Case Fatality Rate and Length of Hospital Stay among Patients with Typhoid Intestinal Perforation in Developing Countries: A Systematic Literature Review

Vittal Mogasale1*, Sachin N. Desai2, Vijayalaxmi V. Mogasale3, Jin Kyung Park4, R. Leon Ochiai5, Thomas F. Wierzba6

1 Policy and Economic Research Centre, Access Department, Development and Delivery Unit, International Vaccine Institute, Seoul, South Korea, 2 Clinical Development and Regulatory Department, Development and Delivery Unit, International Vaccine Institute, Seoul, South Korea, 3 Epidemiology Department, Development and Delivery Unit, International Vaccine Institute, Seoul, South Korea, 4 Biostatistics and Data Management Department, Development and Delivery Unit, International Vaccine Institute, Seoul, South Korea, 5 International Vaccine Institute, Seoul, South Korea, 6 Development and Delivery Unit, International Vaccine Institute, Seoul, South Korea

Abstract

**Background:** Typhoid fever remains a major health problem in the developing world. Intestinal perforation is a lethal complication and continues to occur in impoverished areas despite advances in preventive and therapeutic strategies.

**Objectives:** To estimate the case fatality rate (CFR) and length of hospital stay among patients with typhoid intestinal perforation in developing countries.

**Data Sources:** Peer-reviewed publications listed in PubMed and Google Scholar.

**Study Eligibility:** The publications containing data on CFR or length of hospitalization for typhoid fever from low, lower middle and upper middle income countries based on World Bank classification. Limits are English language, human research and publication date from 1st January 1991 to 31st December 2011.

**Participants:** Subjects with reported typhoid intestinal perforation.

**Interventions:** None, standard practice as reported in the publication.

**Study Appraisal and Synthesis Methods:** Systematic literature review followed by meta-analysis after regional classification on primary data. Descriptive methods were applied on secondary data.

**Results:** From 42 published reports, a total of 4,626 hospitalized typhoid intestinal perforation cases and 706 deaths were recorded (CFR = 15.4%; 95% CI: 13.0%–17.8%) with a significant regional differences. The overall mean length of hospitalization for intestinal perforation from 23 studies was 18.4 days (N = 2,542; 95% CI: 15.6–21.1).

**Limitations:** Most typhoid intestinal perforation studies featured in this review were from a limited number of countries.

**Conclusions:** The CFR estimated in this review is a substantial reduction from the 39.6% reported from a literature review for years 1960 to 1990. Aggressive resuscitation, appropriate antimicrobial coverage, and prompt surgical intervention may have contributed to decrease mortality.

**Implications:** The quantification of intestinal perforation outcomes and its regional disparities as presented here is valuable in prioritizing and targeting typhoid-preventive interventions to the most affected areas.

Citation: Mogasale V, Desai SN, Mogasale V, Park JK, Ochiai RL, et al. (2014) Case Fatality Rate and Length of Hospital Stay among Patients with Typhoid Intestinal Perforation in Developing Countries: A Systematic Literature Review. PLoS ONE 9(4): e93784. doi:10.1371/journal.pone.0093784

Editor: Dongsheng Zhou, State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, China

Received January 11, 2014; Accepted March 8, 2014; Published April 17, 2014

Copyright: © 2014 Mogasale et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work is supported by the Bill and Melinda Gates Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: vmogasale@ivi.int

Introduction

Typhoid fever is caused by the gram negative bacillus *Salmonella enterica* serovar Typhi (*S. typhi*) [1] continues to be a public health problem in developing countries [2]. It is transmitted via the faeco-oral route through ingestion of contaminated food or water. The disease is characterized by prolonged fever, and constitutional symptoms including headache, anorexia and abdominal pain [3]. The systemic involvement in typhoid fever can result in intra-intestinal complications such as encephalopathy, meningitis,
hepatitis, myocarditis and pneumonia, while the most common gastro-intestinal complication is haemorrhage [4]. Intestinal perforation is a potentially fatal complication of typhoid fever secondary to the inflammation and necrosis of Peyer’s patches when not treated early and appropriately. Generally, perforation is a late complication occurring in the third week of illness, though it is reported earlier in second week in developing countries for reasons that are not completely understood [4,5,6,7].

Case fatality rate (CFR) in intestinal perforation is dependent on various factors such as the quality of health care service received, characteristics of the organism and host factors. The diagnostic and therapeutic management for intestinal perforation have changed significantly over the past three decades which has potential implications on mortality, morbidity, hospital costs and societal costs. Aggressive resuscitation and prompt surgical intervention within the first 24 hours of perforation, along with appropriate antimicrobial coverage, are considered key measures in intestinal perforation management in recent days [8,9,10,11]. The appearance and spread of multidrug resistant S. typhi strains is another factor that influences outcomes of typhoid intestinal perforation. Multidrug resistant strains exhibiting resistance to ampicillin, chloramphenicol, trimethoprimsulfamethoxazole have emerged in South East Asia since the late 1980s. They have subsequently spread to other regions of the world, affecting morbidity, mortality and duration of treatment [12,13,14]. Poorer outcomes have been observed in those with late presentation (≥ 24 hours since perforation) [9,15], multiple perforations (>1) [11,15,16,17], and post-operative complications such as faecal fistula [15,18].

A worldwide case series from 1960–90 had reported 1,990 cases of intestinal perforation in 66,157 patients with typhoid fever [19]. The publication reported a 3% perforation rate and a 39.6% CFR among typhoid perforation cases, noting an overall male preponderance. Advanced perforation management and emerging multidrug-resistant S. typhi in recent years could potentially modify characteristics of typhoid intestinal perforation and CFR. We present an updated review of CFR, age and gender characteristics, and length of hospital stay associated with typhoid intestinal perforation by geographical regions from articles published from 1991 to 2011 in low income, lower middle income and upper middle income countries [20].

