

The global burden of typhoid fever

John A. Crump,^{1,2} Stephen P. Luby,³ & Eric D. Mintz³

Objective To use new data to make a revised estimate of the global burden of typhoid fever, an accurate understanding of which is necessary to guide public health decisions for disease control and prevention efforts.

Methods Population-based studies using confirmation by blood culture of typhoid fever cases were sought by computer search of the multilingual scientific literature. Where there were no eligible studies, data were extrapolated from neighbouring countries and regions. Age–incidence curves were used to model rates measured among narrow age cohorts to the general population. One-way sensitivity analysis was performed to explore the sensitivity of the estimate to the assumptions. The burden of paratyphoid fever was derived by a proportional method.

Findings A total of 22 eligible studies were identified. Regions with high incidence of typhoid fever (>100/100 000 cases/year) include south-central Asia and south-east Asia. Regions of medium incidence (10–100/100 000 cases/year) include the rest of Asia, Africa, Latin America and the Caribbean, and Oceania, except for Australia and New Zealand. Europe, North America, and the rest of the developed world have low incidence of typhoid fever (<10/100 000 cases/year). We estimate that typhoid fever caused 21 650 974 illnesses and 216 510 deaths during 2000 and that paratyphoid fever caused 5 412 744 illnesses.

Conclusion New data and improved understanding of typhoid fever epidemiology enabled us to refine the global typhoid burden estimate, which remains considerable. More detailed incidence studies in selected countries and regions, particularly Africa, are needed to further improve the estimate.

Keywords Typhoid fever/epidemiology/blood; Paratyphoid fever/epidemiology; Salmonella enterica/ isolation and purification; Cohort studies; Population surveillance; Cost of illness; Sensitivity and specificity (*source: MeSH, NLM*).

Mots clés Fièvre typhoïde/épidémiologie; Paratyphoïde, Fièvre/épidémiologie; Salmonelle entérique/ isolement et purification; Etude cohorte; Surveillance population; Coût maladie; Sensibilité et spécificité (Epidémiologie) (*source: MeSH, INSERM*).

Palabras clave Fiebre tifoidea/epidemiología; Fiebre paratifoidea/epidemiología; Salmonella enterica/ aislamiento y purificación; Estudios de cohortes; Vigilancia de la población; Costo de la enfermedad; Sensibilidad y especificidad (*fuentes: DeCS, BIREME*).

الكلمات المفتاحية: حمى التيفود؛ إبيدميولوجيا حمى التيفود؛ تحليل الدم؛ الحمى الباراتيفودية؛ إبيدميولوجيا الحمى الباراتيفودية؛ السلمونية المعوية؛ استفراغ وتنقية السلمونية المعوية؛ دراسات الأتراب؛ الترصد السكاني؛ تكاليف المرض؛ الحساسية والنوعية. (المصدر: رؤوس الموضوعات الطبية المكتب الإقليمي لشرق المتوسط).

Bulletin of the World Health Organization 2004;82:346-353.

Voir page 352 le résumé en français. En la página 352 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة 352.

Introduction

The existing estimate of the global burden of typhoid fever is 16 million illnesses and 600 000 deaths annually (1). This estimate was presented at a meeting of the Pan American Health Organization in 1984 and subsequently published in 1986 (2). Although similar estimates were published around the same time (3) and are widely quoted in the typhoid fever literature, the 1984 estimate is subject to several limitations. For example, the methods were not outlined in detail, so the study cannot be reproduced. Furthermore, limited data sources were available at the time the estimate was made and the initial estimate excluded China. The estimate also does not account for the current understanding of the age distribution of typhoid fever.

A variety of changes have taken place since 1984 to indicate that updating the estimate of the global burden of typhoid fever is now both necessary and feasible. The denominator population has changed considerably with the growth of the global population (4). Programmes such as those to improve the safety of water supplies and sanitary conditions have modified the

risk of infection (5). Available typhoid fever incidence data has grown with efforts to improve global disease surveillance (6), the initiation of population-based typhoid fever incidence studies (7, 8), and the publication of vaccine studies from new regions (9). Advances in understanding of the age distribution of typhoid fever allow incidence rates measured among narrow age cohorts to be more accurately extrapolated to the general population (8). The formalization of methods for the assessment of disease burden provides a framework for standardized methods (10).

In light of the above changes and in an effort to provide a more contemporary and precise picture of the disease globally, we developed and applied a method to generate a revised estimate of the disease burden of typhoid fever.

Methods

Typhoid fever incidence data

Studies that potentially contained data on the incidence of typhoid fever were sought by a computer search of the multilingual

¹ Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, MS A-38, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA. Correspondence should be sent to Dr Crump at this address (email: jcrump@cdc.gov).

² Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, USA.

³ Foodborne and Diarrheal Diseases Branch, Centers for Disease Control and Prevention, Atlanta, USA.

Ref. No. 03-002295

(Submitted: 12 February 03 – Final revised version received: 20 August 03 – Accepted: 02 September 03)

scientific literature published between 1966 and 2001. A set of 8620 articles, obtained using the keywords “typhoid”, “typhoid fever”, “enteric fever”, and “*Salmonella* Typhi” was linked with a set of 1 357 515 articles obtained using at least one of the following keywords that dealt with disease burden: “incidence”, “prevalence”, “public health”, “death rate”, “mortality”, “surveillance”, “burden”, “suffering”, “distribution”, “area”, “location”, and “country”, and permutations of the root words “epidemiol-”, “monitor-”, and “geograph-”. The resulting cross-linked set contained 1342 articles, from which 23 articles relating to 22 studies relevant to the stated goal of the search were selected (available on request). Additional (mainly pre-1966) references were sought from citations listed in these 23 articles and from the archives of the authors and experts in the field.

