Management and Outcomes Following Surgery for Gastrointestinal Typhoid

Citation for published version:

Digital Object Identifier (DOI):
10.1007/s00268-018-4624-8

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
World Journal of Surgery

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Abstract

Background Gastrointestinal perforation is the most serious complication of typhoid fever, with a high disease burden in low-income countries. Reliable, prospective, contemporary surgical outcome data are scarce in these settings. This study aimed to investigate surgical outcomes following surgery for intestinal typhoid.

Methods Two multicentre, international prospective cohort studies of consecutive patients undergoing surgery for gastrointestinal typhoid perforation were conducted. Outcomes were measured at 30 days and included mortality, surgical site infection, organ space infection and reintervention rate. Multilevel logistic regression models were used to adjust for clinically plausible explanatory variables. Effect estimates are expressed as odds ratios (ORs) alongside their corresponding 95% confidence intervals.

Results A total of 88 patients across the GlobalSurg 1 and GlobalSurg 2 studies were included, from 11 countries. Children comprised 38.6% (34/88) of included patients. Most patients (87/88) had intestinal perforation. The 30-day mortality rate was 9.1% (8/88), which was higher in children (14.7 vs. 5.6%). Surgical site infection was common, at 67.0% (59/88). Organ site infection was common, with 10.2% of patients affected. An ASA grade of III and above was a strong predictor of 30-day post-operative mortality, at the univariable level and following adjustment for explanatory variables (OR 15.82, 95% CI 1.53–163.57, \(p = 0.021\)).

Conclusions With high mortality and complication rates, outcomes from surgery for intestinal typhoid remain poor. Future studies in this area should focus on sustainable interventions which can reduce perioperative morbidity. At a policy level, improving these outcomes will require both surgical and public health system advances.

Introduction

Typhoid fever is caused primarily by a gram-negative Salmonella enterica species (Salmonella typhi and Salmonella paratyphi). It is commonly transmitted via the faeco-oral route and is epidemic in areas with poor sanitation and limited availability of clean water. One of the common complications of typhoid fever is gastrointestinal perforation, which usually requires emergency surgery [1]. These perforations normally occur in the jejunum or ileum, but there have been several reported cases of colonic and even gallbladder perforations [2]. Perforation typically occurs 2–3 weeks after onset of the disease [3]. The
incidence and outcomes following emergency surgery for typhoid perforation are poorly described with existing studies either single centre or retrospective in nature [4].

The disease is rare in countries with good sanitation, but has continued to be a public health concern in many low- and middle-income countries (LMICs) [5]. The high morbidity and mortality associated with intestinal typhoid is exacerbated by lack of access to medical facilities in remote and rural areas, where delays in presentation can lead to perforation and severe complications in both children and adults [6]. The reported mortality rates in LMICs can be as high as 62–80% and are highest where presentation to medical services is delayed [7, 8]. In survivors of intestinal perforation, there is a high level of morbidity, exerting considerable societal, economic and healthcare burdens.

Difficulties in the prompt diagnosis of typhoid fever serve to compound these issues. The gold standard test for diagnosis of enteric fever is bone marrow culture [9]. Blood cultures to detect S. Typhi and S. Paratyphi are possible, but have a lower sensitivity than bone marrow sampling. Unfortunately, in most LMICs where the disease is endemic, both blood and bone marrow culture are unavailable, unaffordable or not routinely performed [10].

The GlobalSurg Collaborative has demonstrated the feasibility of conducting international high-quality data collection into low-resource centres. This study aimed to investigate surgical outcomes following surgery for gastrointestinal typhoid globally, using an international collaborative research network.

Methods

Study settings

Two international, multicentre, prospective, observational cohort studies were conducted according to pre-specified, published protocols: GlobalSurg 1 between 1 July 2014 and 31 December 2014, and GlobalSurg 2 between 1 January 2016 and 31 July 2016 (NCT02662231 and NCT02179112) [11, 12]. The GlobalSurg group collaborative network methodology has been previously described in detail elsewhere [13]. Local investigators were responsible for ethics or audit registration according to regional or institutional governance protocols. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14].

Patients and procedures

This study is a pre-specified, subgroup analysis of patients who underwent emergency abdominal surgery for typhoid-associated gastrointestinal disease with perforation (including gallbladder). Any hospital providing acute surgical care around the world was eligible to enter patient data. Consecutive patients undergoing emergency (GlobalSurg 1) and emergency or elective (GlobalSurg 2) abdominal surgery were eligible for inclusion. Only patients with intra-operatively, pathologically or microbiologically confirmed typhoid infection were included within this analysis. Patients of any age undergoing surgery by any operative approach (open, laparoscopic and laparoscopic-converted procedures) were eligible for inclusion. Emergency surgery was defined as any unplanned (non-elective) operation, including reoperation after a previous procedure.

Data collection and management

Data were collected on internationally relevant patient, disease and outcome data. This approach aimed to maximise case record completion and data accuracy. Patients were followed up for 30 days after surgery, with the day of surgery taken as day zero [11, 12]. Records were uploaded by local investigators to a secure online website provided using the Research Electronic Data Capture (REDCap) system [15]. The lead investigator at each site was responsible for data accuracy of all cases prior to data submission. Only data with high levels of completeness (> 95%) were accepted for analysis.

