

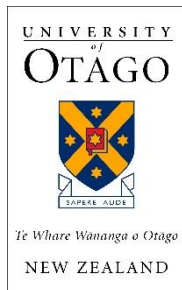
# Complications and mortality of typhoid fever: a global systematic review and meta-analysis

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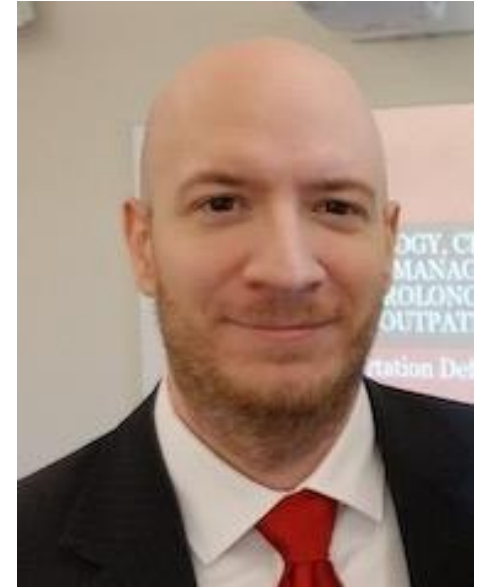
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# Personnel

- **Christian Marchello, PhD**
  - Review lead
  - Developed protocol
  - Screened and abstracted data
  - Main manuscript draft
- **Megan Birkhold, MD**
  - Second reviewer
  - Substantial contributions to manuscript drafts
- **John Crump, MB ChB, MD, DTM&H**
  - Conceptualized study
  - Third reviewer for conflict resolution and editing of manuscript drafts



# Background

- ***Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella* Typhi)**
  - **Symptoms: fever  $\geq 3$  days, headache, malaise, and vomiting**
- **Primary mode of transmission: fecally contaminated food and water**
- **Management and control through antimicrobials, sanitation, and vaccines**

# Background continued...

- **‘Gold standard’ diagnostic method is the culture of blood, bone marrow, or another normally sterile site**
  - **Clinical microbiology services are not widely available in endemic areas**
  - **Culture-based diagnosis has incomplete sensitivity (50-60%)**
- **Delays in diagnosis and treatment occur as a result of barriers to care, such as difficulty accessing tertiary facilities because of delayed referral, distance, and the cost of healthcare**
- **Timely and accurate diagnosis and treatment of typhoid fever in the community is needed to avert complications requiring hospitalization and prevent death**
- **Known complications: typhoid intestinal perforation (TIP), gastrointestinal hemorrhage, hepatitis, cholecystitis, myocarditis, shock, encephalopathy, pneumonia, and anemia**

# Goal

- **To support country-level decisions on typhoid control and to provide contemporary estimates of morbidity and mortality for typhoid fever**