Attempts were made to obtain a full print copy of each article. Studies were selected for inclusion in the global burden estimate if they used blood culture confirmation of cases and used a method that captured cases at all levels of the health-care system (for example, rural clinics, private physicians, hospitals) or by regular household visits. Where more than one eligible study for a country or region was available, the most recent study was selected. If more than one contemporary study was available for a region, the study with the lowest incidence of typhoid fever was selected. This was done in an attempt to account for bias caused by the preferential selection of sites with a high incidence of typhoid fever for studies on typhoid fever vaccine. Although epidemics play a part in typhoid fever epidemiology, studies that were conducted during typhoid fever epidemics were not considered because they did not reflect usual typhoid fever incidence. The volume of source data contributing to the estimate was calculated as person-years of surveillance.

Global population data

The world's population was classified into age and regional strata according to the designations of the United Nations Department of Economic and Social Affairs, Population Division. Briefly, it was divided into seventeen 5-year age strata from 0–4 years, to ≥ 80 years) and 21 regions (eastern Africa, central Africa, northern Africa, southern Africa, western Africa, eastern Asia, south-central Asia, south-eastern Asia, western Asia, eastern Europe, northern Europe, southern Europe, western Europe, Caribbean, central America, South America, North America, Australia/New Zealand, Melanesia, Micronesia, and Polynesia). Year 2000 medium fertility variant estimates were used (4).

Extrapolating between countries

Because eligible studies of typhoid fever incidence were not available for every country or region, it was necessary to extrapolate typhoid fever incidence from one country to another within a region and sometimes from one region to another. Extrapolations between countries and regions were based on geographical proximity and United Nations socioeconomic indicators (11).

Extrapolating between age groups

A large proportion of eligible studies of typhoid fever incidence were conducted among age cohorts representing a narrow age range (for example, school-aged children). Therefore, to adjust the incidence obtained from such measurements to that of the general population in a region, typhoid fever age-incidence curves were generated for high ($>100/100\ 000$ cases/year), medium ($10\text{--}100/100\ 000$ cases/year), and low ($<10/100\ 000$ cases/year) incidence settings. An age-distribution curve for high incidence

typhoid fever was generated from the most rigorous population-based study conducted in a high incidence setting (8). The age-distribution curve for low incidence typhoid fever was generated from the United States national typhoid fever surveillance system (Centers for Disease Control and Prevention, unpublished data, 2000) and was validated by comparison with national typhoid fever surveillance system data from other low incidence regions in western Europe and Australasia. The age-distribution curve for medium incidence typhoid fever was modelled by deriving mean age-specific typhoid incidences from the age-distribution curves for high- and low-incidence typhoid fever. The resulting curves are shown in Fig. 1; the curves are corrected to an overall proportion of 1 to allow comparison of relative age-specific rates.

Estimating the global burden of typhoid fever

After incidence rates were extrapolated within and between regions and between age groups, the total number of typhoid fever cases in 2000 was calculated by age stratum for each region. The sum of total cases by region was calculated as the crude global typhoid fever burden. Because eligible studies of typhoid fever incidence usually used a single blood culture collection to confirm cases, it was necessary to adjust the crude estimate for the global typhoid fever burden to account for under-detection of cases resulting from the limited sensitivity of blood culture for diagnosis of typhoid fever. The blood culture adjustment factor was derived from published literature (12–14). The lower reported sensitivity of 50% (13) was selected in an effort to account for the impact of antimicrobial use on blood culture sensitivity. The specificity of blood culture for the diagnosis of typhoid fever was assumed to be 100%.

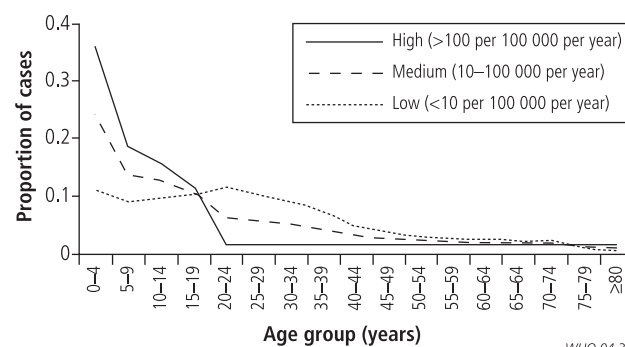
Case-fatality rate

Studies on the incidence of typhoid fever were further reviewed for population-based case-fatality rate estimates. Hospital-based typhoid fever case series and case-fatality rate data from countries with reliable national typhoid fever surveillance systems that employ blood culture confirmation were reviewed. Expert opinion was sought from persons and groups working in the fields of typhoid fever, enteric diseases, and infectious diseases epidemiology. The resulting case-fatality rate estimates were applied to the global total typhoid fever cases to estimate the total number of annual typhoid fever deaths.

Estimating the global burden of paratyphoid fever

Because there is very little reliable, population-based data on the incidence of paratyphoid fever, we sought to estimate incidence

Fig. 1. Distribution of typhoid fever, by age group, at various incidences



WHO 04.39

by extrapolating from our estimate of typhoid fever burden. To do this we used the 1997 global survey of *Salmonella* serotyping practices and results, which was conducted by WHO and the United States Centers for Disease Control and Prevention (CDC), WHO Collaborating Center for Foodborne Disease Surveillance. In this survey, each WHO Member State was sent a questionnaire asking whether or not a given country had public health surveillance for *Salmonella* infections (typhoid and/or non-typhoid) and whether or not serotyping was performed as part of the surveillance. Member States were then asked to provide information on the total number of *Salmonella* isolates for 1990 and 1995, and to list, by serotype and number of isolates, the 15 most commonly isolated *Salmonella* serotypes from people in 1990 and 1995 (15). The ratio derived from the survey was validated by comparison with ratios seen in population-based studies of typhoid fever incidence that also reported data on paratyphoid fever.