Patient variables included demographic details (age, gender, country, diabetes status, smoking status, American Society of Anesthesiologists (ASA) grade), operative details (time to operation, operative approach, WHO safer surgery checklist use, primary procedure performed) and outcomes (30-day mortality, 30-day reintervention, 30-day surgical site infection (SSI) and 30-day organ site infection (OSI) rates). Antibiotic prophylaxis was defined as antibiotics which were administered over the perioperative period, either at induction or during operation prior to opening a contaminated space, or antibiotic therapy that was commenced prior to operation but continued over the perioperative period. Due to the lack of microbiological data and resistance data, it was not feasible to collect data on which antibiotics were administered. As typhoid commonly affects children in low- and middle-income countries and paediatric surgery is commonly performed in separate units, we chose to compare outcomes across children and adults to provide further detail in these groups.

Outcome variables

The primary outcome measure was the 30-day post-operative mortality rate. The secondary outcome measures included the 30-day reintervention rate, the 30-day organ space infection rate and the surgical site infection rate,
during the data collection periods (Fig. 1). Table 1
gical procedure for gastrointestinal typhoid perforation
A total of 88 patients from 11 countries underwent a sur-
Results
Prevention (CDC) definitions for SSI [16].
SSI was defined as one of:
- Purulent drainage from the superficial or deep (fascia or
  muscle) incision but not from within the organ/space
  component of the surgical site;
- At least one of: pain or tenderness; localised swelling;
  redness; heat; fever; and the incision is opened
deliberately or spontaneously dehiscences;
- Abscess within the wound (clinically or radiologically
detected).

Organ space infections were recorded separately and
defined as intra-abdominal/pelvic infections detected clin-
cally/symptomatically, radiologically or intra-operatively.
Online training modules were completed by collaborators
prior to data collection.

Statistical analysis
Data were summarised using simple percentages for cate-
gorical variables, or means for continuous data which had a
parametric distribution. Summary statistical tests for dif-
fences across treatment groups were performed, with the
Chi-square test for categorical data and Kruskal–Wallis for
continuous data. Patient groups were cross-tabulated based
on age, with children being classed as under 16 years of
age and adults 16 and over. Univariable models were
constructed to estimate the effect size of clinically plausi-
ble explanatory variables on 30-day outcomes following
surgery for typhoid perforation. Multilevel models were
then used to create models adjusted for clinically plausible
explanatory variables. These multilevel models adjusted
for the individual patient-level risk (level 1) and then for
country effects (level 2). Effect estimates are presented as
odds ratios, alongside the corresponding 95% confidence
intervals. Statistical significance was taken at the level of
p < 0.05. All analyses were performed in the R statistical
programming program (R Foundation for Statistical Com-
puting, Vienna, AUT) using the Summarizer and Tidyverse
packages.

Results
A total of 88 patients from 11 countries underwent a sur-
gical procedure for gastrointestinal typhoid perforation
during the data collection periods (Fig. 1). Table 1
describes the baseline demographics of included patients.
One patient was included from a high HDI country, two
from middle HDI countries and 85 patients from low HDI
countries. Validation performed in the GlobalSurg 2 data
set demonstrated this approach to have a 93.3% case
ascertainment rate and a high accuracy for categorical
predictors (Cohen’s kappa coefficients > 0.90), continuous
predictors (Pearson’s correlation coefficient 0.99) and
mortality rate (kappa 0.91).

Patient and intervention characteristics
Of the included study population, 54 were over or equal to
16 years of age and 34 were children. The mean age of
adult patients was 31.5 years (SD 16.1) and was predom-
inantly male (68.5 vs. 22.2%). There were a considerable
number of children who underwent surgery for gastroin-
testinal typhoid perforation (N = 34, 38.6%), with a mean
age of 8.2 years (SD 3.8) with equal numbers of males and
females (44.1 vs. 44.1%). Patients were largely healthy
prior to surgery, with minimal comorbidity, and low ASA
grades (61.4% ASA 1–2). Most patients were non-smokers
(N = 74, 84.1%), and diabetes was rare in this patient
cohort (N = 3 3.4%). The majority (N = 61, 69.3%) of
patients were operated upon after 6 h of admission. All
patients underwent open surgery (laparotomy). Sixteen
(18.2%) patients had bowel resection, whilst 55 (62.5%)
were oversewn or closed primarily without resection. The
WHO surgical safety checklist was used in 52 (59.1%)
patients. Patient characteristics are detailed in Table 1 and
operative characteristics in Table 2.

Outcomes following surgery for intestinal typhoid
Outcomes following surgical intervention for typhoid are
detailed in Tables 3, 4 and 5. Out of 88 patients, eight
(9.1%) died within 30 days of surgery. Children had a
higher mortality rate than adults (14.7 vs. 5.6%), which
was not statistically significant (p = 0.146). At the uni-
variable level, an ASA grade of III or above was signifi-
cantly associated with 30-day post-operative mortality (OR
15.40, 95% CI 2.55–296.00, p = 0.013). Use of the WHO
surgical checklist showed a weak association with lower
30-day mortality compared to whether a checklist was
unavailable or was available but was not used (OR 0.28,
95% CI 0.05–1.36, p = 0.112). In the adjusted multilevel
model, gender could not be included as it prevented model
convergence, due to a low event rate in the respective
gender groups. The association between higher mortality
and ASA grade of III or above persisted in the multilevel
model (OR 15.82, 95% CI 1.53–163.57, p = 0.021).

Following surgery for intestinal typhoid, a high surgical
site infection rate was observed at 67.0% (59/88). There
was also a high organ space infection rate at 10.2% (9/88).
Children had a similar rate of SSI to adults (67.6 vs.
66.7%). An ASA grade of III and above was weakly
associated at the univariable level with surgical site
infection (OR 2.31, 95% CI 0.88–6.61, p = 0.099) and
female sex (OR 2.98, 95% CI 1.03–10.01, \( p = 0.056 \)). When explanatory variables were adjusted for in multi-variable analysis, there were no associations between entered explanatory factors and SSI.