# Methods: study selection

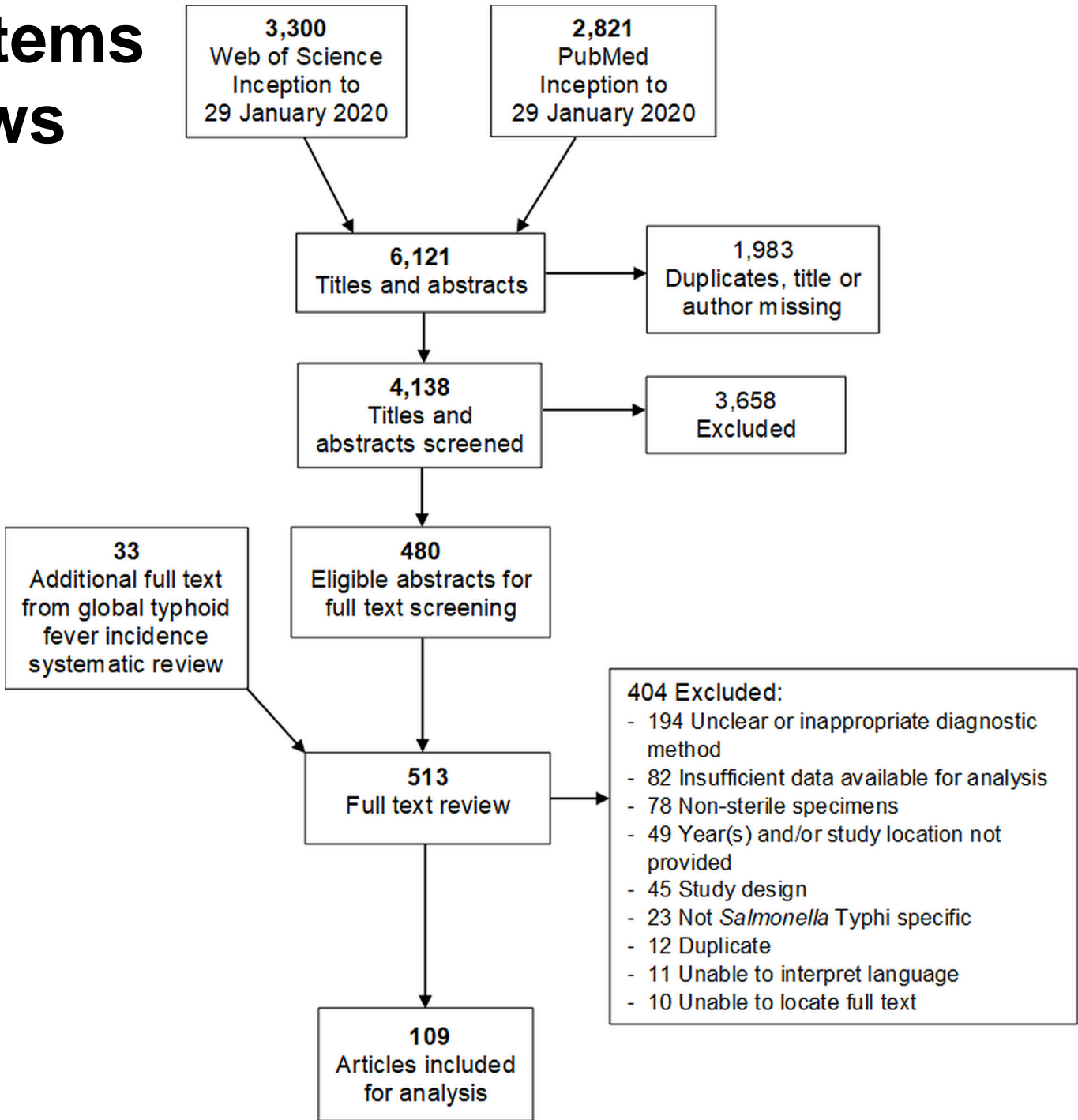
**Databases: PubMed and Web of Science searched for articles published from 1 January 1980 through 29 January 2020. No restrictions for age of population, country, or language.**

- **‘Non-surgical studies’ reporting the proportion of participants with *Salmonella* Typhi infection who had typhoid-associated complications or who died**
  - **Ascertained by culture of a normally sterile site (e.g., blood)**
- **Surgical studies of patients with intestinal perforation**
  - **Gross intraoperative findings contained the keywords ‘terminal ileum,’ ‘antimesenteric perforation,’ or ‘confirmed at laparotomy’ to assign perforations as TIP**
  - **Postoperative criteria including the use of histopathology stains or immunohistochemistry**

# Methods: abstraction and analysis

- **Two investigators independently:**
  - Reviewed studies to meet inclusion criteria
  - Abstracted study characteristics, proportion data (CFR and prevalence of complications), and delay in care
- **Study quality:**
  - Stratifying non-surgical and surgical analyses, and by region, sub-region, age, and study recruitment setting
  - Heterogeneity using  $I^2$
- Proportions were compared by  $X^2$  test, means by t-test, and the relationship between delay in care and CFR by Pearson's correlation coefficient ( $r$ ), in R version 4.0.2

# Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)





# Results

- **Among the 109 articles, one (0.9%) collected data in 5 countries, resulting in 113 study sites**
  - **84 (74.3%) non-surgical sites of typhoid fever participants**
  - **29 (25.7%) were surgical sites of TIP**
- **Data were collected from 1965 through 2018**
- **Among 84 non-surgical studies:**
  - **14,007 confirmed cases - median (IQR) of 64 (25-190) cases per study**
  - **70 (83.3%) hospital-based with 12,889 (92.0%) cases**
  - **14 (16.7%) community-based with 1,118 (8.0%) cases**

# **Results: typhoid fever complications**

- **There were 2,719 (26.3%) complication events among 10,335 cases of confirmed typhoid fever**
- **Two most prevalent complications:**
  - **Delirium: 705 (26.6%) of 2,648 confirmed cases**
  - **Anemia in 1,017 (21.4%) of 4,756 confirmed cases**
- **Severe complications:**
  - **TIP: 80 (1.3%) of 6,064 confirmed cases**
  - **Gastrointestinal hemorrhage: 119 (3.1%) of 3,868 confirmed cases**

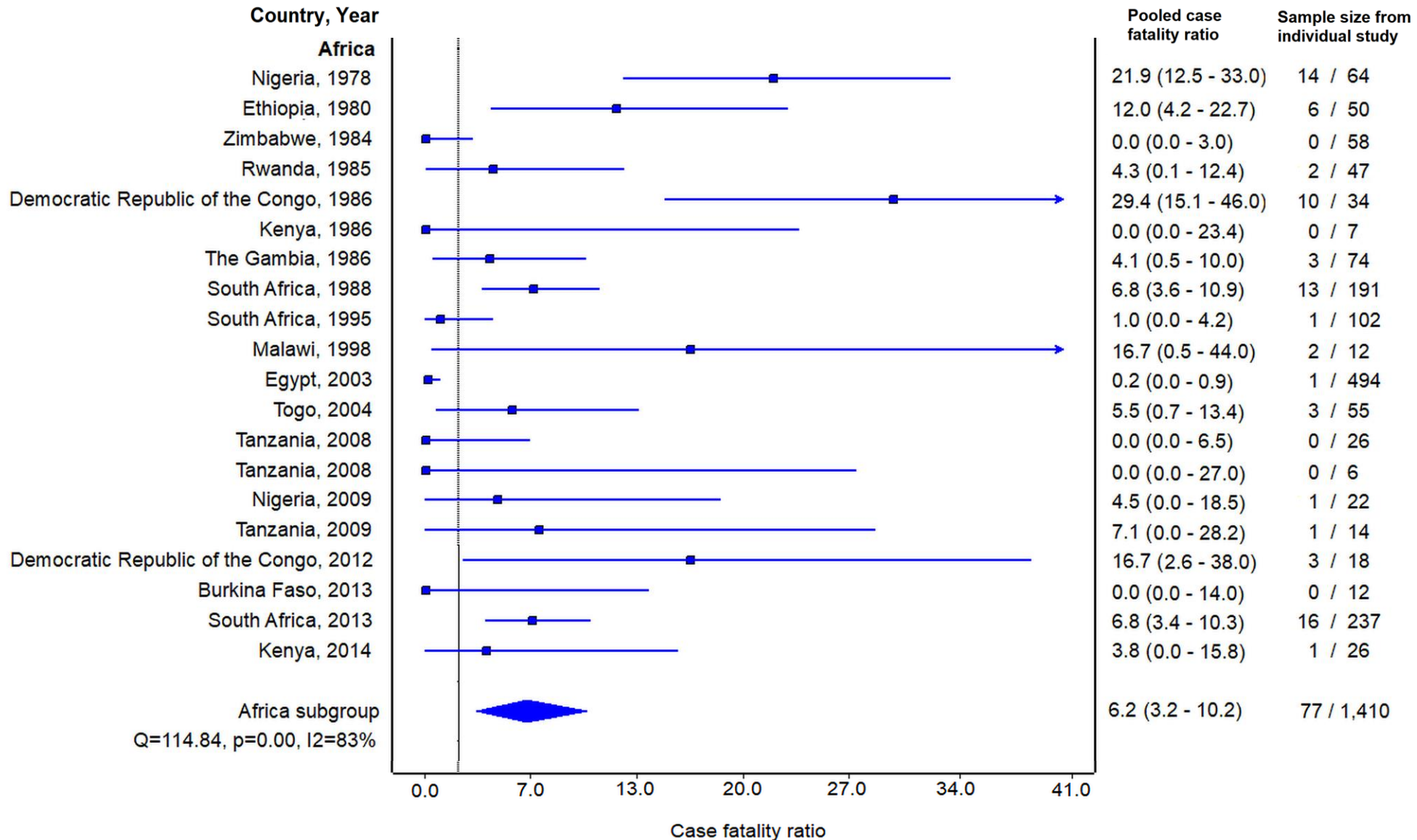
# Results: outcomes of typhoid intestinal perforation