Sensitivity analysis

One-way sensitivity analysis was conducted by varying source data inputs from the least conservative (highest) to the most conservative (lowest) figures on typhoid fever incidence, and by adjusting age-incidence curves, by varying the sensitivity of a single blood culture, and by varying the typhoid fever case-fatality rate.

Results

Typhoid fever incidence data

In total, 22 studies of typhoid fever incidence employed blood culture confirmation of cases and used a method that captured cases at all levels of the health-care system or by regular household visits. The 22 studies represent approximately 1.8 million person-years of surveillance and include data from 13 countries. Of the 21 regions, only 6 (29%) contained countries with national typhoid fever surveillance systems that routinely use blood culture confirmation and detection of cases by enhanced passive surveillance (Table 1). The countries wealthy enough to support highly developed national typhoid fever surveillance systems generally experience a low incidence of typhoid fever and contribute little to the global burden of typhoid fever.

Global population data

The United Nations medium fertility variant year 2000 global population estimate is 6 091 349 000. The distribution of the global population by area and region is listed in Table 2.

Extrapolating between countries

The 22 studies contain data for 13 countries representing 9 (43%) of the 21 United Nations regions. An additional four (19%) of the regions include countries with national typhoid fever surveillance systems that routinely use blood culture confirmation and detection of cases by enhanced passive surveillance. Because data points were available for only 13 (62%) of the regions (Table 1), extrapolation between regions was done on the basis of geographical proximity and socioeconomic conditions (11). This method was used to classify regions into high, medium, and low incidence (Fig. 2).

Extrapolating between age groups

For 18 (86%) of the 22 eligible typhoid fever incidence studies, incidence was measured in a narrow age cohort only. For these studies, incidence was calculated for the overall population

by extrapolating using the appropriate age-incidence curve developed for high, medium, and low incidence settings using published studies (8) and national surveillance data (Fig. 1). Overall regional typhoid fever rates are listed in Table 2 and are classified into high (>100/100 000 cases/year), medium (10-100/100 000 cases/year), and low (<10/100 000 cases/year) incidence settings.

Estimating the global burden of typhoid fever

After making age and country extrapolations, typhoid fever incidence was compiled by region and area, and then applied to corresponding population estimates to derive a crude total of 10 825 487. To account for the sensitivity of blood culture for diagnosing typhoid fever, we applied an adjustment factor of 2 to our crude global total typhoid case burden. This adjustment produced a global typhoid fever case burden estimate of 21 650 974 (Table 2).

Case-fatality rate

No population-based studies on typhoid fever incidence were found that both captured case-fatality rate data and were large enough to accurately estimate case-fatality rate. A conservative case-fatality rate of 1% was chosen on the basis of conservative estimates from hospital-based typhoid fever studies (16), mortality data from countries with reliable national typhoid fever surveillance systems that employ blood culture confirmation of cases (17), and expert opinion. When applied to the global typhoid fever case burden estimate of 21 650 974, the case-fatality rate yields 216 510 deaths annually.

Estimating the global burden of paratyphoid fever

The 1997 global survey of *Salmonella* serotyping practices and results achieved country response rates by WHO region ranging from 34% to 70%. Worldwide, 3572 *Salmonella* Typhi isolates and 888 Paratyphi isolates were reported (15). This corresponds to 0.25 paratyphoid fever illnesses for every typhoid fever illness. The ratio was validated by review of the 8 (36%) of 22 population-based typhoid fever incidence studies that also report paratyphoid fever data (9, 18-24). The number of paratyphoid fever illnesses ranged from 0.11 to 0.35 for every typhoid fever illness. By applying the proportion 0.25 to the global typhoid fever estimate, we derived an estimate of 5 412 744 paratyphoid fever cases.

Sensitivity analysis

The results of the one-way sensitivity analysis are summarized in Table 3.

Discussion

Changes in the global epidemiology of typhoid fever

We estimate that typhoid fever caused 21 650 974 illnesses and 216 510 deaths during 2000 and that paratyphoid fever caused 5 412 744 illnesses. The previous estimates of 16 million illnesses and 600 000 deaths were made 16 years ago. The growth of the global population by approximately 20%, from 4.8 billion to 6.1 billion, contributes to the larger contemporary global typhoid fever burden. However, methodological differences may play a substantial role that is difficult to assess. For example, the differences in the methodology used to obtain the estimates confound efforts to draw inferences about the apparent increase of the global typhoid fever burden. In fact, there is some evidence that