**Sensitivity analyses**

We compared the patient characteristics and the outcomes of both the GlobalSurg 1 and GlobalSurg 2 studies (Tables s1 and s2). The event rates of organ space infection (\( p = 0.062 \)) and mortality (\( p = 0.062 \)) were lower in the GlobalSurg 2 study; however, most other characteristics remained comparable.

**Discussion**

This international, multicentre, prospective study has demonstrated substantial post-operative morbidity following surgery for intestinal typhoid. We identified a 30-day post-operative mortality rate of 9.1%, which was higher in children, and a high surgical site infection rate of 67.0%. As typhoid and paratyphoid disproportionately affects patients in LMICs, this high complication rate following surgery has substantial repercussions for both patients and healthcare systems. Concerningly, children appear to have similarly poor outcomes following surgery for typhoid perforation. The incidence of typhoid and paratyphoid is widespread and remains a key public health issue across LMICs [17]. With growing resistance to first-line antimicrobials, surgery for intestinal typhoid is likely to become more common and the healthcare burden of post-operative
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
<th>Child (&lt;16 years) N = 34</th>
<th>Adult (≥16 years) N = 54</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td></td>
<td>8.2 (3.8)</td>
<td>31.5 (16.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>15 (44.1)</td>
<td>37 (68.5)</td>
<td>0.064</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>15 (44.1)</td>
<td>12 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>4 (11.8)</td>
<td>5 (9.3)</td>
<td></td>
</tr>
<tr>
<td>ASA I (Normal/healthy)</td>
<td></td>
<td>9 (26.5)</td>
<td>19 (35.2)</td>
<td>0.257</td>
</tr>
<tr>
<td>II (Mild systemic disease)</td>
<td></td>
<td>8 (23.5)</td>
<td>18 (33.3)</td>
<td></td>
</tr>
<tr>
<td>III (Severe systemic disease)</td>
<td></td>
<td>12 (35.3)</td>
<td>11 (20.4)</td>
<td></td>
</tr>
<tr>
<td>IV (Severe systemic disease, constant threat to life)</td>
<td></td>
<td>2 (5.9)</td>
<td>5 (9.3)</td>
<td></td>
</tr>
<tr>
<td>V (Not expected to survive without the operation)</td>
<td></td>
<td>1 (2.9)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td>34 (100.0)</td>
<td>40 (74.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>0 (0.0)</td>
<td>12 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>0 (0.0)</td>
<td>2 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>34 (100.0)</td>
<td>51 (94.4)</td>
<td>0.162</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>0 (0.0)</td>
<td>3 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>3 (8.8)</td>
<td>5 (9.3)</td>
<td>0.945</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>31 (91.2)</td>
<td>49 (90.7)</td>
<td></td>
</tr>
<tr>
<td>Time to operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=6 h</td>
<td></td>
<td>4 (11.8)</td>
<td>22 (40.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>&gt;6 h</td>
<td></td>
<td>29 (85.3)</td>
<td>32 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Bowel resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>9 (26.5)</td>
<td>13 (24.1)</td>
<td>0.800</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>25 (73.5)</td>
<td>41 (75.9)</td>
<td></td>
</tr>
<tr>
<td>WHO safer surgery checklist used?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, not available</td>
<td></td>
<td>12 (35.3)</td>
<td>10 (18.5)</td>
<td>0.205</td>
</tr>
<tr>
<td>No, but available</td>
<td></td>
<td>5 (14.7)</td>
<td>9 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>17 (50.0)</td>
<td>35 (64.8)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are n (%), unless otherwise indicated. All tests are Chi-square, where a Kruskal–Wallis test has been applied.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Operative characteristics</th>
<th>Child (&lt;16 years) N = 34</th>
<th>Adult (≥16 years) N = 54</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G58 Small bowel: excision of small bowel</td>
<td></td>
<td>5 (14.7)</td>
<td>9 (16.7)</td>
<td>0.272</td>
</tr>
<tr>
<td>G67 Small bowel: other open operations on small bowel</td>
<td></td>
<td>0 (0.0)</td>
<td>2 (3.7)</td>
<td></td>
</tr>
<tr>
<td>G74 Small bowel: formation of ileostomy</td>
<td></td>
<td>2 (5.9)</td>
<td>10 (18.5)</td>
<td></td>
</tr>
<tr>
<td>G784 Small bowel: closure of perforation</td>
<td></td>
<td>25 (73.5)</td>
<td>30 (55.6)</td>
<td></td>
</tr>
<tr>
<td>H06 Colon: extended excision of right hemicolon</td>
<td></td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>H07 Colon: excision of right hemicolon</td>
<td></td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>H15 Colon: formation of any colonic stoma</td>
<td></td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>J23 Gallbladder: other open operations on gall bladder</td>
<td></td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>T28 Abdomen: repair of anterior abdominal wall</td>
<td></td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are n (%), unless otherwise indicated. All tests are Chi-square.
complications will continue to increase [18]. Surgical site infection, for instance, is not only expensive for healthcare systems, but associated with serious complications and longer lengths of stay [19]. In LMICs, prolonged hospital admissions after surgery for typhoid in patients of working age can result in the absence from work and societal commitments, which subsequently impacts on family units and communities. In children, this can mean time away from education, which is particularly important in the context of wider efforts to reduce inequalities in low- and middle-income countries. Patients and families who have lost earnings and are required to pay for a prolonged treatment are at risk of catastrophic impoverishment with dire long-term consequences [20].