- **2,971 TIP cases**
  - **2,921 (98.3%) from surgical studies**
  - **50 (1.7%) from non-surgical studies**
- **TIP in Asia**
  - **46 (4.6%) of 999 TIP cases died**
  - **Median (IQR) CFR of TIP across 12 studies was 1.0% (0.0-8.4%)**
- **TIP in Africa**
  - **387 (19.7%) of 1,967 TIP cases died**
  - **Median (IQR) CFR of TIP across 23 studies was 20.0% (13.7-28.0%)**

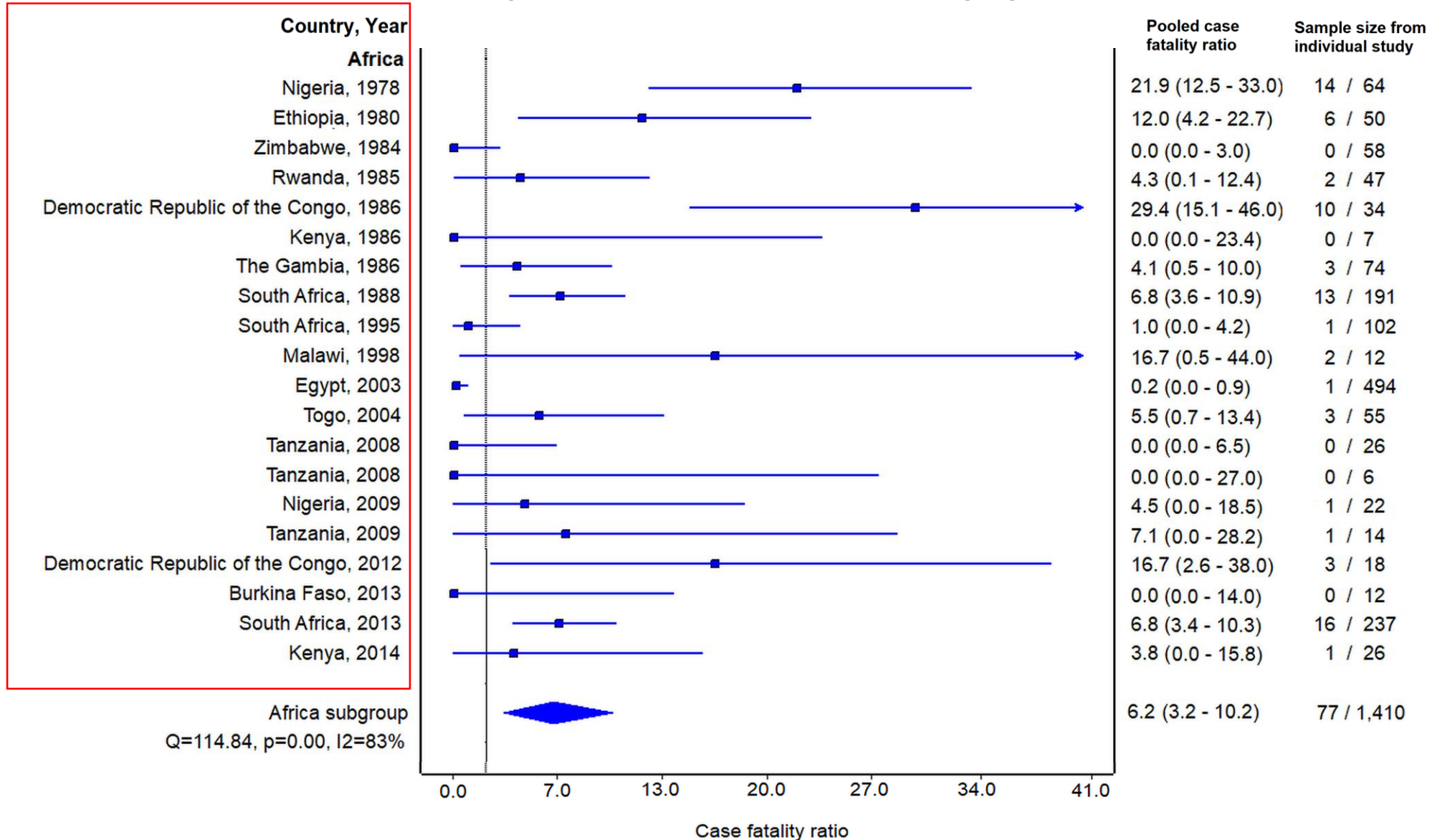
# Results: typhoid fever mortality

- Among 13,303 confirmed typhoid cases from studies reporting mortality, 250 died, for a CFR of 1.9%
- Pooled CFR (95% CI) estimate: 2.0% (1.4-2.8%)
  - Oceania 7.2% (0.0-20.4%) – 2 studies
  - Americas 6.7% (0.0-19.9%) – 3 studies
  - Africa 5.4% (2.7-8.9%) – 22 studies
  - Europe 1.0% (0.0-6.8%) – 1 study
  - Asia 0.9% (0.6-1.3%) – 51 studies
- When stratified by hospital and non-hospital studies:
  - No deaths among 866 confirmed typhoid cases in 12 non-hospital sites
  - 250 deaths (2.0%) among 12,437 hospital-based confirmed cases ( $\chi^2=16.7$ ;  $p<0.01$ )