Table 1. Typhoid surveillance and incidence studies by geographical location

United Nations classification of Area/Region	Regional typhoid surveillance ^a	Typhoid incidence studies			
		Country	Number	Year(s) ^b	Reference
Africa					
Eastern Africa	No	— ^c	— ^c	— ^c	— ^c
Middle Africa	No	—	—	—	—
Northern Africa	No	Egypt	2	1972–73, 1978–81	27, 28
Southern Africa	No	South Africa	1	1985–88	42, 43
Western Africa	No	—	—	—	—
Asia					
Eastern Asia	No	China	1	1995–96	9
South-central Asia	No	India	2	1974–75, 1995–96	8, 30
		Nepal	1	1986–87	44
South-eastern Asia	No	Indonesia	1	1986–89	19
		Viet Nam	2	1995–96, 1998–2000	7, 32
Western Asia	No	—	—	—	—
Europe					
Eastern Europe	No	Poland	1	1961–63	38
		USSR	4	1961–62, 1962–64 1963–64, 1966–67	20–22, 31
Northern Europe	Yes	—	—	—	—
Southern Europe	Yes	Yugoslavia	2	1954–60, 1960–63	23, 24
Western Europe	Yes	—	—	—	—
Latin America/Caribbean					
Caribbean	No	—	—	—	—
Central America	No	—	—	—	—
South America	Yes	Guyana	1	1960–67	29
		Chile	3	1982–87, 1983–86, 1986–89	18, 25, 26
Northern America					
Northern America	Yes	—	—	—	—
Oceania					
Australia/New Zealand	Yes	—	—	—	—
Melanesia	No	—	—	—	—
Micronesia	No	—	—	—	—
Polynesia	No	Tonga	1	1966–73	39

^a Region contains at least one country with national typhoid fever surveillance systems that employ blood culture confirmation of cases.

^b Most recent study contributes to country or region incidence estimate.

^c No eligible typhoid incidence studies.

typhoid fever incidence rates have declined over the past several decades. For Chile (5, 18, 25, 26), Egypt (27, 28), India (14, 29, 30), the former Soviet Union (20–22, 31), and Viet Nam (7, 32), multiple data points available over time from each country indicate a secular trend towards declining typhoid fever incidence for all countries except Viet Nam; this trend is consistent with improvements in sanitary conditions and reductions in diarrhoeal disease morbidity and mortality reported from some countries and regions (5, 33). Accurately tracking changes of global typhoid burden, therefore, will require the adoption of a standard method for generating estimates.

Limitations of the revised global typhoid fever burden estimate

To further refine the estimate of the global burden of typhoid fever, improvements are needed in both the quantity and quality of source data. Only 22 studies were eligible to contribute inci-

dence data to our estimate. The 1.8 million person-years of surveillance available to make this estimate represent <0.001% of the approximately 250 billion person-years that have occurred since 1950. Whole regions lacked either eligible population-based studies of typhoid fever incidence or surveillance systems that might measure typhoid fever incidence at the population level. The lack of data is most notable for eastern, central, and western Africa. Population-based studies from Egypt in the northern Africa region are in the middle incidence range, but a single study from South Africa places the southern Africa region in the high incidence range. In contrast to hospital-based studies conducted in south-central and south-east Asia, where *Salmonella Typhi* is a leading cause of bloodstream infection (34), in similar studies conducted in sub-Saharan Africa the organism has not predominated (35–37). This may suggest that the typhoid situation in the rest of the African continent might reflect more closely that seen in Egypt than that seen in

Table 2. Crude typhoid fever incidence rates by region, 2000

Area/Region	Typhoid cases	Population	Crude Incidence ^a	Incidence classification
Africa				
Eastern Africa ^b	98 560	255 500 000	39	Medium
Middle Africa ^b	36 857	95 385 000	39	Medium
Northern Africa	58 210	175 037 000	33	Medium
Southern Africa	123 473	52 887 000	233	High
Western Africa ^b	91 737	241 102 000	38	Medium
Area total	408 837	819 911 000	50	Medium
Asia				
Eastern Asia	182 927	1 483 111 000	12	Medium
South-central Asia	9 299 064	1 495 977 000	622	High
South-eastern Asia	575 407	521 983 000	110	High
Western Asia ^b	61 481	187 463 000	33	Medium
Area total	10 118 879	3 688 534 000	274	High
Europe				
Eastern Europe	15 940	306 654 000	5	Low
Northern Europe	143	93 736 000	<1	Low
Southern Europe	2785	144 861 000	2	Low
Western Europe	276	184 077 000	<1	Low
Area total	19 144	729 328 000	3	Low
Latin America/Caribbean				
Caribbean ^b	19 889	37 757 000	53	Medium
Central America ^b	79 164	135 497 000	58	Medium
South America	174 465	341 434 000	51	Medium
Area total	273 518	514 688 000	53	Medium
Northern America				
Northern America	453	308 636 000	<1	Low
Area total	453	308 636 000	<1	Low
Oceania				
Australia/New Zealand	62	22 598 000	<1	Low
Melanesia ^b	3897	6 489 000	60	Medium
Micronesia ^b	326	539 000	60	Medium
Polynesia	371	626 000	59	Medium
Area total	4656	30 252 000	15	Medium
Global				
Crude total	10 825 487	6 091 349 000	178	High
Adjusted total	21 650 974	6 091 349 000	355	

^a Per 100 000 persons per year.

^b Region incidence estimate derived by extrapolation.

South Africa. However, this uncertainty remains a key concern in terms of the reliability of our estimate. Population-based studies of typhoid fever incidence are needed elsewhere in Africa to clarify the typhoid fever situation for the continent. Such epidemiological data are needed to guide decision-making by public health officials for disease prevention and control programmes.

We also faced issues of data quality. Several of the studies that contribute to the new estimate of global typhoid fever burden were conducted during the 1950s, 1960s, and 1970s (20–23, 27–31, 38, 39). Since these studies were conducted, changes in the determinants of typhoid fever incidence, such as improvements in water supply and sanitary conditions (5), raise questions about the validity of these historical data for the year 2000 estimate. We elected to consider all eligible studies because of the limited number of data points available, but where multiple studies were reported for the same country, we chose

the most recent estimate to limit the effect of secular changes in typhoid fever incidence.