Methodology

Search strategy and selection criteria

A systematic literature review was carried out using PubMed electronic database for typhoid fever intestinal perforation related publications in English from 1st January 1991 to 31st December 2011. The search was repeated using the Google Scholar electronic database for additional publications. The key terms used in the search were “Typhoid Fever”, “Enteric Fever”, “Salmonella Typhi”, and “Intestinal Perforation”. The selection criteria and search terms for the study inclusion are listed in Table 1. Two researchers conducted independent reviews based on defined search strategy and criteria, and compared the results before selecting final papers. One researcher extracted data and another researcher matched the data with original papers to verify for its correctness. No written protocol was developed.

Analytical method

An important aspect of this review was to capture the regional differences in CFR due to typhoid intestinal perforation, age and gender characteristics, and length of hospital stay. To identify the regional differences, we categorized the studies by geographical regions, namely: Asian countries, African countries and countries in other regions.

We have deployed meta-analysis approach [21] for validating and summarizing results so that a regional comparison of variables can be made. In this review, we have applied heterogeneity test to compare dissimilarity between results extracted from various primary studies based on a random effect model. The heterogeneity test was utilized to verify the validity of results and to potentially eliminate the effect of study quality and publication bias (the association of publication probability with the statistical significance of study results) [22,23]. We considered the results of various studies comparable if no heterogeneity in the results was observed.

To perform meta-analysis, first, data on CFR, male to female ratio, age and length of stay in hospitalized intestinal perforation cases were extracted from selected publications. The data was classified by three geographical regions and listed in descending chronological order of year of publication. Then, the test for heterogeneity was conducted for CFR and male to female ratio to explore the true effects. The mean and corresponding 95% confidence interval for individual studies were estimated based on a random effect model and a graphical overview of the results was obtained by forest plot. We did not estimate 95% confidence interval of individual studies and heterogeneity test by using meta-analysis for age and length of hospital stay as variance was not available.

The validated results from meta-analysis for various regions were compared using Kruskal-Wallis test [24] to assess whether there was a significant difference in results from different geographical regions. If a significant difference between regions was observed, a simultaneous multiple paired comparison was performed to test inequalities between three possible combinations of two regions each. We applied nonparametric Kruskal-Wallis test on CFR, male to female ratio, age and length of hospital stay to compare the three regions. The box plot was generated to show data dispersion within each region and the strength of linear relationship between time and perforation outcome was tested using Spearman correlation coefficient [25,26].

The analysis was performed using statistical software R while all statistical comparisons were tested for overall significance level at 5% (alpha = 0.05).

The selected papers had some additional information on the characteristics of intestinal perforation such as presenting symptoms, duration of illness, management procedures and post-operative complications. These features were summarized using descriptive methods.

Results

A total of 3,941 results on typhoid fever were narrowed down to 168 publications pertaining to typhoid intestinal perforation. When 168 abstracts were reviewed, we found 37 eligible papers based on the selection criteria. Supplementary literature search using Google Scholar identified 220 papers from which 9 additional papers were found eligible for the review (Figure 1).

Upon review of the 46 papers identified from low income, lower middle income and upper middle income countries, we found two of the papers analysed the same data set [27,28]. We chose the article with the most comprehensive information [28]; noted in the figure 1 as exclusion based on common dataset. An additional two papers were excluded as they had presented CFR in specific surgical procedures that could not be generalized [29,30]; noted in the figure 1 as exclusion based on being not generalizable. One study presenting 12 typhoid perforation cases in a tertiary hospital
in Nigeria with an outlier CFR was excluded since the study population was not representative. These subjects were referred late, presenting in critically ill condition after treatment failure [31]. Of the remaining 42 papers included in final review (Table 2) [5,6,7,11,15,16,17,18,32,33,34,35,36,37,38,39,40,41,42,43,44,45, 46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63], twelve articles contained data from before and after 1990 [6,7,15,33,45,46,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63]. Though the analysis pre-

Table 1. Selection criteria for study inclusion.

| Selection criteria                                                                 |
|-----------------------------------------------------------------------------------|
| Published in English in peer reviewed journal from 1st January 1991 to 31st December 2011 |
| Presents typhoid intestinal perforation case fatality rate or length of stay in hospitalized patients |
| Includes data at least from 1990 or afterwards                                      |
| Contains data from low income, lower middle income and upper middle income countries based on World Bank classification- “Country and Lending Groups by income”, 2011 [20]. |

Search terms in PubMed

- (Typhoid fever) OR (Enteric Fever) OR (Salmonella Typhi) AND (Intestinal perforation) OR (perforation))

doi:10.1371/journal.pone.0093784.t001

Figure 1. Study selection flow diagram. CFR = case fatality rate.
doi:10.1371/journal.pone.0093784.g001
Table 2. Case fatality rate (CFR) in hospitalized typhoid intestinal perforation cases by study (1991–2011).