We identified high morbidity rates associated with surgery for typhoid perforation. The reasons for this relate to the disease itself, as well patient and broader health system factors. Morbidity rates may reflect international variation in access to care and to supporting resources to enable clinical staff to deliver safe surgery. Several other reasons for this disparity should also be considered. Firstly, lack of timely access to high-quality medical care may lead to delays in presentation leading to more advanced disease requiring surgical care. Secondly, a lack of capacity in surgery and perioperative care in LMIC settings may compound risks of delay in presentation, leading to preventable SSI and death [21]. Lack of appropriate post-operative care, including intensive care facilities, may contribute to this. Finally, shortages of facilities to perform routine microbiological testing may result in ineffectual prophylactic antibiotic usage where antimicrobial resistance exists.

This study employed a multicentre, prospective approach with standardised outcome assessment and definitions. This contrasts with much of the current literature describing outcomes following surgery for intestinal

### Table 3 30-day outcomes

<table>
<thead>
<tr>
<th></th>
<th>Child (≤16 years)</th>
<th>Adult (≥16 years)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (30 days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>29 (85.3)</td>
<td>51 (94.4)</td>
<td>0.146</td>
</tr>
<tr>
<td>Died</td>
<td>5 (14.7)</td>
<td>3 (5.6)</td>
<td></td>
</tr>
</tbody>
</table>

| **Reintervention (30 days)** | | | |
| No                       | 25 (73.5)        | 44 (81.5)         | 0.377   |
| Yes                      | 9 (26.5)         | 10 (18.5)         |         |

| **Surgical site infection (30 days)** | | | |
| No                       | 11 (32.4)        | 18 (33.3)         | 0.924   |
| Yes                      | 23 (67.6)        | 36 (66.7)         |         |

| **Organ space infection (30 days)** | | | |
| No                       | 30 (88.2)        | 48 (88.9)         | 0.684   |
| Yes                      | 4 (11.8)         | 5 (9.3)           |         |
| Missing                  | 0 (0.0)          | 1 (1.9)           |         |

Numbers are n (%), unless otherwise indicated. All tests are Chi-square

### Table 4 Model for 30-day mortality

<table>
<thead>
<tr>
<th></th>
<th>Alive</th>
<th>Died</th>
<th>OR (univariable)</th>
<th>OR (multilevel)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22 (15.2)</td>
<td>27.6 (32)</td>
<td>1.02 (0.98–1.05, p = 0.378)</td>
<td>1.02 (0.98–1.06, p = 0.290)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (65.3)</td>
<td>5 (71.4)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Female</td>
<td>25 (34.7)</td>
<td>2 (28.6)</td>
<td>0.75 (0.10–3.77, p = 0.744)</td>
<td>–</td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under III</td>
<td>55 (68.8)</td>
<td>1 (12.5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>III and above</td>
<td>25 (31.2)</td>
<td>7 (87.5)</td>
<td>15.40 (2.55–296.00, p = 0.013)</td>
<td>14.03 (1.55–127.16, p = 0.019)</td>
</tr>
<tr>
<td><strong>Time to operation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 h</td>
<td>25 (31.6)</td>
<td>1 (12.5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥6 h</td>
<td>54 (68.4)</td>
<td>7 (87.5)</td>
<td>3.24 (0.54–62.28, p = 0.283)</td>
<td>2.46 (0.25–24.36, p = 0.442)</td>
</tr>
<tr>
<td><strong>WHO safer surgery checklist used?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, not available</td>
<td>18 (22.5)</td>
<td>4 (50.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No, but available</td>
<td>13 (16.2)</td>
<td>1 (12.5)</td>
<td>0.35 (0.02–2.69, p = 0.367)</td>
<td>0.51 (0.04–6.69, p = 0.611)</td>
</tr>
<tr>
<td>Yes</td>
<td>49 (61.3)</td>
<td>3 (37.5)</td>
<td>0.28 (0.05–1.36, p = 0.112)</td>
<td>0.36 (0.06–2.12, p = 0.259)</td>
</tr>
<tr>
<td><strong>Antibiotic prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8 (100.0)</td>
<td>0 (0.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yes</td>
<td>72 (90.0)</td>
<td>8 (100.0)</td>
<td>12,849,865.87 (0.00-NA, p = 0.994)</td>
<td>–</td>
</tr>
</tbody>
</table>

Univariable and multilevel models for 30-day mortality. Effect estimates are presented as odds ratios (ORs) alongside the corresponding 95% confidence interval

World J Surg
typhoid, which are retrospective in nature. Our study found markedly higher complication rates compared to the current literature, with a surgical site infection between 20 and 40% higher than those previously reported. This is likely due to the prospective nature of our study and the fact that validated outcome definitions were employed for the diagnosis of SSI, and all collaborators were trained in SSI assessment using online quality assurance modules. Much of the current evidence is also single centre in nature, which may reduce its applicability and generalisability across already diverse LMIC populations. In contrast to this, our study included patients across 15 countries, capturing practice in a variety of settings. One notable aspect of this study is the variety of presentations captured, including a case of gallbladder typhoid requiring cholecystectomy. Gallbladder typhoid has previously been reported and is famously associated with ‘Typhoid Mary’, an American cook who was found to be an asymptomatic carrier of typhoid, with bacteria residing in her gallbladder [22].

Although the collaborative research methodology employed by this study has been characterised elsewhere in detail, this study to our knowledge is the first to use such an approach to study complications of communicable disease. Our study has shown such data can be collected accurately and reliably, demonstrated by validation which has found the data set to be 93.3% accurate. Collaborative working enables additional resources and research infrastructure to be made available in settings where resources may be otherwise limited.