Reliance on typhoid vaccine studies to contribute data to our global typhoid burden estimate also raises concerns over data quality. To achieve favourable sample sizes, typhoid vaccine studies are preferentially conducted at sites that are known to experience high incidence of typhoid fever, introducing a bias towards overestimation of incidence in the region where the study was conducted. We attempted to account for this bias by selecting the most conservative regional incidence rates for our calculations.

In one-way sensitivity analysis, the sensitivity of the diagnostic test has the greatest impact on the variability of the estimate of global typhoid fever burden. The authors of the 1984 estimate do not report making an adjustment for diagnostic test sensitivity. This adjustment probably accounts for the largest

Fig. 2. Geographical distribution of typhoid fever

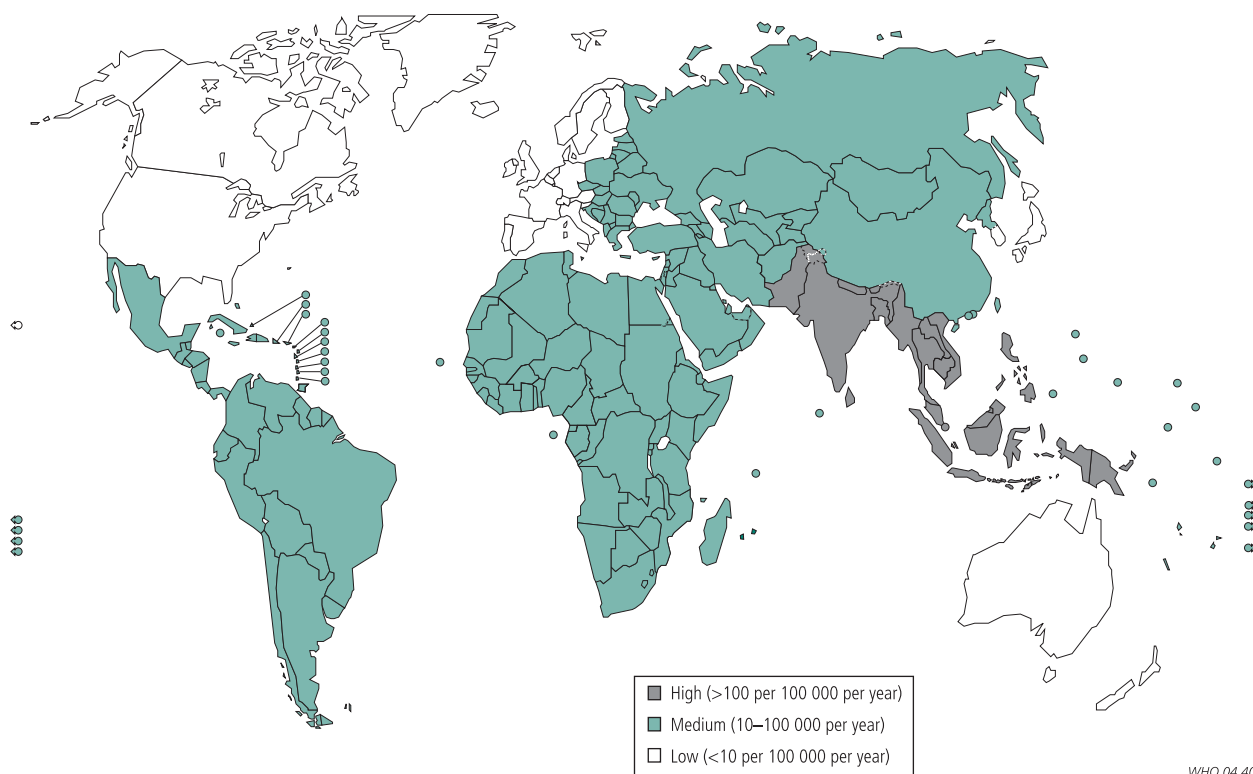


Table 3. Sensitivity analysis of typhoid fever incidence and case-fatality rate

Variable	Data input	Estimate
Incidence data selection	Most conservative (lowest)	10 825 487
	Least conservative (highest)	16 371 420
Age incidence adjustment	Adjusted (high, medium, low)	10 825 487
	Adjusted (high, low)	11 110 627
	Not adjusted	13 433 150
Blood culture sensitivity (%)	100	10 825 487
	75	14 433 983
	50	21 650 974
	25	43 301 948
Case-fatality rate (%)	5	1 082 549
	1	216 510
	0.1	21 651

methodological and quantitative difference between our estimate and the old one. Blood culture sensitivity is determined by the combined effects of the volume of blood collected, the timing of collection, and antimicrobial use (12–14). We could not account for these factors for the studies that contributed to our global typhoid burden estimate because they were not routinely reported. Instead, we chose to apply a conservative sensitivity of 50% to all studies. The impact of the global epidemic of antimicrobial use (40) on the detection of typhoid fever cases by blood culture is not well characterized but could have considerable impact on culture-based approaches to case confirmation. The estimated number of deaths due to typhoid

fever is important for decision-makers in public health policy, yet case-fatality rate data from population-based studies of typhoid fever are lacking. The reliability of the case-fatality rate of 1% selected for this estimate should be evaluated in population-based studies to facilitate a more accurate estimation of the number of deaths due to typhoid fever.

The challenge of global surveillance for febrile illnesses

The etiologies and incidence of febrile illnesses such as typhoid fever have proved difficult to determine. The implementation of population-based typhoid fever and febrile illness surveillance studies in selected regions could add considerably to the accuracy of the global typhoid fever burden estimate. Recently described rapid methods for estimating typhoid fever incidence may make this feasible (41). An accurate picture of the global epidemiology of typhoid fever will be necessary to prioritize the use of scarce health-care resources for disease control and to efficiently target the use of vaccines (32) and other preventive measures for typhoid fever. ■

Acknowledgements

We acknowledge the invaluable advice and assistance of Claire-Lise Chaignat, Department of Communicable Disease Surveillance and Response, and Claudia Stein, Evidence for Information and Policy, WHO, Geneva, Switzerland. We also acknowledge Robert V. Tauxe, Foodborne and Diarrhoeal Diseases Branch, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA for his helpful comments and suggestions on the manuscript.

