INTRODUCTION

This article introduces a collection of studies undertaken within the “Tackling Typhoid” (T2) project, which aimed to consolidate the current body of literature on national and regional typhoid fever trends in incidence, mortality, and severe complications. The T2 project included a systematic review of the literature and eight-country case studies in Chile, Nigeria, South Africa, Pakistan, India, Bangladesh, Thailand, and Vietnam. Case studies examined typhoid and paratyphoid fever incidence trends in conjunction with changes in relevant contextual factors, such as water treatment and distribution, sanitation infrastructure, female literacy, poverty rates, and diarrheal mortality, and included in-depth interviews with local public health experts to identify local interventions and control measures that were implemented to reduce the transmission of typhoid fever directly or indirectly by targeting other infectious diseases.

The studies in this supplement collectively characterize global and regional trends in typhoid and paratyphoid fever, and the findings can inform recommendations on interventions and policies that can best help curb the continued spread of this disease.

Epidemiology. Typhoid and paratyphoid fever are enteric infections caused by the bacteria Salmonella enterica serovar Typhi (S. Typhi) and Paratyphi A, B, and C (S. Paratyphi A, B, and C), respectively, collectively referred to as typhoidal Salmonella, and the causes of enteric fever.1 Humans are the only reservoir for Salmonella Typhi with disease transmission occurring via the fecal-oral route, usually through the consumption of food or water contaminated by human feces.2 An estimated 17 million cases of typhoid and paratyphoid fever illnesses occurred globally in 2015,3 mostly in South Asia, Southeast Asia, and sub-Saharan Africa, with both the largest burden and incidence occurring in South Asia (Figure 1).3,4 Left untreated, both typhoid and paratyphoid fever may be fatal1 with 178,000 deaths estimated worldwide in 2015.3

Although considerable literature exists on typhoid fever incidence, most endemic countries do not have well-established population-based national surveillance systems for typhoid fever. In addition, some countries that use passive surveillance use clinical diagnoses with limited ability to confirm typhoid fever cases by blood culture. Most data are, therefore, collected from hospital-based studies, leaving substantial knowledge gaps in certain geographies, especially where health-care usage is low. A review of global burden5 showed that from 1954 to 2000 only 13 countries had population-based surveillance data for typhoid fever, only two of which were in Africa—Egypt and South Africa. At the time, both these countries had surveillance data from the control arms of vaccination trials only,5 although considerably more data have become available since. Data from Ministry of Health surveillance reports in Thailand highlight a shift from S. Typhi as the primary typhoidal Salmonella bacteria isolated to S. Paratyphi.6 Thailand is broken down into seven regions, of which four are showing this transition between 2004 and 2014.6,8 Within the Bangkok and Vicinities region, two provinces (Bangkok and Samut Prakan) of the six that comprise the region show S. Typhi incidence decreasing as S. Paratyphi increases.6,7 This shift is also observed in three provinces (Ratchaburi, Kanchanaburi, and Phetchaburi) from the western region of Thailand.6,7 Although improvements in water, sanitation infrastructure, and public health measures have led to the virtual disappearance of typhoid fever transmission within the developed world, residual cases largely occur in travelers returning from countries where typhoid fever remains endemic.9 Knowledge of local disease burden, risk factors for acquisition, transmission characteristics, and implemented control measures are essential in developing strategies for prioritized and optimally targeted typhoid and paratyphoid fever control, and elimination.

Morbidity. Typhoid fever incidence has decreased to very low levels in developed countries such as the United States
was estimated to be 200 cases per 100,000 person-years. A study assessed 1,872 cases of typhoid fever from 2008 to 2012 of which 86% were associated with foreign travel. The small number of cases still being acquired domestically demonstrates that typhoid fever remains a constant, albeit minor problem within the United States.