| Country      | Year of publication | Study period | Hospitalized typhoid perforation cases | Deaths | CFR   | Reference |
|--------------|---------------------|--------------|----------------------------------------|--------|-------|-----------|
| Africa       |                     |              |                                        |        |       |           |
| Nigeria      | 2011                | 2002–2009    | 153                                    | 16     | 10.5% | [18]      |
| Nigeria      | 2010                | 2004–2008    | 46                                     | 13     | 28.3% | [32]      |
| Ghana        | 2009                | 2000–2005    | 650                                    | 82     | 12.6% | [33]      |
| Nigeria      | 2008                | 1990–2004    | 105                                    | 14     | 13.3% | [34]      |
| Nigeria      | 2008                | 1995–2004    | 89                                     | 17     | 19.1% | [17]      |
| Nigeria      | 2007                | 1996–2005    | 184                                    | 42     | 22.8% | [5]       |
| Nigeria      | 2007                | 1980–2005    | 20                                     | 4      | 20.0% | [35]      |
| Ghana        | 2007                | 2001–2005    | 522                                    | 61     | 11.7% | [36]      |
| Nigeria      | 2007                | 2004–2006    | 53                                     | 8      | 15.1% | [11]      |
| Ghana        | 2007                | 2002–2005    | 248                                    | 27     | 10.9% | [37]      |
| Togo         | 2005                | 2003         | 112                                    | 18     | 16.1% | [38]      |
| Nigeria      | 2005                | 1994–2003    | 101                                    | 14     | 13.9% | [39]      |
| Nigeria      | 2004                | 1997–2003    | 47                                     | 6      | 12.8% | [40]      |
| Ivory Coast  | 2004                | 1995–1998    | 64                                     | 22     | 34.4% | [41]      |
| Nigeria      | 2004                | 1996–2000    | 43                                     | 6      | 14.0% | [42]      |
| Nigeria      | 2003                | 1998–2001    | 105                                    | 17     | 16.2% | [43]      |
| Nigeria      | 2003                | 1990–2000    | 108                                    | 27     | 25.0% | [44]      |
| Nigeria      | 2002                | 1989–1998    | 60                                     | 15     | 25.0% | [45]      |
| Nigeria      | 2001                | 1984–1999    | 106                                    | 25     | 23.6% | [6]       |
| Ethiopia     | 2000                | 1984–1995    | 27                                     | 10     | 37.0% | [46]      |
| Nigeria      | 1999                | 1987–1996    | 64                                     | 25     | 39.1% | [7]       |
| Nigeria      | 1998                | 1991–1994    | 75                                     | 15     | 20.0% | [47]      |
| Nigeria      | 1997                | 1989–1990    | 50                                     | 14     | 28.0% | [15]      |
| Nigeria      | 1992                | 1986–1990    | 18                                     | 5      | 27.8% | [48]      |
| Ghana        | 1992                | 1978–1991    | 195                                    | 61     | 31.3% | [49]      |
| Asia         |                     |              |                                        |        |       |           |
| Pakistan     | 2009                | 2003–2008    | 44                                     | 6      | 13.6% | [50]      |
| Pakistan     | 2006                | 2003–2005    | 112                                    | 8      | 7.1%  | [51]      |
| Nepal        | 2006                | 2002–2004    | 102                                    | 7      | 6.9%  | [16]      |
| Pakistan     | 2006                | 1998–2000    | 32                                     | 4      | 12.5% | [52]      |
| Pakistan     | 2005                | 2002–2004    | 72                                     | 10     | 13.9% | [53]      |
| Vietnam      | 2004                | 1997–1998    | 27                                     | 1      | 3.7%  | [54]      |
| India        | 2003                | 2000–2001    | 200                                    | 21     | 10.5% | [55]      |
| India        | 2001                | 1990–1998    | 100                                    | 7      | 7.0%  | [9]       |
| Pakistan     | 2000                | 1991–1994    | 76                                     | 17     | 22.4% | [56]      |
| India        | 1997                | 1990–1995    | 110                                    | 18     | 16.4% | [28]      |
| Pakistan     | 1997                | 1994–1995    | 140                                    | 12     | 8.6%  | [57]      |
| India        | 1994                | 1987–1990    | 65                                     | 13     | 20.0% | [58]      |
| Others       |                     |              |                                        |        |       |           |
| Turkey       | 2010                | 1994–2010    | 22                                     | 1      | 4.6%  | [59]      |
| Turkey       | 2007                | 1978–2004    | 82                                     | 9      | 11.0% | [60]      |
| Turkey       | 2002                | 1990–2000    | 42                                     | 2      | 4.8%  | [61]      |
| Mexico       | 1998                | 1985–1994    | 116                                    | 2      | 1.7%  | [62]      |
| Turkey       | 1995                | 1987–1993    | 39                                     | 4      | 10.3% | [63]      |
| Overall      | 4,626               |              | 706                                    |        |       |           |

Note: Studies are listed in the table by descending order of publication year.
doi:10.1371/journal.pone.0093784.t002
Table 3. Length of hospital stay among typhoid intestinal perforation cases by study (1991–2011).