Conflicts of interest: none declared.

Résumé

La charge mondiale de typhoïde

Objectif Utiliser de nouvelles données pour procéder à une estimation révisée de la charge mondiale de typhoïde, qu'il est nécessaire de connaître avec précision pour orienter les décisions de santé publique en matière de prévention et de lutte.

Méthodes Les études en population avec confirmation des cas de typhoïde par hémoculture ont été identifiées par une recherche documentaire informatisée de la littérature scientifique multilingue. Lorsqu'aucune étude ne répondait aux critères de recherche, les données étaient extrapolées à partir des pays et régions voisins. Des courbes d'incidence en fonction de l'âge ont été utilisées pour traduire dans la population générale les taux mesurés sur des cohortes correspondant à des tranches d'âge étroites. Une analyse de sensibilité unilatérale a été effectuée pour déterminer la sensibilité de l'estimation aux hypothèses de départ. La charge de paratyphoïde a été dérivée de celle de la typhoïde selon une méthode proportionnelle.

Résultats Au total, 22 études répondant aux critères de recherche ont été identifiées. Les régions de forte incidence de la typhoïde

(>100 cas pour 100 000 habitants par an) sont l'Asie du Sud et du centre et l'Asie du Sud-Est. Les régions d'incidence moyenne (10-100 cas pour 100 000 habitants par an) sont le reste de l'Asie, l'Afrique, l'Amérique latine, les Caraïbes et l'Océanie à l'exception de l'Australie et de la Nouvelle-Zélande. En Europe, en Amérique du Nord et dans le reste du monde développé, l'incidence de la typhoïde est faible (<10 cas pour 100 000 habitants par an). D'après nos estimations, la typhoïde a provoqué 21 650 974 cas de maladie et 216 510 décès en 2000 et la paratyphoïde 5 412 744 cas de maladie.

Conclusion De nouvelles données, jointes à une amélioration de la connaissance de l'épidémiologie de la typhoïde, nous ont permis d'affiner l'estimation de la charge mondiale de typhoïde, laquelle reste considérable. Des études plus détaillées de l'incidence de la maladie dans certains pays et régions, notamment en Afrique, sont nécessaires pour obtenir une estimation encore plus exacte.

Resumen

La carga mundial de fiebre tifoidea

Objetivo Usar nuevos datos para hacer una estimación revisada de la carga mundial de fiebre tifoidea, a fin de determinar exactamente qué debe hacerse para orientar las decisiones de salud pública encaminadas a controlar y prevenir la enfermedad.

Métodos Se hizo una búsqueda computadorizada en la literatura científica multilingüe para encontrar estudios poblacionales en los que se confirmara el diagnóstico de fiebre tifoidea mediante hemocultivo. En los casos en que ningún estudio reunía las condiciones requeridas, los datos se extrapolaron a partir de los países y regiones vecinas. Se usaron curvas de edad-incidencia para, a partir de las mediciones realizadas en cohortes estrechas de edad, modelizar las tasas correspondientes a la población general. Se hizo un análisis de sensibilidad unidireccional para determinar la sensibilidad del cálculo a los supuestos utilizados. La carga de fiebre paratifoidea se calculó mediante un método proporcional.

Resultados Se hallaron en total 22 estudios que reunían los

requisitos establecidos. Las regiones con alta incidencia de fiebre tifoidea (más de 100/100 000 casos/año) son Asia centromeridional y Asia sudoriental. Las regiones de incidencia media (10-100/100 000 casos/año) comprenden el resto de Asia, África, América Latina y el Caribe y Oceanía, salvo Australia y Nueva Zelanda. Europa, América del Norte y el resto del mundo desarrollado tienen una baja incidencia de fiebre tifoidea (menos de 10/100 000 casos/año). Calculamos que la fiebre tifoidea causó 21 650 974 casos y 216 510 defunciones durante el año 2000, y la fiebre paratifoidea 5 412 744 casos.

Conclusión Los nuevos datos y el mejor conocimiento de la epidemiología de la fiebre tifoidea nos permitieron calcular con mayor precisión la carga mundial de esa enfermedad, que sigue siendo considerable. Es necesario realizar estudios de incidencia más detallados en determinados países y regiones, sobre todo en África, para obtener estimaciones aún más precisas.

ملخص

العبء العالمي لحمى التيفوئيد

وسط آسيا وجنوب شرق آسيا. أما المناطق ذات معدل الوقوع المتوسط (١٠ إلى ١٠٠ لكل ١٠٠ ٠٠٠ حالة/عام) فتشمل سائر مناطق قارة آسيا، وأفريقيا، وأمريكا اللاتينية والكاريبي، وأوقيانوس باستثناء استراليا ونيوزيلندا. ولوحظ انخفاض معدل وقوع المرض في أوروبا، وأمريكا الشمالية، وسائر البلدان المتقدمة (أقل من ١٠ حالات لكل ١٠٠ ٠٠٠ حالة/عام). ويُقدر أن حمى التيفوئيد سببت ٢١ ٦٥٠ ٩٧٤ حالة مرضية و٢١٦ ٥١٠ حالة وفاة في عام ٢٠٠٠، وأن الحمى الباراتيفوئيدية سببت ٥ ٤١٢ ٧٤٤ حالة مرضية.

