on correction factors**

Panel: Research in context

Systematic review

We did three systematic literature reviews using PubMed and Embase data bases as well WHO and Pan American Health Organisation (PAHO) publication databanks. For the population-based, longitudinal studies of blood-culture confirmed typhoid fever review, we used the key words ("typhoid" OR "typhoid fever" OR "*Salmonella* Typhi" OR "*S.* Typhi" OR "salmonella infection" OR "enteric fever") AND ("incidence" OR "rate" OR "frequency" OR "prevalence" OR "morbidity" OR "burden" OR "surveillance" OR "epidemiology"). For the sensitivity sensitivity of blood culture in typhoid fever confirmation review, we used the key terms ("typhoid" OR "typhoid fever" OR "*Salmonella* Typhi" OR "*S.* Typhi" OR "salmonella infection" OR "enteric fever") AND ("blood" OR "blood culture" OR "culture of blood" OR "diagnostics" OR "sensitivity" OR "positivity"). For the increased risk of typhoid fever due to lack of access to improved water review, we used the key terms ("typhoid" OR "typhoid fever" OR "*Salmonella* Typhi" OR "*S.* Typhi" OR "salmonella infection" OR "enteric fever") AND ("risk factors" OR "predictive factors" OR "associated factors" OR "attributed factors" OR "exposure factors" OR "related factors" OR "predisposing factors"). Except for the sensitivity of blood culture in typhoid fever confirmation review, searches were restricted to publications from 1990–2013. All searches were limited to English language and studies of human individuals.

Interpretation

On the basis of systematic literature reviews, we synthesised typhoid fever disease burden in LMICs. After the recent licensure of a typhoid conjugate vaccine in India, disease burden estimates in high-risk populations that might be targeted for vaccination are globally needed. This analysis provides the first set of incidence estimates differentiated by risk-population, age, country, and region. The approach can help in the assessment of age-targeted and risk-targeted strategies for typhoid conjugate vaccination to support policy and financing decisions.

data can inform national, regional, or global level decision makers as well.

We have used a rigorous approach in selecting background information and correction factors for disease burden estimates. Two researchers did three systematic literature reviews using at least two databases with consensus-based paper selection. We excluded several papers used in a previous disease burden study[3] for various reasons such as model-based incidence estimation,[62] repeated information from same sites,[62–64] older studies predating our cutoff period,[60] non-longitudinal design, and absence of diagnostic blood-culture.[65,66] Unlike past studies, we did additional scenario analysis for CFRs. Also, the use of probabilistic sensitivity analysis in our study allows for better understanding of the uncertainty in typhoid burden estimates than with previous studies.

The high-incidence estimate for south Asia is consistent with studies of travellers from high-income countries.[67–70] However, the high incidence figures for Africa, to which one Kenyan study contributes heavily,[25] need careful interpretation. The south African datapoint is decades old, whereas a recent review of community-acquired bloodstream infections in Africa showed fewer than 10% of isolates were *S typhi*.[71] Evidence of typhoid fever in Africa has been reported from hospital-based studies[72,73] and an upsurge of typhoid fever outbreaks has been noted in the past decade, as evidenced in Zambia, Zimbabwe, Uganda, Malawi, Mozambique, South Africa, Democratic Republic of Congo, and Côte d'Ivoire.[74] However, more robust and direct evidence is needed and estimates of African incidence might be better elucidated from a multicountry burden study currently underway in ten countries.

Our study had limitations. One methodological limitation is that we corrected for only one typhoid risk factor, whereas many other risk factors (eg, poor sanitation, food contamination, and urbanisation and population density) might affect the incidence of typhoid fever. A more complex geospatial model might be needed to account for other typhoid-related risk factors. Also, the risk-factor surrogate, improved water, might not fully represent safe water because improved water could become contaminated, as occurs during outbreaks. The typhoid CFR is calculated for patients who received medical care. Our estimated number of typhoid deaths is therefore conservative. Since the number of datapoints is insufficient to test whether the endpoints are consistent across time, we applied data from different years to the 2010 population, assuming that the incidence did not change overtime. This assumption is similar to those of past studies of typhoid fever global disease burden.[2,3]

The study design and intensity of typhoid fever surveillance across different studies were variable, which might have biased our data. In the absence of data, the site-specific correction assumed similar risk of typhoid fever in those refusing and accepting to provide blood for culture and in those who visit or do not visit health

facilities. We could not account for previous antibiotic use and volume of blood taken, which are known to affect blood-culture sensitivity. Also, fever surveillance studies might have underestimated typhoid fever incidence in children younger than 2 years because of atypical presentations and difficulty in drawing blood for culture. Similarly, we could not measure bias because of the strict inclusion criteria of placebo groups in clinical trials.

The data for Latin American and the Caribbean are limited to two clinical trials[40,41] done more than 20 years ago, and this might have overestimated the typhoid burden due to improved water and sanitation in recent years. On the other hand, we might have underestimated the incidence from older data because increasing urbanisation and population density in recent years might have increased risk of typhoid fever. Latin America and parts of Asia and Africa are poorly represented in this review and hence typhoid fever surveillance in these locations is necessary for better understanding of current disease burden. Finally, our review does not include publications that are not in English. However, we believe this limitation will have minimal implications for our findings since the previous systematic literature review[3] searching for papers in Spanish, Italian, French, and Portuguese did not find any published work on typhoid fever incidence from 1980 to 2009.

In conclusion, this revised global typhoid burden study estimated a lower number of typhoid fever cases and deaths than the most recently published estimates, particularly because of the use of more conservative methods resulting from adjustment for a water-related risk factor and updated diagnostic sensitivity of blood culture. The burden of typhoid fever continues to be high in Asia; and published data from Africa suggest a greater burden than previously thought. The results from this analysis are useful in informing policies of typhoid vaccination and developing guidance on effective control measures.

Contributors

BM, RLO, VM, and TFW conceived the study; VM, BM, and RLO wrote the initial draft; VVM, ER, and VM did the systematic literature reviews; YEK, JSL, JKP, BM, and VM did the analyses; TFW and RLO gave critical inputs throughout the study; VM and BM incorporated inputs from internal and external reviewers.

Declaration of interests

RLO currently works for Sanofi Pasteur (a producer of typhoid vaccine), although much of the work was done during his employment at the International Vaccine Institute. The other authors declare no competing interests.

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