| Country   | Age range (mean) | Number of cases | Mean length of stay (days) | Study period | Year of publication | Reference |
|-----------|------------------|-----------------|----------------------------|--------------|---------------------|-----------|
| Africa    |                  |                 |                            |              |                     |           |
| Nigeria   | 3–15 (9.6)       | 153             | 21.0                       | 8–67         | 2002–2009           | 2011 [18] |
| Nigeria   | 9–15 (9.5)       | 46              | 22.9                       | 4–46         | 2004–2008           | 2010 [32] |
| Ghana     | 1–15 (8.8)       | 650             | 14.4                       | 1–77         | 2001–2005           | 2009 [33] |
| Nigeria   | 15–72 (2.7)      | 105             | 16.1                       | NA           | 1990–2004           | 2008 [34] |
| Nigeria   | 1–15 (9.1)       | 89              | 22.0                       | 18–42        | 1995–2004           | 2008 [17] |
| Nigeria   | 4–15 (6.8)       | 184             | 35.8                       | 8–196        | 1996–2005           | 2007 [5]  |
| Nigeria   | 2–55 (12.3)      | 53              | 16.1                       | 8–57         | 2004–2006           | 2007 [11] |
| Ghana     | 11–45 (25.7)     | 20              | 16.3                       | 0–32         | 1980–2005           | 2007 [35] |
| Nigeria   | 16–55 (24.9)     | 248             | 12.4                       | 5–46         | 2002–2005           | 2007 [37] |
| Nigeria   | 4–85 (19.9)      | 101             | 18.0                       | NA           | 1994–2003           | 2005 [39] |
| Ivory Coast| 5–63 (34)        | 64              | 30.0                       | 8–52         | 1995–1998           | 2004 [41] |
| Nigeria   | 6–32 (15.9)      | 43              | 21.6                       | 8–74         | 1996–2000           | 2004 [42] |
| Nigeria   | 3–14 (8.8)       | 105             | 24.6                       | 11–54        | 1990–2000           | 2003 [44] |
| Nigeria   | 1–67 (24.3)      | 60              | 11.7                       | 1–60         | 1989–1998           | 2002 [45] |
| Nigeria   | 3–14 (10)        | 106             | 23.6                       | NA           | 1984–1999           | 2001 [6]  |
| Nigeria   | 1–12 (8)         | 64              | 20.6                       | 12–48        | 1989–1998           | 1999 [7]  |
| Asia      |                  |                 |                            |              |                     |           |
| Pakistan  | 10–45 (29.4)     | 44              | 17.6                       | NA           | 2003–2008           | 2009 [50] |
| Nepal     | 14–78 (28.4)     | 102             | 8.5                        | NA           | 2002–2004           | 2006 [16] |
| Pakistan  | 15–30            | 32              | 16.5                       | NA           | 1998–2000           | 2006 [52] |
| India     | 5–58 (24.0)      | 110             | 15.8                       | NA           | 1990–1995           | 1997 [28] |
| Others    |                  |                 |                            |              |                     |           |
| Turkey    | 7–68 (36.3)      | 82              | 11.7                       | 5–25         | 1978–2004           | 2007 [60] |
| Turkey    | 4–14 (10.4)      | 42              | 13.4                       | 7–23         | 1990–2000           | 2002 [61] |
| Turkey    | 3–76             | 39              | 12.0                       | NA           | 1987–1993           | 1995 [63] |

SD = standard deviation, NA = not available. Note: Studies are listed in the table by descending order of publication year.
doi:10.1371/journal.pone.0093784.t003
dominantly included data after 1990, the complete period ranged from 1978–2010. Of these 42 papers, 23 presented data on length of hospital stay (Table 3) [5,6,7,11,16,17,18,28,32,33,34,35,37,39,41,42,44,45,50,52,60,61,63].

The majority of publications came from five countries: Nigeria, Ghana, Pakistan, India and Turkey. We categorized 4,626 typhoid intestinal perforation cases from 11 countries into three geographical regions, Africa, Asia and others (Table 2). Two studies that assessed socio-economic status reported that around 78% to 88% of typhoid intestinal perforation cases were observed among people from low socio-economic strata [39,45].

The common presenting symptoms of typhoid intestinal perforation in the reviewed papers were fever, abdominal pain, diarrhoea, constipation, vomiting and abdominal distension. The mean duration from the onset of illness to the presentation of typhoid perforation at hospital was 10.6 days (SD = 2.1, min = 7.4, max = 15.7) from 1,925 cases reported in 25 studies. Over the years, aggressive surgical procedures became popular.

![Figure 2. Forest plot showing mean case fatality rate for intestinal perforation along with 95% confidence interval based on studies published from 1991 to 2011.](http://example.com/doi:10.1371/journal.pone.0093784.g002)

| Study | Proportion | 95%-CI |
|-------|------------|--------|
| Africa | 0.10       | [0.06; 0.16] |
| Africa | 0.28       | [0.16; 0.43] |
| Africa | 0.13       | [0.10; 0.15] |
| Africa | 0.13       | [0.07; 0.21] |
| Africa | 0.19       | [0.12; 0.29] |
| Africa | 0.23       | [0.17; 0.30] |
| Africa | 0.20       | [0.06; 0.44] |
| Africa | 0.12       | [0.09; 0.15] |
| Africa | 0.15       | [0.07; 0.28] |
| Africa | 0.11       | [0.07; 0.15] |
| Africa | 0.16       | [0.10; 0.24] |
| Africa | 0.14       | [0.08; 0.22] |
| Africa | 0.13       | [0.05; 0.26] |
| Africa | 0.34       | [0.23; 0.47] |
| Africa | 0.14       | [0.05; 0.28] |
| Africa | 0.16       | [0.10; 0.25] |
| Africa | 0.25       | [0.17; 0.34] |
| Africa | 0.25       | [0.15; 0.38] |
| Africa | 0.24       | [0.16; 0.33] |
| Africa | 0.37       | [0.19; 0.58] |
| Africa | 0.39       | [0.27; 0.52] |
| Africa | 0.20       | [0.12; 0.31] |
| Africa | 0.28       | [0.16; 0.42] |
| Africa | 0.28       | [0.10; 0.53] |
| Africa | 0.31       | [0.25; 0.38] |
| Asia   | 0.14       | [0.05; 0.27] |
| Asia   | 0.07       | [0.03; 0.14] |
| Asia   | 0.07       | [0.03; 0.14] |
| Asia   | 0.12       | [0.04; 0.29] |
| Asia   | 0.14       | [0.07; 0.24] |
| Asia   | 0.04       | [0.00; 0.19] |
| Asia   | 0.10       | [0.07; 0.16] |
| Asia   | 0.07       | [0.03; 0.14] |
| Asia   | 0.22       | [0.14; 0.33] |
| Asia   | 0.16       | [0.10; 0.25] |
| Asia   | 0.09       | [0.05; 0.14] |
| Asia   | 0.20       | [0.11; 0.32] |
| Others | 0.05       | [0.00; 0.23] |
| Others | 0.11       | [0.05; 0.20] |
| Others | 0.05       | [0.01; 0.16] |
| Others | 0.02       | [0.00; 0.06] |
| Others | 0.10       | [0.03; 0.24] |
| Overall| 0.16       | [0.13; 0.18] |
| Africa | 0.20       | [0.17; 0.22] |
| Asia   | 0.11       | [0.08; 0.13] |
| Others | 0.06       | [0.01; 0.10] |
conservative methods and simple drainage [8,9,27,48,63]. Among 26 papers that described surgical procedures, 23 reported simple closure or two layered closure as the most practiced surgical procedure. Solitary perforations were observed in 76% of the operated typhoid perforation cases that reported number of perforations per case (N = 2,903), while the remaining cases involved multiple perforations. Postoperative complications were common and were reported in at least 57% of the 2,063 cases that described the complications. The common complications were: wound infection, wound dehiscence (breaking open of the wound along surgical suture), persistent peritonitis, intra-abdominal abscess and entero-cutaneous fistula, all of which were often associated with increased hospital stay [6]. Around 18% (140/792) of operated perforation cases were re-operated due to the complications [17,18,32,34,37,47,56] while, re-perforation was observed during the surgery in half (52/98) of the reported re-operated cases [37,56].