الخصيلة: أتاحت لنا المعطيات الجديدة والفهم الأفضل لإبيدميولوجيا (وباثيات) حمى التيفوئيد تحديث التقديرات الخاصة بعبء التيفوئيد في العالم، والذي ما يزال لا يستهان به. وما يزال هناك احتياج لدراسة معدل وقوع الحالات بشكل أكثر عمقاً في بلدان ومناطق مثقاة، ولاسيماً أفريقيا، بغية الحصول على تقديرات أحدث.

الغرض: استخدام المعطيات الجديدة للحصول على تقديرات منقحة لعبء العالمي لحمى التيفوئيد، نظراً لضرورة الفهم الدقيق لهذا العبء لتوجيه قرارات الصحة العمومية نحو تعزيز جهود مكافحة المرض والوقاية منه.

الطريقة: تم تقصي الدراسات السكانية المتعلقة بحالات حمى التيفوئيد المؤكدة بمزرعة الدم، وذلك بالبحث الحاسوبي في الدراسات العلمية المنشورة المتعددة اللغات. وفي حالة عدم توفر دراسات يعتد بها، تم استقراء المعطيات من البلدان والأقاليم المجاورة. وتم استخدام منحنيات العمر ووقوع المرض لتخطيط المعدلات المقاسة بين الأتراب المتقاربين في العمر بالنسبة إلى عامة السكان. وأجري تحليل حساسية أحادي الاتجاه لاستطلاع مدى حساسية التقديرات للافتراضات المطروحة. وتم استنباط عبء الحمى الباراتيفوئيدية بطريقة تناسبية.

الموجودات: تم تحديد ٢٢ دراسة مقبولة وتبين أن المناطق ذات معدل الوقوع المرتفع لحمى التيفوئيد (أكثر من ١٠٠ لكل ١٠٠ ٠٠٠ حالة/عام) تشمل جنوب