Although most cases of typhoid fever occur in Asia and Africa, considerable regional differences exist, both within and between countries. Data from the Diseases of the Most Impoverished (DOMI) population-based surveillance study, led by the International Vaccine Institute (Seoul, South Korea), estimated the overall incidence of 493.5 cases per 100,000 person-years in children aged 5–15 years in an urban slum in Kolkata, India (2003–2004). A similar population-based study conducted in the Dong Thap Province in the south of Vietnam from December 1995 to December 1996 estimated typhoid fever incidence at 198 per 100,000 person-years. A comparable incidence was observed in Dhaka between January 2003 and January 2004 where typhoid fever incidence was estimated to be 200 cases per 100,000 person-years. Most previous typhoid fever estimates from sub-Saharan African countries were from hospital-based studies, although earlier population-based studies from Kenya did suggest high rates in an urban slum of 247 cases per 100,000 person-years observed between 2007 and 2009. This study also showed 15-fold higher incidence in urban children compared with their rural counterparts. A recent publication describes population-based studies of typhoid fever and invasive nontyphoidal Salmonella disease in 12 sites in 10 countries across sub-Saharan Africa. Incidence ranges from 0 to 383 cases per 100,000 person-years across the 12 sites. Although poor infrastructure and unstable governments make the establishment of robust disease surveillance systems difficult in resource-constrained settings, these new data from sub-Saharan Africa will help in forming more accurate future estimations of the global burden.

Age-specific typhoid incidence. Typhoid fever incidence varies by age. In endemic countries, the highest incidence is in younger children, whereas incidence is similar in all age groups in low-burden settings. A study from 2004 used data from published studies to extrapolate incidence rates by age group and reported the highest incidence in children under the age of 5 years in high incidence settings. Modeled estimates from the 2015 Global Burden of Disease study (GBD 2015) showed typhoid fever incidence rates decreasing as age increased. Furthermore, results from the DOMI study conducted in five endemic countries demonstrate substantial heterogeneity in typhoid fever incidence across age groups. The heterogeneity across age groups was observed in all DOMI study sites and sites from the Typhoid Fever Surveillance in Africa Program.

Mortality. Mortality from typhoid and paratyphoid fevers is difficult to estimate, because cases identified with typhoid fever during surveillance should receive appropriate clinical management and deaths presumed due to typhoid should receive scrutiny to rule out other possible causes. Nonetheless, typhoid and paratyphoid fevers were estimated to be associated with approximately 200,000 deaths in 2000 with an absolute number of deaths estimated to be the highest in Africa and South Asia. Figure 2 presents global typhoid and paratyphoid mortality estimates from GBD 2015. Deaths due to paratyphoid fever tend to be lower than those of typhoid fever. However, this difference could be attributed to the incidence of paratyphoid fever being lower than that of typhoid in many settings. The number of paratyphoid fever deaths is estimated to be the greatest in South Asia, where its incidence is also the greatest although far lower than that of typhoid. Before the introduction of antimicrobials, death occurred in as many as 33% of typhoid fever patients in hospital and community settings from developing countries and was seen in upward of 10% of cases in developed countries. The use of antimicrobials initially lowered typhoid fever case fatality below 2% but the emergence of antimicrobial resistant strains in high-burden countries has been a growing concern in recent years.

Strategies for typhoid control and preventive measures. A range of strategies exist to prevent and control typhoid fever (Table 1). Factors such as crowding, poor sanitation, unsafe water, and unsafe food production and handling processes contribute to Salmonella Typhi and Salmonella Paratyphi transmission. Therefore, measures to interrupt transmission through improvements in sanitation, drinking water, and food production need to be included in comprehensive prevention.
strategies for enteric fever. In addition to the aforementioned strategies that target risk factors, interventions focused on timely diagnosis and appropriate clinical management can also improve typhoid fever outcomes (Table 1).

The use of vaccines in the control of typhoid fever has been successful as a preventative measure and during outbreak situations in many contexts. In China, during the 1999 typhoid outbreak, the Vi capsular polysaccharide (ViCPS) vaccine showed a protective efficacy of 73% in children previously vaccinated and 71% in children who received the vaccine during the outbreak. In Thailand in 1977 a national typhoid immunization program was implemented in schoolchildren using the heat/phenol-inactivated typhoid vaccine. After the introduction of this program the isolation rate of S. Typhi decreased from 4.6% in 1976 to 0.3% in 1985.