The overall mean CFR among typhoid perforation cases was 15.4% (95% CI; 13.0%–17.8%), with the highest rates observed in African countries (19.5%; 95% CI; 16.6%–22.4%) followed by Asian countries (10.7%; 95% CI; 8.0%–13.4%) and countries from other regions (5.55%; 95% CI; 1.45%–9.65%), (Table 4). The meta-analysis showed a significant heterogeneity in both Africa and Asia (Table 4) and the forest plot (Figure 2) indicated that point estimates do not have high credence. Overall mean CFR between three regions was significantly different as shown by nonparametric Kruskal-Wallis test (Table 4). The box plot showed that the CFR of Africa derived the significant difference from that of other two regions (Figure 3).

To estimate trends in CFR, a scatter plot of CFR in patients with perforation against time was drawn for African and Asian regions applying the rate to the final year of the study period. The Spearman correlation coefficient of CFR were −0.68 (p<0.01) and −0.4 (p = 0.2) for Africa and Asia respectively which indicates a declining trend in CFR of typhoid intestinal perforation (Figure 4). The decline is statistically significant in African region only.

Papers presenting information on gender (n = 40), suggested that males were 2.16 times more likely to be hospitalized compared to females (95% CI = 1.1–4.0) for typhoid intestinal perforation (Table 4). The male to female ratio was significantly higher in Asia and other regions compared to Africa, while there was no statistical difference between male to female ratio of hospitalized typhoid intestinal perforation cases between Asia and other regions (Figure 3).

Based on 35 studies reporting age data, the unweighted mean age of hospitalization among all patients was 19.3 years. The overall difference in reported age at hospitalization for intestinal perforation is significantly different between the regions (p = 0.023, Table 4). African region displayed a significantly lower mean age at hospitalization (Figure 3) compared to other regions.

Based on the review of 23 relevant papers, the longest duration of hospitalization following intestinal perforation was estimated in African region (20.4 days). The overall unweighted mean length of hospitalization from all studies was 18.4 days (Table 4). The mean of length of hospital stay was significantly higher in Africa compared to average length of hospital stay in other regions (Figure 3).

Several investigators in the African region have followed up intestinal perforation cases for a longer duration. They have reported deaths due to malnutrition, resulting either from an entero-cutaneous fistula or peristomal ulcerations [6,34,41]. Development of entero-cutaneous fistula was strongly linked with increased mortality [15,18,28,34]. While most studies describe deaths occurring within a few weeks following intestinal perforation, a cohort of 64 postoperative cases found considerable mortality of 3–6 months (64%) and after 6 months (27%) secondary to postoperative complications [41].
Table 4. Mean values for weighted case fatality rate, male to female ratio, age and length of hospital stay by region in studies published from 1991 to 2011.

| Variables                  | Region   | No. of Studies | Total (N) | Average (N) | Mean [95% CI]       | Heterogeneity (p-value) | p-value* |
|----------------------------|----------|----------------|-----------|-------------|----------------------|-------------------------|----------|
| Case fatality rate*        | Overall  | 42             | 4626      | 110.1       | 0.154 [0.130; 0.178] | <0.001                  | <0.001   |
|                            | Africa   | 25             | 3245      | 129.8       | 0.195 [0.165; 0.224] | <0.001                  |          |
|                            | Asia     | 12             | 1080      | 90.0        | 0.107 [0.080; 0.134] | 0.016                   |          |
|                            | Others   | 5              | 301       | 60.2        | 0.055 [0.014; 0.096] | 0.062                   |          |
| Male to female ratio*      | Overall  | 40             | 4456      | 111.4       | 2.160 [1.151; 4.031] | 1.0                     | 0.001    |
|                            | Africa   | 25             | 3230      | 129.2       | 1.716 [0.777; 3.786] | 1.0                     |          |
|                            | Asia     | 12             | 1080      | 90.0        | 3.094 [0.986; 9.705] | 1.0                     |          |
|                            | Others   | 3              | 146       | 48.7        | 3.406 [0.339; 34.271] | 0.979                   |          |
| Weighted age (year)        | Overall  | 35             | 4016      | 114.7       | 19.286 [16.329; 22.244] | 0.023                   |          |
|                            | Africa   | 24             | 3218      | 134.1       | 16.697 [13.605; 19.787] |                         |          |
|                            | Asia     | 7              | 536       | 76.6        | 23.684 [17.385; 29.983] | NA                     |          |
|                            | Others   | 4              | 262       | 65.5        | 27.130 [7.283; 46.977] |                         |          |
| Mean stay (day)            | Overall  | 23             | 2542      | 110.5       | 18.374 [15.624; 21.124] | 0.030                   |          |
|                            | Africa   | 16             | 2091      | 130.9       | 20.443 [17.065; 23.821] |                         |          |
|                            | Asia     | 4              | 288       | 72.0        | 14.600 [8.022; 21.177] | NA                     |          |
|                            | Others   | 3              | 163       | 54.3        | 12.367 [10.113; 14.621] |                         |          |