There are several limitations which must be considered when interpreting the results of this study. The sample size is small, although 88 patients undergoing surgery are a large series of intestinal typhoid compared with the existing literature. Secondly, this is a study which pools together data from two of the GlobalSurg studies. A period of 12 months exists between the first and second GlobalSurg study, which may lead to a temporal bias from trends in typhoid incidence. However, in sensitivity analyses comparing both studies limited differences were seen. We did not collect data surrounding the serotype or other specific microbiological parameters of typhoid or paratyphoid as doing so would have been impractical within the confines of this study and limited access to diagnostic resources in included settings. This therefore made it impractical to collect information on antibiotic therapy, including type of antibiotics and administration patterns, as without knowing which bacteria are likely to be present it would not be possible to estimate whether this was appropriately targeted. Finally, as this study was purely observational in nature no causative inference can be drawn between factors associated with outcomes in this study.

Surgery for typhoid is accompanied by substantial morbidity and disproportionately affects a young LMIC population, as reported in the previous studies [4, 21, 23]. Subsequently, funders and policymakers should identify means of reducing the overall burden of morbidity and impact of typhoid upon communities. This should aim to address three key areas: disease prevention, access to prompt surgical care and on improving outcomes. Children are a key group who we have demonstrated to have high mortality rates, and improving outcomes in this group should be a priority. Prevention of typhoid through improved sanitation and vaccination programmes should continue and efforts increased. Improving access to healthcare, particularly surgical care, at an earlier time in the disease process should be a priority. Future research should

### Table 5 Model for 30-day surgical site infection

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
<th>OR (univariable)</th>
<th>OR (multilevel)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.9 (16)</td>
<td>22.3 (17.8)</td>
<td>1.00 (0.97–1.03, p = 0.889)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (80.8)</td>
<td>31 (58.5)</td>
<td>–</td>
</tr>
<tr>
<td>Female</td>
<td>5 (19.2)</td>
<td>22 (41.5)</td>
<td>2.98 (1.03–10.01, p = 0.056)</td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under III</td>
<td>22 (75.9)</td>
<td>34 (57.6)</td>
<td>–</td>
</tr>
<tr>
<td>III and above</td>
<td>7 (24.1)</td>
<td>25 (42.4)</td>
<td>2.31 (0.88–6.61, p = 0.099)</td>
</tr>
<tr>
<td><strong>Time to operation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 h</td>
<td>10 (35.7)</td>
<td>16 (27.1)</td>
<td>–</td>
</tr>
<tr>
<td>&gt;6 h</td>
<td>18 (64.3)</td>
<td>43 (72.9)</td>
<td>1.49 (0.56–3.90, p = 0.415)</td>
</tr>
<tr>
<td><strong>WHO safer surgery checklist used?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, not available</td>
<td>9 (31.0)</td>
<td>13 (22.0)</td>
<td>–</td>
</tr>
<tr>
<td>No, but available</td>
<td>5 (17.2)</td>
<td>9 (15.3)</td>
<td>1.25 (0.32–5.22, p = 0.755)</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (51.7)</td>
<td>37 (62.7)</td>
<td>1.71 (0.59–4.84, p = 0.313)</td>
</tr>
<tr>
<td><strong>Antibiotic prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (10.3)</td>
<td>5 (8.5)</td>
<td>–</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (89.7)</td>
<td>54 (91.5)</td>
<td>1.25 (0.24–5.48, p = 0.775)</td>
</tr>
</tbody>
</table>

Univariable and multilevel models for 30-day mortality. Effect estimates are presented as odds ratios (ORs) alongside the corresponding 95% confidence interval.
focus on identifying durable vaccinations for typhoid, addressing inequalities in access to health care and reducing morbidity rates following surgery for typhoid. Addressing these issues is particularly important, as resistance to antimicrobial agents is increasing. Preventing typhoid will reduce antibiotic usage and preserve current antibiotics for use in severe cases.

Summary and recommendations

1. Surgery for typhoid is accompanied by substantial morbidity LMIC population as reported in previous studies. Almost half of the included study population were children, who similarly high mortality rates and morbidity rates.

2. Funders and policymakers should identify means of reducing the overall burden of morbidity and impact of typhoid upon communities. This should aim to address three key areas: sanitation, vaccination and access to prompt surgical care.

3. Focus should shift to prevention of typhoid through improved sanitation and vaccination programmes. This approach has had great successes recently, with the eradication of smallpox and polio. Preventing typhoid will reduce the number of patients requiring operation and ensure patients can enjoy fewer absences at work or school. Improving access to health care, particularly surgical care, at an earlier time in the disease process should be a priority. Doing so will enable patients with typhoid to present to health care earlier point in their disease process where antibiotic therapy may be more effective and an operation avoided. Addressing these issues is particularly important, as resistance to antimicrobial agents is increasing. Delivery of non-antibiotic means of preventing typhoid will reduce antibiotic usage and preserve current antibiotics for use in severe cases.

4. Future research should focus on identifying means of reducing morbidity in patients undergoing surgery for typhoid perforation, in particular reducing the incidence of surgical site infection. Further trials should attempt to identify the optimal skin preparation agent, the role of antibiotic prophylaxis and whether the use of laparoscopy may reduce infection rates after surgery for typhoid perforation.

Acknowledgements

Organisations assisting in dissemination and/or translation (alphabetical): Asian Medical Students’ Association (AMSA), Association of Surgeons in Training (ASIT), College of Surgeons of East, Central and Southern Africa (COSECSA), Cutting Edge Manipal, Egyptian Medical Student Research Association (EMRA), International Collaboration For Essential Surgery (ICES), International Federation of Medical Student Associations (IFMSA), Italian Society of Colorectal Surgery (SICCR), Lifebox Foundation, School of Surgery, Student Audit and Research in Surgery (STARSurg), The Electives Network, United Kingdom National Research Collaborative, World Society of Emergency Surgery (WSES), World Surgical Association (WSA).