Early diagnosis of typhoid and paratyphoid fever. From a clinician’s perspective typhoid and paratyphoid fever are indistinguishable. Furthermore, many other acute febrile illnesses such as dengue, leptospirosis, and malaria may present a clinical picture similar to that of typhoid fever. Accurate diagnosis requires laboratory confirmation. The development of practical, affordable, and accurate (i.e., both
sensitive and specific) diagnostic tools is key to typhoid fever management and control. Typhoid fever can be diagnosed using a number of methods including culture of blood, bone marrow, or stool, and nucleic acid amplification tests (NAAT) for detecting bacterial nucleic acids in appropriate body fluids including blood or bone marrow. Techniques such as NAAT and bone marrow cultures are not, however, feasible in low-resource settings, and blood culture or Widal tests are more commonly used.

Not all diagnostic methods perform equally well. Bacterial culture with bone marrow offers the greatest sensitivity at upward of 80%. However, bone marrow aspiration and culture is expensive and invasive and is not commonly used in practice. Consequently, although less sensitive, blood culture remains the practical standard for typhoid fever diagnosis. A recent systematic review of 10 studies examined the sensitivity of blood cultures relative to bone marrow cultures from a recent systematic review of 10 studies examined the sensitivity of blood cultures relative to bone marrow cultures. Accurately estimating the burden of typhoid fever and other invasive Salmonella infections depend, in part, on the availability of locally improved laboratory diagnostics and relevant data on burden and contextual factors. Accurately estimating the burden of typhoid fever is challenging because data are scarce and derived from varied methods. There is uncertainty around the relative value of investments in health systems and large-scale engineering interventions, such as investments in water and sanitation, food safety measures, public awareness, improved diagnostics, treatment strategies, and immunization programs.

### Table 1

| Level                        | Interventions                                      |
|------------------------------|----------------------------------------------------|
| Water and sanitation         | Ready access to potable water                       |
|                               | Use of improved sanitation                         |
|                               | Sewage collection and treatment                    |
| Health systems                | Accurate, rapid, diagnosis, and antimicrobial       |
|                               | susceptibility testing                              |
|                               | Identification and treatment of chronic carriers    |
|                               | Appropriate antimicrobial treatment                 |
|                               | Vaccination*                                       |
|                               | Food safety regulations, implementation, and        |
|                               | enforcement                                         |
| Education                    | Handwashing before eating and before                |
|                               | food preparation and after defecation*              |
|                               | Food safety education                               |

*Vaccines for paratyphoid fever are not available.

CONCLUSION

Despite more information of higher quality available now than ever before, and a range of proven options for prevention, gaps remain in our understanding of typhoid fever burden and the best way to implement prevention strategies in low-resource settings. The findings from our comprehensive exercise to characterize trends in typhoid fever both globally and within endemic countries, summarized in this supplement, will help to fill some of these remaining gaps. The decisions to implement appropriate public health measures and preventive strategies for typhoid fever and other invasive Salmonella infections depend, in part, on the availability of locally improved laboratory diagnostics and relevant data on burden and contextual factors. Accurately estimating the burden of typhoid fever is challenging because data are scarce and derived from varied methods. There is uncertainty around the relative value of investments in health systems and large-scale engineering interventions, such as investments in water and sanitation, food safety measures, public awareness, improved diagnostics, treatment strategies, and immunization programs.
conjugate vaccine used as a complementary tool with the methods, and therapeutic procedures both within and between countries with endemic typhoid fever suggests that enteric fever cannot be eliminated by a single solution in every setting. There is hope regarding the control of enteric fever with the availability of the new Tybar TCV conjugate vaccine used as a complementary tool with the usual public health recommendations on water supply and sanitation.

Received January 15, 2018. Accepted for publication March 8, 2018.

Financial support: Funding for this study (Grant # OPP1126230, Principal Investigator Zulfiqar A. Bhutta) to the Centre for Global Child Health, Hospital for Sick Children, Toronto, was provided by the Bill & Melinda Gates Foundation (https://www.gatesfoundation.org/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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