N = sample size, NA = not applicable,
* weighted mean,
region comparison by Kruskal-Wallis test.
doi:10.1371/journal.pone.0093784.t004
Discussion

The review suggests a substantial reduction in typhoid intestinal perforation CFR from 39.6% reported from a literature review conducted for years 1960 to 1990 to 15.4% for years 1991 to 2011. The declining CFR trends in Africa and Asia within current review period indicates a gradual fall over the time. Based on a three-decade study, Chatterjee et al noted a declining trend of CFR in hospitalized typhoid perforation cases in India from 47.2% (1966–78) to 17.7% (1981–88) and 7% (1990–98) [9]. Our review denotes that the falling trend of typhoid intestinal perforation CFR is not confined to India, but also evident in other developing countries. As illustrated in the Indian case review mentioned above, improved typhoid perforation management practices over the years may be responsible for the positive effect in reducing the CFR and possibly offsetting increased complications due to multidrug resistance. Improving access to diagnosis, treatment and case management could further contribute to decrease in CFR.

While declining over the last five decades, this review indicates that even today more than one in 10 patients with typhoid intestinal perforation in Africa and Asia will die. The review also implies a high variability of perforation CFR within each of Africa, Asia and other regions; yet African region has significantly higher CFR. Not only people hospitalized for typhoid intestinal perforation seems younger in Africa compared to Asia and other regions, but also appear to stay longer in hospitals for treatment. The review suggests typhoid intestinal perforation occurs most commonly in the second week of illness, and is associated with a high proportion of postoperative complications.

This review has four important global public health implications. First, as noted above, typhoid intestinal perforation CFR is high even today in Africa and Asia, alerting to the importance of typhoid prevention and control activities in those regions. Second, it suggests that there is an opportunity to reduce typhoid intestinal perforation burden by improving access to care and management, such as aggressive resuscitation, better surgical facilities and use of appropriate antibiotics. Third, it implies that a higher morbidity is likely to be shouldered in countries with increased length of hospital stays where younger people are affected. This is based on the fact that these longer hospital stays are associated with more severe disease or complications [6,11,34,37], which also imply higher treatment costs, and greater loss of productivity. Thus morbidity of typhoid could be significant enough to warrant prevention activities in some regions where even if incidence is not that high. Fourth, it provides some basic information needed for estimating disease and economic burden of typhoid in developing countries. The CFR is useful in model based estimation of typhoid intestinal perforation deaths at the country and regional levels. Length of hospital stay is useful in estimating direct medical costs and productivity loss associated with typhoid intestinal perforation. The significant difference in the characteristics of typhoid intestinal perforation between the regions, particularly between Africa and Asia, necessitates the need for separate regional data inputs in modelling the disease and economic burden.

This review also brings out an important research agenda. We noted delayed deaths even beyond six months occurring due to intestinal perforation, particularly as a result of malnutrition. However, most studies did not report follow-up results of patients for a long enough time to properly identify the delayed deaths. It is important to follow-up typhoid intestinal perforation cases for sufficient time to better understand the CFR in future studies.

Most intestinal perforation studies featured in this review are from one of three countries per continent. Nigeria, Pakistan and Turkey over represent Africa, Asia and the other regions, respectively. Thus, the regional average could be influenced by these selected countries in their respective sub-regions: West Africa, the Indian subcontinent and the Middle East. There were only a few studies from other regions which may bias the ability to draw meaningful conclusions due to limited data. The analysis includes only English literature and hence information published in other languages is not represented. This exclusion bias affects data from francophone Africa, from where only a handful of studies were published in English. Twenty three studies published...
in languages other than English were excluded before screening, some of which might have contained data on typhoid intestinal perforation.

Because some studies containing data before and after the 1990 cut-off time point were included in the analysis, it should be noted that some data before the cut-off time (>1990) could have been included in the review. Though these reports did not separate the data by decade, the bulk of the data was within the review period (>1990). For this reason, we feel that the majority of cases reflect the time period of interest.

We may have slightly underestimated the length of hospital stay for intestinal perforation cases. Length of hospital stay could be shorter for those who died due to intestinal perforation than those who survived. Some of the studies presented here do not classify length of stay by survival state and therefore reports are inclusive of those who have died which are likely to be an underestimate.

**Conclusion**

This review estimated an overall average case fatality rate of 15.4% among hospitalized intestinal perforation cases with higher case fatality rates in African region followed by Asia. The results imply that younger people are hospitalized for typhoid intestinal perforation in Africa and remain hospitalized longer compared to Asia and other developing regions. Typhoid prevention activities such as the provision of clean water, sanitation, personal hygiene measures, and vaccination should be prioritized in Africa as well as in Asia to limit number of deaths resulting from typhoid intestinal perforation. We emphasize the need for a regional approach in typhoid research, prevention and control activities. Estimation of regional typhoid disease and economic burden would be valuable in informing resource allocation strategies aimed at preventing and controlling typhoid.

**Supporting Information**

**Checklist S1 PRISMA checklist.** (DOC)

**Acknowledgments**

The authors wish to acknowledge statistical input from Ms. Jihui Lee and review inputs from Drs. Florian Marks, Vera von Kalckreuth and Raul Gomez Roman.