Writing group: Theophilus TK Anyomih, Thomas M Drake, James Glasbey, J Edward Fitzgerald, Rinu Otis, Ewen M Harrison, Stephen Tabiri (Overall guarantor).


Collaborators

GlobalSurg

National leads

Nigeria, A. O. Ademuyiwa (Nigeria); Ghana, S. Tabiri; India, Cutting Edge Manipal, M. Mohan; Sri Lanka, J. Jayakumar

Local Collaborators

Bangladesh: Ashrarur Rahman Mitul, Khalid Mahmud (Dhaka Shishu (Children) Hospital), Margub Hussain, Haziz Hakim, Tapan Kumar (Dhaka Medical College Hospital), Antje Oosterkamp (Lamb Hospital).

India: Francis Abantanga, Kwaku Boakye-Yiadom, Mohammed Bukari (Komfo Anokye Teaching Hospital), Frank Owusu (Offinso District Hospital), Joseph Awuku-Asabre, Stephen Tabiri, Lemuel Davies Bray (University For Development Studies, School of Medicine and Health Sciences, General Surgery Department, Tamale Teaching Hospital).

Ghana: SS Prasad, Anand Kirishnan, Nidhi Gyanchandani (KMC Hospital), Byalapudi Seshu Kumar, Muthukumararan Rangarajan (Kovai Medical Centre and Hospital), Sriram Bhat, Anjana Sreedhuran, S.V. Kinmera (Kasturba Medical College), Yella Reddy, Caran Venu-gopal, Sunil Kumar (PES Institute of Medical Sciences & Research), Abhishek Mittal (Safdarjung Hospital, New Delhi), Shrvan Nad-kami, Harish Neelamraju Lakshmi, Puneet Malik (Sawai Man Singh Medical College & Hospitals, Jaipur, Rajasthan), Neel Limaye, Srivinas Pai, Pratik Jain (SDM College of Medical Sciences and Hospital), Monty Khajanchi, Savni Satoskar, Rajeev Satoskar (Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital), Abid Bin Mahamood (Travancore Medical College Hospital).

Malawi: Ross Coomber, Kenneth Johnson, Jennifer Nowers (Queen Elizabeth Hospital).

Nigeria: Aminu Mohammad, Lofto-John Anyanwu, Abdulrahman Sheshe (Aminu Kano Teaching Hospital), Alaba Adesina, Olubukola Faturoni, Ogechukwu Taiwo (Babcock University Teaching Hospital), Muhammad Habib Ibrahim, Abdulrasheed A Nasir, Siyaka Iroha Suleiman (Federal Medical Centre, Birnin Kebbi), Adewale Adeniyi, Opeoluwa Adesanya, Ademola Adebanjo (Federal Medical Centre), Omolara Williams, Kazeem Atobatele, Ayokunle Ogunyemi, Mobolaji Oludara, Olabode Oshodi, Roland Osoji (Lagos State University Teaching Hospital) (Lagos State University Teaching Hospital), Adesoji Ademuyiwa, AbdullRazzaq Oluwagbemiga Lawal, Felix

Acknowledgements

Funded by DFID-MRC-Wellcome Trust Joint Global Health Trial Development Grant (MR/N022114/1) and a National Institute of Health Research (NIHR) Global Health Research Unit Grant (NIHR 17-0799). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.
Alakaloko, Olumide Elebute, Adedapo Osinowo, Christopher Bod-\(\text{e}(\text{Lagos University Teaching Hospital}), \text{Abidemi Adesuyi (National Hospital Abuja), Adesoji Tade, Adeleke Adekoya, Collins Nwokoro (Olubisi Onabanjo University Teaching Hospital)}, \text{Omobolaji O A. \text{Ayandipo, Taiwo Akeem Lawal, Akinlabi A. Aja (University College Hospital), Samuel Sani Ali, Babatunde Odeyemi, Samson Olori (University of Abuja Teaching Hospital), Ademola Popoola, Ademola Adeyeye, James Adeniran (University of Ilorin Teaching Hospital).}

Pakistan: \text{Kamran Faisal Bhopal}, Zainab Ifikhar, Muhammad Mohsin Furqan (Bahawal Victoria Hospital), Bakhtir Nighat, Masood Jawaid, Abdul Khalique (Dow University Hospital), Ahsan Zil-E-Ali, Anam Rashid (Fatima Memorial Hospital), Hasnain Abbas Dharmashi, Tahira Naqvi, Ahmad Faraz (Karachi Medical and Dental College, Abbasi Shaheed Hospital), Abdul Wahid Anwar, Taher Muhammad Yaseen, Ghina Shamim Shamsi, Ghina Shamsi, Taher Yaseen, Wahid Anwer (the Indus Hospital).

Sri Lanka: Prasad Pitigala Arachchi, Wanigasekara Senanayake Mudiyanelage Kithsiri Janakantha Senanayake, Lalith Asanka Jayasooriya Jayasooriya Arachchige (Department of General Surgery, Teaching Hospital Kandy), Sivasuriya Sivaganesha, Dulan Irusha Samaraweera, Vimalakanthan Thanusun (National Hospital of Sri Lanka).