References

1. *The world health report 1996: Fighting disease, fostering development*. Geneva: World Health Organization; 1996.
2. Edelman R, Levine MM. Summary of an international workshop on typhoid fever. *Reviews of Infectious Diseases* 1986;8:329-49.
3. Institute of Medicine. *New vaccine development: establishing priorities, Vol. 2. Diseases of importance in developing countries. Comparisons of disease burdens*. Washington (DC): National Academy Press; 1986.
4. *The sex and age distribution of the world populations. The 1996 revision*. New York: United Nations; 1997.
5. WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation. *Global water supply and sanitation assessment 2000 report*. Geneva: WHO/UNICEF; 2000.
6. Martinez L. Global infectious disease surveillance. *International Journal of Infectious Diseases* 2000;4:222-8.
7. Lin F-YC, Ho VA, Bay PV, Thuy NTT, Bryla D, Thanh TC, et al. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. *The American Journal of Tropical Medicine and Hygiene* 2000;62: 644-8.
8. Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B, et al. Typhoid fever in children aged less than 5 years. *Lancet* 1999;354:734-7.
9. Yang HH, Wu CG, Xie GZ, Gu QW, Wang BR, Wang LY, et al. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. *Bulletin of the World Health Organization* 2001;79:625-31.
10. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1991 and projected to 2020. In: Murray CJL, Lopez AD, editors. *Global burden of disease and injury series*, 1st ed. Vol. 1. Boston (MA): Harvard University Press; 1996.
11. United Nations Children's Fund. *The state of the world's children 1996*. New York: Oxford University Press; 1996.
12. Hoffman SL, Edman DC, Punjabi NH, Lesmana M, Cholid A, Sundah S, et al. Bone marrow aspirate culture superior to streptokinase clot culture and 8 mL 1:10 blood-to-broth ratio blood culture for diagnosis of typhoid fever. *The American Journal of Tropical Medicine and Hygiene* 1986;35:836-9.
13. Gilman RH, Termini M, Levine MM, Hernandez-Mendoza P, Hornick RB. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of *Salmonella* Typhi in typhoid fever. *Lancet* 1975;1:1211-3.
14. Wain J, Bay PVB, Vinh H, Duong NM, Diep TS, Walsh AL, et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *Journal of Clinical Microbiology* 2001;39:1571-6.
15. Herikstad H, Motarjemi Y, Tauxe RV. *Salmonella* surveillance: a global survey of public health serotyping. *Epidemiology and Infection* 2002;129:1-8.
16. Butler T, Knight J, Nath SK, Speelman P, Roy SK, Azad MAK. Typhoid fever complicated by intestinal perforation: a persisting fatal disease requiring surgical management. *Reviews of Infectious Diseases* 1985;7:244-56.
17. Helfrick DL, Olsen SJ, Bishop RD, Tauxe RV, Hoekstra RM, Slutsker L, et al. *An atlas of Salmonella in the United States: serotype-specific surveillance, 1968-1998*. Atlanta (GA): United States Department of Health and Human Services; 2000.
18. Black RE, Levine MM, Ferreccio C, Clements ML, Lanata C, Rooney J, et al. Efficacy of one or two doses of Ty21a *Salmonella* Typhi vaccine in enteric-coated capsules in a controlled field trial. *Vaccine* 1990;8:81-4.
19. Simanjuntak CH, Paleologo FP, Punjabi NH, Darmowigoto R, Soeprawoto, Totosudirjo H, et al. Oral immunisation against typhoid fever in Indonesia with Ty21a vaccine. *Lancet* 1991;338:1055-9.
20. Hejfec LB. Results of the study of typhoid vaccines in four controlled field trials in the USSR. *Bulletin of the World Health Organization* 1965;32:1-14.
21. Hejfec LB, Salmin LV, Lejtman MZ, Kuz'minova ML, Vasil'eva AV, Levina LA, et al. A controlled field trial and laboratory study of five typhoid vaccines in the USSR. *Bulletin of the World Health Organization* 1966;34:321-39.
22. Hejfec LB, Levina LA, Kuz'minova ML, Salmin LV, Slavina AM, Vasil'eva AV. Controlled field trials of paratyphoid B vaccine and evaluation of the effectiveness of a single administration of typhoid vaccine. *Bulletin of the World Health Organization* 1968;38:907-15.
23. Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of phenol and alcohol typhoid vaccines. *Bulletin of the World Health Organization* 1962;26:357-69.
24. Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of acetone-dried and inactivated and heat-phenol-inactivated typhoid vaccines in Yugoslavia. *Bulletin of the World Health Organization* 1964;30:623-30.
25. Levine MM, Ferreccio C, Black RE, Germanier R. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. *Lancet* 1987;1:1049-52.
26. Levine MM, Ferreccio C, Cryz S, Ortiz E. Comparison of enteric-coated capsules and liquid formulation of Ty21a typhoid vaccine in randomised controlled field trial. *Lancet* 1990;336:891-4.
27. Wahdan MH, Sippel JE, Mikhail IA, Rahka AE, Anderson ES, Sparks HA, et al. Controlled field trial of a typhoid vaccine prepared with a nonmotile mutant of *Salmonella* Typhi Ty2. *Bulletin of the World Health Organization* 1975;52:69-73.
28. Wahdan MH, Serie C, Cerisier Y, Sallam S, Germanier R. A controlled field trial of live *Salmonella* Typhi strain Ty 21a oral vaccine against typhoid: three-year results. *The Journal of Infectious Diseases* 1982;145:292-5.
29. Ashcroft MT, Singh B, Nicholson CC, Ritchie JM, Sobryan E, Williams F. A seven-year field trial of two typhoid vaccines in Guyana. *Lancet* 1967;2:1056-9.
30. Chuttani CS, Prakash K, Gupta P, Grover V, Kumar A. Controlled field trial of high-dose oral killed typhoid vaccine in India. *Bulletin of the World Health Organization* 1977;55:643-4.
31. Hejfec LB, Levina LA, Kuz'minova ML, Slavina AM, Drozd AK, Tonojan IA, et al. A controlled field trial to evaluate the protective capacity of a single dose of acetone-killed agar-grown and heat-killed broth-grown typhoid vaccines. *Bulletin of the World Health Organization* 1969;40:903-7.
32. Ying FY, Ho VA, Kheim HB, Trach DD, Bay PV, Thanh TC, et al. The efficacy of a *Salmonella* Typhi Vi conjugate vaccine in two-to-five-year-old children. *The New England Journal of Medicine* 2001;344:1263-9.
33. El-Rafie M, Hassouna WA, Hirschhorn N, Loza S, Miller P, Nagaty A, et al. Effect of diarrhoeal disease control on infant and childhood mortality in Egypt. Report from the National Control of Diarrhoeal Diseases Project. *Lancet* 1990;335:334-8.
34. Woods CW, Murdoch DR, Zimmerman MD, Belbase RH, Basnyat B, Archibald LK, et al. Etiology of febrile illness in urban Nepal. *The American Journal of Tropical Medicine and Hygiene* 2001;65:149.
35. Archibald LK, den Dulk MO, Pallangyo KJ, Reller LB. Fatal Mycobacterium tuberculosis bloodstream infections in febrile hospitalized adults in Dar es Salaam, Tanzania. *Clinical Infectious Diseases* 1998;26:290-6.
36. Archibald LK, McDonald LC, Nwanyanwu O, Kazembe P, Dobbie H, Tokars J, et al. A hospital-based prevalence survey of bloodstream infections in febrile patients in Malawi: implications for diagnosis and therapy. *The Journal of Infectious Diseases* 2000;181:1414-20.
37. Vugia DJ, Kiehlbauch JA, Yeboue K, N'Gichi JM, Lacina D, Maran M, et al. Pathogens and predictors of fatal septicemia associated with human immunodeficiency virus infection in Ivory Coast, West Africa. *The Journal of Infectious Diseases* 1993;168:564-70.
38. Polish Typhoid Committee. Evaluation of typhoid vaccines in the laboratory and in a controlled field trial in Poland. *Bulletin of the World Health Organization* 1965;32:15-27.
39. Tapa S, Cvjetanovic B. Controlled field trial on the effectiveness of one and two doses of acetone-inactivated and dried typhoid vaccine. *Bulletin of the World Health Organization* 1975;52:75-80.
40. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance in developing countries. *Emerging Infectious Diseases* 1999;5:18-27.
41. Crump JA, Youssef FG, Luby SP, Wasfy MO, Rangel JM, Talaat M, et al. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. *Emerging Infectious Diseases* 2003;9:539-44.
42. Klugman KP, Gilbertson IT, Koornhof HJ, Robbins JB, Schneerson R, Schulz D, et al. Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. *Lancet* 1987;2:1165-9.
43. Klugman KP, Koornhof HJ, Robbins JB, Le Cam NN. Immunogenicity, efficacy, and serological correlate of protection of *Salmonella* Typhi Vi capsular polysaccharide vaccine three years after immunization. *Vaccine* 1996;14:435-8.
44. Acharya IL, Lowe CU, Thapa R, Gurubacharya VL, Shrestha MB, Cadoz M, et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella* Typhi. *The New England Journal of Medicine* 1987;317:1101-4.