**Author Contributions**

Conceived and designed the experiments: VM TFW. Performed the experiments: VM SND VVM JKP RLO TFW. Contributed reagents/materials/analysis tools: VM SND VVM JKP RLO TFW. Wrote the paper: VM SND JKP VVM RLO TFW.

**References**

1. Bhutta ZA (2006) Current concepts in the diagnosis and treatment of typhoid fever. BMJ 333: 78–82.
2. Crump JA, Lubly SP, Mintz ED (2004) The global burden of typhoid fever. Bull World Health Organization 82: 340–354.
3. Parry CM, Heyen TT, Dougan G, White NJ, Farrar JJ (2002) Typhoid fever. N Engl J Med 347: 1770–1782.
4. WHO (2003) Background document: The diagnosis, treatment and prevention of typhoid fever. World Health Organization. Geneva, Switzerland.
5. Uba AF, Chidran LB, Iwun AM, Mohammed AM (2007) Typhoid intestinal perforation in children: a continuing scourge in a developing country. Pediatr Surg Int 23: 33–39.
6. Rahman GA, Abubakar AM, Johnson AW, Adeniran JO (2001) Typhoid ileal perforation in Nigerian children: an analysis of 106 operative cases. Pediatr Surg Int 17: 620–629.
7. Ameh EA (1999) Typhoid ileal perforation in children: a scourge in developing countries. Ann Trop Paediatr 19: 267–272.
8. Ukwenu AA, Ahmed A, Garba ES (2011) Progress in management of typhoid perforation. Ann Afr Med 10: 259–265.
9. Chatterjee H, Jagdish S, Pai D, Satish N, Jayadev D, et al. (2001) Changing trends in outcome of typhoid ileal perforations over three decades in Pondicherry. Trop Gastroenterol 22: 153–158.
10. Richèn J (1991) Management of bowel perforation in typhoid fever. Trop Doct 21: 149–152.
11. Edino ST, Yakubu AA, Mohammed AZ, Abubakar IS (2009) The range of abdominal surgical reagents/materials/analysis tools: VM SND VVM JKP RLO TFW. Wrote the paper: VM SND JKP VVM RLO TFW.
12. Bhutta ZA, Naqvi SH, Razzaq RA, Farooqui BJ (1991) Multidrug-resistant typhoid in children: presentation and clinical features. Rev Infect Dis 13: 832–836.
13. Misra SB, Breching NJ, Haet CA (1996) Multi-drug resistant typhoid: a global problem. J Med Microbiol 44: 317–319.
14. Bhutta ZA (1996) Impact of age and drug resistance on mortality in typhoid fever. Arch Dis Child 71: 214–217.
15. Adesunkanmi AR, Ajo O (1997) The prognostic factors in typhoid ileal perforation: a prospective study of 50 patients. J R Coll Surg Edinb 42: 395–399.
16. Karmacharya B, Sharma VK (2006) Results of typhoid perforation management: our experience in Bir Hospital, Nepal. Kathmandu Univ Med J (KUMJ) 4: 22–24.
17. Ekenze SO, Okoro PE, Amah CC, Enike HA, Ikefuna AN (2006) Typhoid ileal perforation: analysis of morbidity and mortality in 89 children. Niger J Clin Pract 11: 58–62.
18. Nasir AA, Abdur-Rahman LO, Adeniran JO (2011) Predictor of mortality in children with typhoid intestinal perforation in a Tertiary Hospital in Nigeria. Pediatr Surg Int.
19. van Batenburg JP, Stockenbrugger R (1994) Typhoid perforation. A review of the literature since 1960. Trop Geogr Med 46: 336–339.
20. WorldBank (2011) Country and Lending Groups: by income. World Bank.
21. Glass GV (1976) Primary, Secondary, and Meta-Analysis of Research. Educational Researcher 5: 3–8.
22. Sutton AJ, Abrams KR, Jones DR, Sheldon TA (2000) Methods for Meta-analysis in Medical Research. John Wiley & Sons.
23. Sterne JAC, Harbord RM (2004) Funnel plots in meta-analysis. The Stata Journal 4: 127–141.
24. Kruikal WH, Wallis WA (1952) Use of Ranks in One-Criterion Variance Analysis. Journal of the American Statistical Association 47: 503–521.
25. Spearman C (1904) The proof and measurement of association between two things. Amer J Psychol 15: 72–101.
26. Halley SB, Cummings SR, Browner WS, Grady DG, Newman TB (2007) Designing Clinical Research. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.
27. Talwar S, Ladhina BL, Jain S, Prasad P (1997) Choice of incision in surgical management of small bowel perforations in enteric fever. Trop Gastroenterol 18: 78–79.
28. Talwar S, Sharma RK, Mittal DK, Prasad P (1997) Typhoid enteric perforation. Aust N Z J Surg 67: 351–353.
29. Singh KP, Singh K, Kohli JS (1991) Choice of surgical procedure in typhoid perforation: experience in 42 cases. J Ind Med Assoc 89: 255–256.
30. Shukla VK, Sahoo SP, Chahwan VS, Pandey M, Garna AM (2004) Enteric perforation—single-layer closure. Dig Dis Sci 49: 161–164.
31. Osifo OD, Ogjemwenyi SO (2010) Typhoid ileal perforation in children in Benin city. Afr J Paediatr Surg 7: 96–100.
32. Nuhu A, Dabasa S, Hamea A (2010) Operative management of typhoid ileal perforation in children. Afr J Paediatr Surg 7: 9–13.
33. Abantang FA, Nimako B, Amoah M (2009) The range of abdominal surgical emergencies in children older than 1 year at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. Afr Ann Med 8: 236–242.