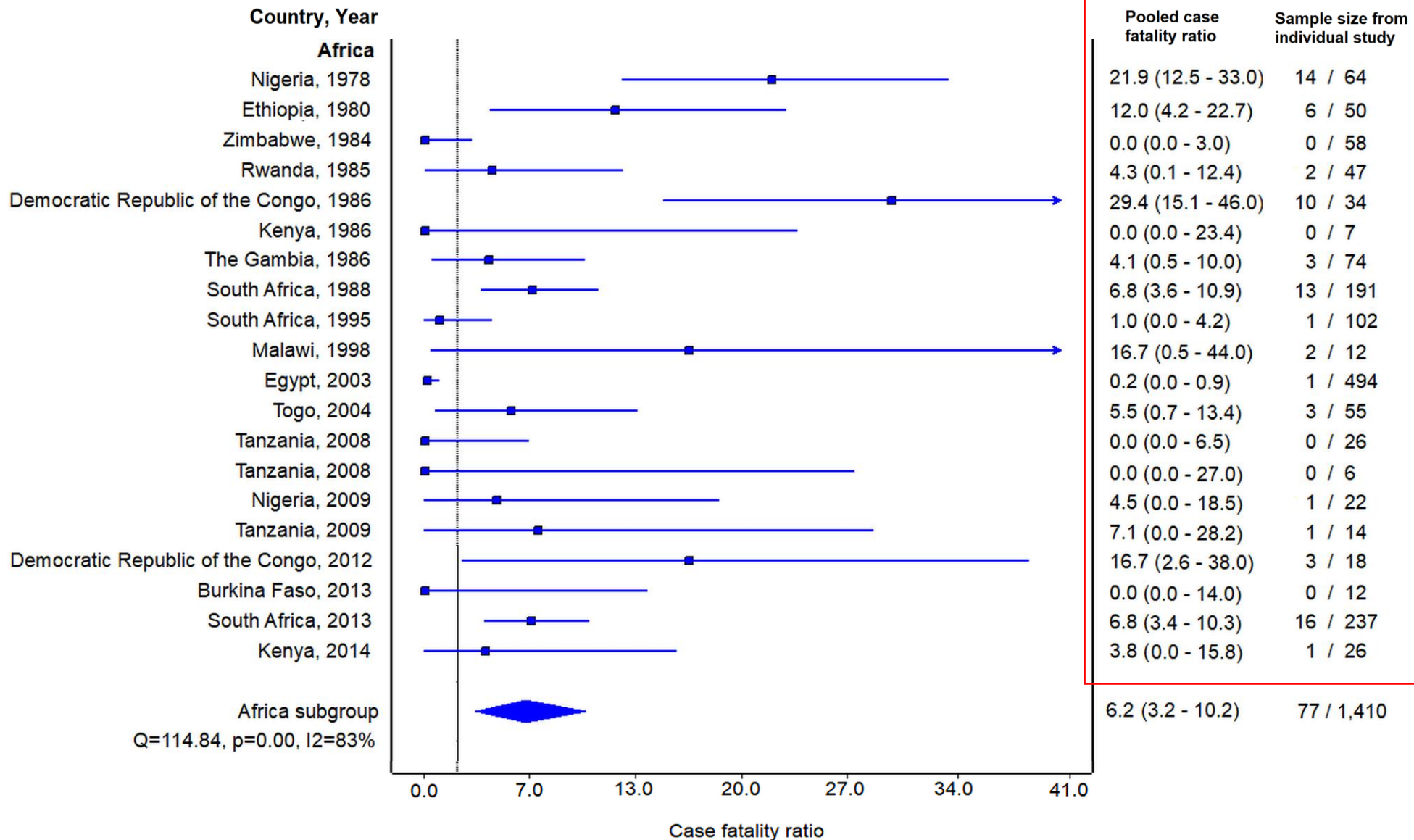
# Results: typhoid case fatality ratio among non-surgical hospital-based study sites in Africa, by year, 1978-2014