Global Surg 2

Local Collaborators

Benin: Lawani Ismail; Ghana, Stephen Tabiri; Malaysia, Yong Yong Tew; Nigeria, Adesoji O Ademuyiwa; Pakistan, Tanzeela Gala

Benin: Fernande Djivoh, Lawani Ismail, Francis Dossou (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Djidjor Moti Selo, Dansou Gaspard Gbessi, Bruno Noupouzonkou, Yacouboj Moumou Souaibou, (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Kpemahouo Renen Keke, Fred Hodonou (Clinique Vignon), Ernest Yemalin Stephane Ahou-Zahid Syibrah (Hospital Keningau); Pui Xin Chin, Afizah Salleh, Nurul ‘Ain Wan Mohd Nasir, Pigeneswaren Yoganathan, (Hospital Keningau); Eu Xian Lee, Jian Er Saw, Li Jing Yeang, Pei Ying Koh, Muhammad (Aminu Kano Teaching Hospital); Samson Olori, Philip Mshelbwala, Babatunde Odeyemi, Garba Samson, Oyediran Kehinde (University of Abuja Teaching Hospital); Anthony Ajiboye, Ademola Adeyeye (University of Ilorin Teaching Hospital); Stephen Kache, Jonathan Ajah, Jerry Makama (Barau Dikko Teaching Hospital, Kaduna State University, Kaduna); Ahmed Adamu, Suleiman Baba, Mohammad Aliyu, Shamsudeen Aliyu, Afikyu Ukwenya, Halima Aliyu, Tunde Sholadoye, Mohammad Danijan, Oluseyi Ogunsua (Abdułły Bello University Teaching Hospital Zaria); Loify John Anyanwu, Abdurrahman Sheshe, Aminu Mohammad (Aminu Kano Teaching Hospital); Samson Olori, Philip Mshelbwala, Babatunde Odeyemi, Garba Samson, Oyediran Kehinde (University of Ilorin Teaching Hospital); Anthony Ajiboye, Ademola Adeyeye, Isaac Amole, Olajide Abiola, Akin Olaolorun ( Bowen University Teaching Hospital);

Pakistan: Najia Nadeem, Muhammad Saqlain (Allied Hospital, Faisalabad); Jibrar Abbasy, Abdul Rehman Alvi, Tanzeela Gala, Noman Shahzad (Aga Khan University); Kamran Faisal Bhopal, Zainab Ifikhar, Muhammad Talha Butt, Syed Asaar ul Raz, Asdaq Ahmed, Ali Khan Niazi (Bahawal Victoria Hospital); Ibrahim Raza, Fatima Baluch, Ahmed Raza, Ahmad Bani-Sadar, Ahmad Uzair Ahmed, Muhammad Adil, Awaiz Raza, (King Edward Medical University, Mayo Hospital, Lahore); Mahmood Javaid, Muhammad Waqar, Maryam Ali Khan (CMH Lahore Medical and Dental College); Mohammad Mohsin Arshad, Mohammadamish Anjai (Nishtar Medical College and Hospital).

Nigeria: Akinlabi Aja, Omobolaji Ayandipo, Taiwo Lawal, Adebisi Abdurrzzaaq, (University College Hospital, Ibadan);

Global Surg 2

Local Collaborators

Benin: Lawani Ismail; Ghana, Stephen Tabiri; Malaysia, Yong Yong Tew; Nigeria, Adesoji O Ademuyiwa; Pakistan, Tanzeela Gala

Benin: Fernande Djivoh, Lawani Ismail, Francis Dossou (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Djidjor Moti Selo, Dansou Gaspard Gbessi, Bruno Noupouzonkou, Yacouboj Moumou Souaibou, (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Kpemahouo Renen Keke, Fred Hodonou (Clinique Vignon), Ernest Yemalin Stephane Ahou-Zahid Syibrah (Hospital Keningau); Pui Xin Chin, Afizah Salleh, Nurul ‘Ain Wan Mohd Nasir, Pigeneswaren Yoganathan, (Hospital Keningau); Eu Xian Lee, Jian Er Saw, Li Jing Yeang, Pei Ying Koh, Muhammad (Aminu Kano Teaching Hospital); Samson Olori, Philip Mshelbwala, Babatunde Odeyemi, Garba Samson, Oyediran Kehinde (University of Abuja Teaching Hospital); Anthony Ajiboye, Ademola Adeyeye, Isaac Amole, Olajide Abiola, Akin Olaolorun ( Bowen University Teaching Hospital);

Pakistan: Najia Nadeem, Muhammad Saqlain (Allied Hospital, Faisalabad); Jibrar Abbasy, Abdul Rehman Alvi, Tanzeela Gala, Noman Shahzad (Aga Khan University); Kamran Faisal Bhopal, Zainab Ifikhar, Muhammad Talha Butt, Syed Asaar ul Raz, Asdaq Ahmed, Ali Khan Niazi (Bahawal Victoria Hospital); Ibrahim Raza, Fatima Baluch, Ahmed Raza, Ahmad Bani-Sadar, Ahmad Uzair Ahmed, Muhammad Adil, Awaiz Raza, (King Edward Medical University, Mayo Hospital, Lahore); Mahmood Javaid, Muhammad Waqar, Maryam Ali Khan (CMH Lahore Medical and Dental College); Mohammad Mohsin Arshad, Mohammadamish Anjai (Nishtar Medical College and Hospital).