34. Tade AO, Ayode BA, Olawoye AA (2004) Pattern of presentation and management of typhoid intestinal perforation in Sagamu, South-West Nigeria: a 15 year study. Niger J Med 17: 387–390.
35. Osun OE, Osifo OD (2007) Pattern and outcome of typhoid perforation in Benin city. Journal of Medicine and Biomedical Research 6: 13–18.
36. Clegg-Lamptey JN, Hodasi WM, Dakubo JC (2007) Typhoid ileal perforation in Ghana: a five-year retrospective study. Trop Doct 37: 231–233.
37. Olubunle-Vyboh M (2007) Postoperative complications after surgery for typhoid ileal perforation in adults in Kumasi, West Afr J Med 26: 32–36.
38. Saxe JM, Cropssey R (2005) Is operative management effective in treatment of perforated typhoid? Am J Surg 189: 342–344.
39. Ugwu BT, Yilok SJ, Kidmas AT, Opulunsa AS (2005) Typhoid intestinal perforation in north central Nigeria. West African journal of medicine 24: 1–6.
40. Edino ST, Mohammed AZ, Uba AF, Sheshe AA, Anumah M, et al. (2004) Typhoid enteric perforation in north western Nigeria. Nigerian journal of medicine: journal of the National Association of Resident Doctors of Nigeria 13: 345–349.
41. Kouame J, Kouadio L, Turquin HT (2004) Typhoid ileal perforation: surgical experience of 64 cases. Acta Chir Belg 104: 445–447.
42. Naaya H, Eni U, Chama C (2004) Typhoid perforation in Maiduguri, Nigeria. Annals of African Medicine 3: 69–72.
43. Agbakwuru EA, Adesunkanmi AR, Fadiora SO, Olayinka OS, Adenomu AO, et al. (2003) A review of typhoid perforation in a rural African hospital. West Afr J Med 22: 22–25.
44. Irabor DO (2003) Fifteen years of typhoid perforation in children in Ibadan: still a millstone around the surgeon’s neck. The Nigerian J Sur Res 5: 92–99.
45. Omegbeyo JA, Daramola OO, Onyegbutulem HC, Balogun WF, Ogundoye OO (2002) Retrospective analysis of typhoid fever in a tropical tertiary health facility. Trop Gastroenterol 23: 9–12.
46. Worku B (2000) Typhoid fever in an Ethiopian children’s hospital: 1984–1995. Ethiop J Health Dev 14: 311–315.
47. Meier DE, Tarpley JL (1998) Typhoid intestinal perforations in Nigerian children. World J Surg 22: 319–323.
48. Nwihuba DA, Ehrabor GE, Akinola DO (1992) Typhoid and paratyphoid fever: a retrospective study. Trop Gastroenterol 13: 56–63.
49. Mock CN, Amaral J, Visser LE (1992) Improvement in survival from typhoid ileal perforation. Results of 221 operative cases. Ann Surg 215: 244–249.
50. Ansari AG, Naqvi SQH, Ghumro AA, Jamali AH, Talpur AA (2009) Management of typhoid ileal perforation: a surgical experience of 44 cases. Gom J Med Sci 7: 27–29.
51. Malik AM, Laghari AA, Mallah Q, Qureshi GA, Talpur AH, et al. (2006) Different surgical options and ileostomy in typhoid perforation. World J Med Sci 1: 112–116.
52. Ahmed MN, Niaz MP, Amin MA, Khan MH, Parhar AB (2006) Typhoid perforation still a common problem: situation in Pakistan in comparison to other countries of low human development. J Pak Med Assoc 56: 230–232.
53. Aziz M, Qadir A, Fainzullah (2005) Prognostic factors in typhoid perforation. J Coll Physicians Surg Pak 15: 704–707.
54. Nguyen QC, Everest P, Tran TK, House D, Murch S, et al. (2004) A clinical, microbiological, and pathological study of intestinal perforation associated with typhoid fever. Clin Infect Dis 39: 61–67.
55. Beniwal US, Jindal D, Sharma J, Jain S, Shyam G (2003) Comparative study of operative procedures in typhoid perforation. Indian J Surg 65: 172–177.
56. Khan A, Khan CH (2000) Typhoid enteric perforation. J Surgery Pakistan 5(2): 37–39.
57. Khan TM, Khan FM, Khan M, Shahabuddin, Khan OA (1997) Experience with typhoid ileal perforation. JPMH 11: 175–181.
58. Gupta V, Gupta SK, Shukla VK, Gupta S (1994) Perforated typhoid enteritis in children. Postgrad Med J 70: 19–22.
59. Sumner A, Kemik O, Dulger AC, Olmez A, Hasirci I, et al. (2010) Outcome of surgical treatment of intestinal perforation in typhoid fever. World J Gastroenterol 16: 4164–4168.
60. Atamanalp SS, Aydilnih B, Ozturk G, Oren D, Bassooglu M, et al. (2007) Typhoid intestinal perforations: twenty-six year experience. World J Surg 31: 1883–1888.
61. Oren A, Dokacu AI, Cigdem MK, Ozturk H, Otcu S, et al. (2002) Factors effecting morbidity in typhoid intestinal perforation in children. Pediatr Surg Int 18: 696–700.
62. Athie CG, Guizar CB, Alcantara AV, Alcaraz GH, Montalvo EJ (1998) Twenty-five years of experience in the surgical treatment of perforation of the ileum caused by Salmonella typhi at the General Hospital of Mexico City, Mexico. Surgery 123: 632–636.
63. Akgun Y, Bac B, Boylu S, Ahan N, Tacyildiz I (1995) Typhoid enteric perforation. Br J Surg 82: 1512–1513.