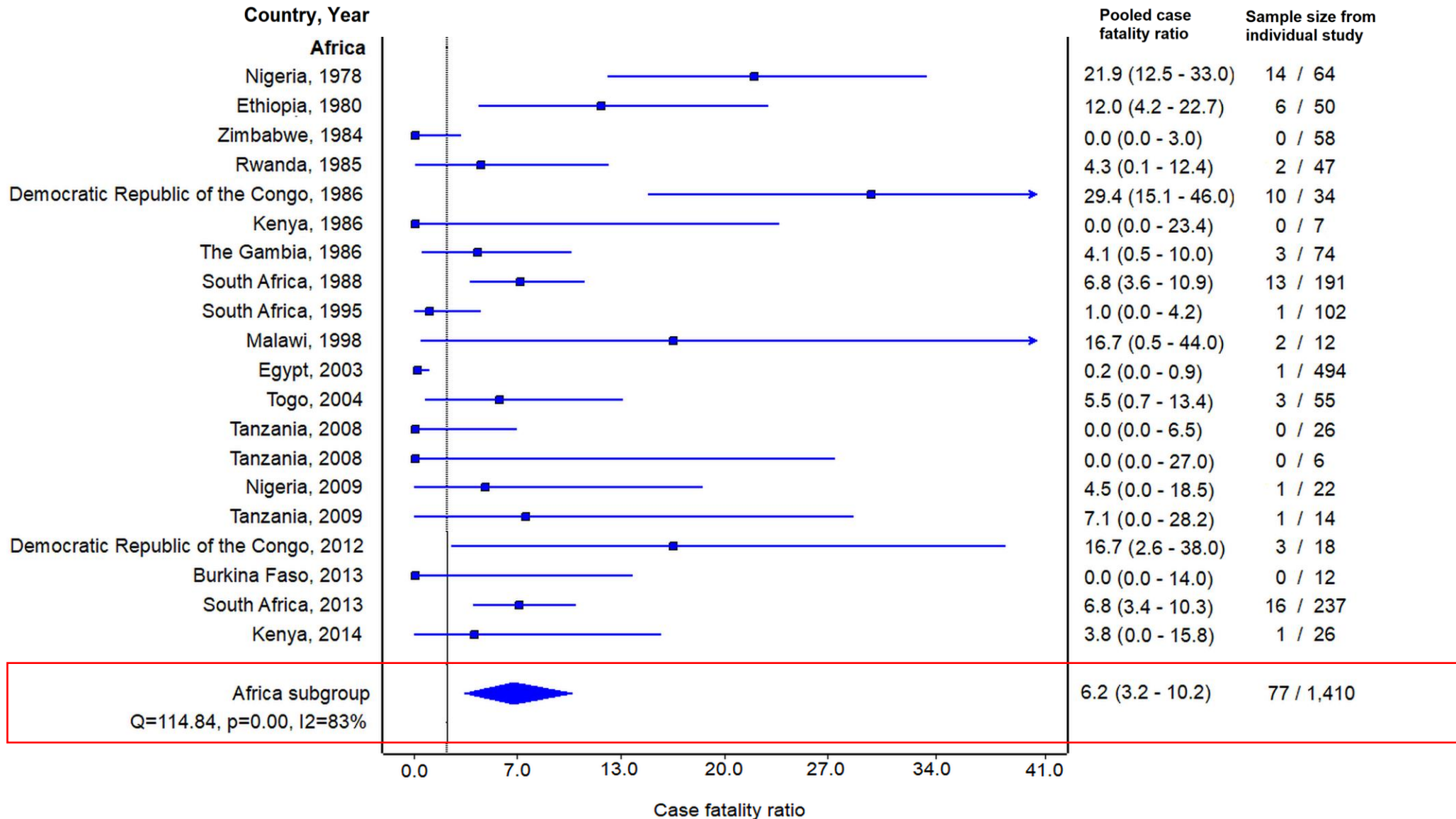
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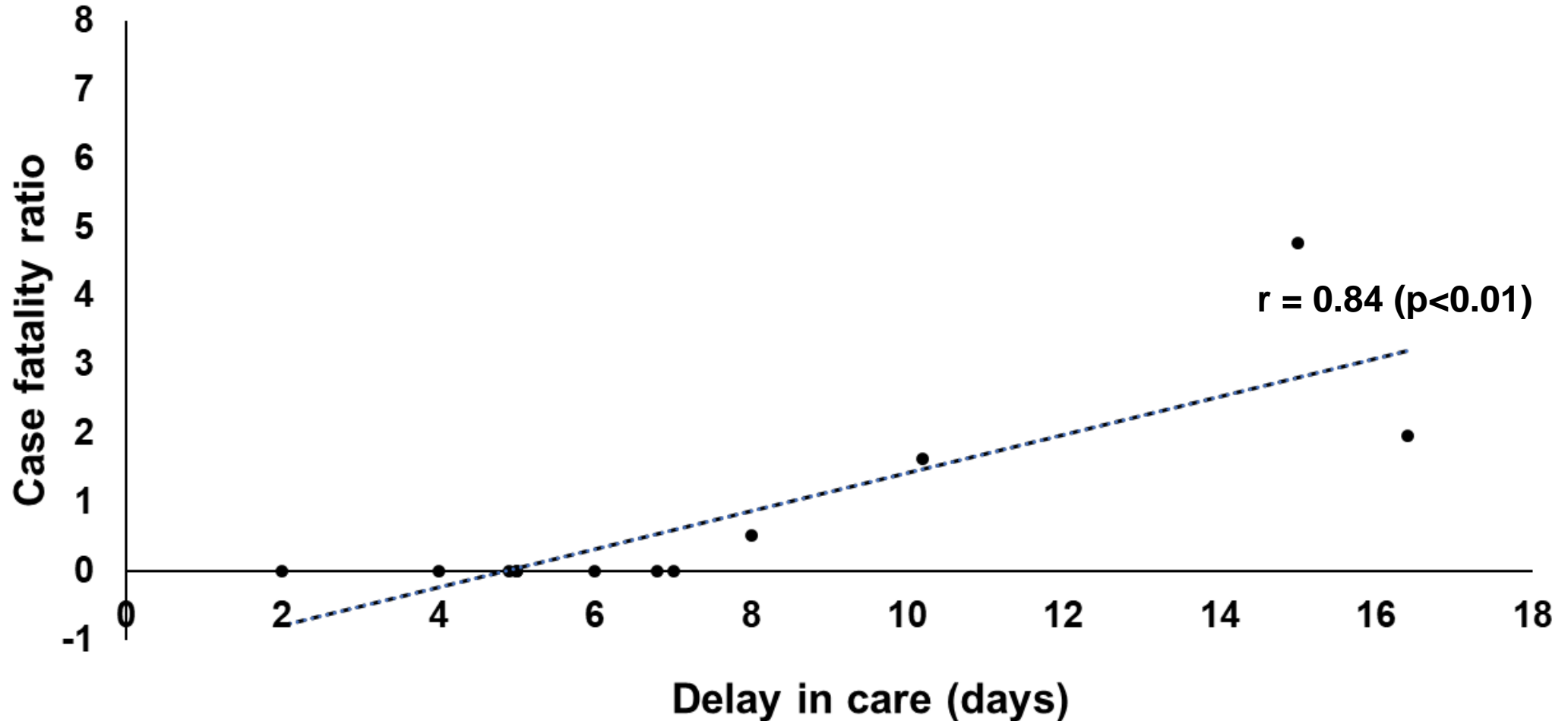


# Results: typhoid case fatality ratio among non-surgical hospital-based study sites in Africa, by year, 1978-2014





# Results: Scatterplot of case fatality ratio against delay in care with trendline, 12 eligible estimates from the Asia region



# Conclusions

- **Among predominantly hospitalized typhoid fever patients, we demonstrate a substantial prevalence of typhoid complications and death**
- **We estimated a CFR of 2.0%, with significant variation between Africa and Asia**
- **One in five patients with TIP in Africa died**
- **Considerable typhoid fever morbidity and mortality that could be averted with prevention efforts**

# Acknowledgements

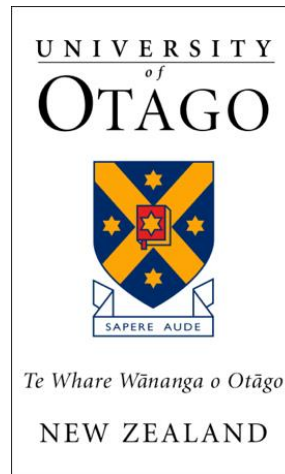
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# Thank you!

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