Nigeria: Akinlabi Aja, Omobolaji Ayandipo, Taiwo Lawal, Adebisi Abdurrzzaaq, (University College Hospital, Ibadan);

Global Surg 2

Local Collaborators

Benin: Lawani Ismail; Ghana, Stephen Tabiri; Malaysia, Yong Yong Tew; Nigeria, Adesoji O Ademuyiwa; Pakistan, Tanzeela Gala

Benin: Fernande Djivoh, Lawani Ismail, Francis Dossou (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Djidjor Moti Selo, Dansou Gaspard Gbessi, Bruno Noupouzonkou, Yacouboj Moumou Souaibou, (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Kpemahouo Renen Keke, Fred Hodonou (Clinique Vignon), Ernest Yemalin Stephane Ahou-Zahid Syibrah (Hospital Keningau); Pui Xin Chin, Afizah Salleh, Nurul ‘Ain Wan Mohd Nasir, Pigeneswaren Yoganathan, (Hospital Keningau); Eu Xian Lee, Jian Er Saw, Li Jing Yeang, Pei Ying Koh, Muhammad (Aminu Kano Teaching Hospital); Samson Olori, Philip Mshelbwala, Babatunde Odeyemi, Garba Samson, Oyediran Kehinde (University of Abuja Teaching Hospital); Anthony Ajiboye, Ademola Adeyeye, Isaac Amole, Olajide Abiola, Akin Olaolorun ( Bowen University Teaching Hospital);

Pakistan: Najia Nadeem, Muhammad Saqlain (Allied Hospital, Faisalabad); Jibrar Abbasy, Abdul Rehman Alvi, Tanzeela Gala, Noman Shahzad (Aga Khan University); Kamran Faisal Bhopal, Zainab Ifikhar, Muhammad Talha Butt, Syed Asaar ul Raz, Asdaq Ahmed, Ali Khan Niazi (Bahawal Victoria Hospital); Ibrahim Raza, Fatima Baluch, Ahmed Raza, Ahmad Bani-Sadar, Ahmad Uzair Ahmed, Muhammad Adil, Awaiz Raza, (King Edward Medical University, Mayo Hospital, Lahore); Mahmood Javaid, Muhammad Waqar, Maryam Ali Khan (CMH Lahore Medical and Dental College); Mohammad Mohsin Arshad, Mohammadamish Anjai (Nishtar Medical College and Hospital).

Nigeria: Akinlabi Aja, Omobolaji Ayandipo, Taiwo Lawal, Adebisi Abdurrzzaaq, (University College Hospital, Ibadan);

Global Surg 2

Local Collaborators

Benin: Lawani Ismail; Ghana, Stephen Tabiri; Malaysia, Yong Yong Tew; Nigeria, Adesoji O Ademuyiwa; Pakistan, Tanzeela Gala

Benin: Fernande Djivoh, Lawani Ismail, Francis Dossou (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Djidjor Moti Selo, Dansou Gaspard Gbessi, Bruno Noupouzonkou, Yacouboj Moumou Souaibou, (Centre National Hospitalier Et Universitaire Hubert Koutoukou Maga); Kpemahouo Renen Keke, Fred Hodonou (Clinique Vignon), Ernest Yemalin Stephane Ahou-Zahid Syibrah (Hospital Keningau); Pui Xin Chin, Afizah Salleh, Nurul ‘Ain Wan Mohd Nasir, Pigeneswaren Yoganathan, (Hospital Keningau); Eu Xian Lee, Jian Er Saw, Li Jing Yeang, Pei Ying Koh, Muhammad (Aminu Kano Teaching Hospital); Samson Olori, Philip Mshelbwala, Babatunde Odeyemi, Garba Samson, Oyediran Kehinde (University of Abuja Teaching Hospital); Anthony Ajiboye, Ademola Adeyeye, Isaac Amole, Olajide Abiola, Akin Olaolorun ( Bowen University Teaching Hospital);

Pakistan: Najia Nadeem, Muhammad Saqlain (Allied Hospital, Faisalabad); Jibrar Abbasy, Abdul Rehman Alvi, Tanzeela Gala, Noman Shahzad (Aga Khan University); Kamran Faisal Bhopal, Zainab Ifikhar, Muhammad Talha Butt, Syed Asaar ul Raz, Asdaq Ahmed, Ali Khan Niazi (Bahawal Victoria Hospital); Ibrahim Raza, Fatima Baluch, Ahmed Raza, Ahmad Bani-Sadar, Ahmad Uzair Ahmed, Muhammad Adil, Awaiz Raza, (King Edward Medical University, Mayo Hospital, Lahore); Mahmood Javaid, Muhammad Waqar, Maryam Ali Khan (CMH Lahore Medical and Dental College); Mohammad Mohsin Arshad, Mohammadamish Anjai (Nishtar Medical College and Hospital).

Nigeria: Akinlabi Aja, Omobolaji Ayandipo, Taiwo Lawal, Adebisi Abdurrzzaaq, (University College Hospital, Ibadan);
(Komfo Anokye Teaching Hospital), Paul Wondoh (Upper West Regional Hospital).

Nigeria: Danjuma Sale (Barau Dikko Teaching Hospital), Lawal Abdullahi (Kano Aminu), Olabisi Osagie (University of Abuja Teaching Hospital), Omolara Faboya (Lagos Lasuth), Adedeji Fatuga (Lagos Luth), Agboola Taiwo (Babcock University Teaching Hospital), Emeka Nwabuoku (Ahmadu Bello University Teaching Hospital).

Pakistan: Zain Ali Khan (Bahawal Victoria Hospital, Bahawalpur).

Rwanda: Jennifer Rickard (Centre Hospitalier Universitaire De Kigali).

Malaysia: Choy Ling Tan (Hospital Sultanah Aminah), Jia Yng Siaw (Hospital Sibu), Sir Young Yam (Penang Medical College), Ling Wilson (Sarawak General Hospital), Mohamed Rezal Abdul Aziz (University Malaya Medical Centre).

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

marrow, and rose-spot cultures for recovery of salmonella typhi in typhoid fever. Lancet 305:1211–1213