Typhoid Fever

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Typhoid fever is caused by infection with *Salmonella enterica* serovar Typhi. The completion of the genome sequence of two *Salmonella enterica* serovar Typhi isolates is leading to new insights into the biology of this pathogen. Approximately 16 million cases occur worldwide each year. The lack of culture facilities in endemic areas and the poor performance of the Widal test means the disease is frequently unconfirmed. Simple new serologic tests are being developed and show promise. Resistance to chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole is widespread in Asia and some areas of Africa, although fully susceptible isolates have re-emerged in some countries. Fluoroquinolones, third-generation cephalosporins, and azithromycin are effective alternatives. Low-level fluoroquinolone resistance (indicated by resistance to nalidixic acid) is now common in Asia and results in a suboptimal response to fluoroquinolones. Two vaccines are licensed and others are being developed, but neither licensed vaccine is used in endemic areas as a public health measure.

Introduction

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies *enterica* serovar Typhi (*S.* Typhi) [1]. Paratyphoid fever, caused by infection with *S. enterica* serovar Paratyphi A, B, or rarely C, is similar to typhoid fever but usually is less severe and less common. Typhoid and paratyphoid fever (collectively enteric fever) are endemic in many areas of Asia, particularly the Indian subcontinent, Africa, and Latin America. It is estimated there are at least 16 million cases worldwide each year with 600,000 deaths. In developed countries, typhoid fever principally occurs in returning travelers and immigrants visiting their country of origin. In the past, typhoid and paratyphoid fever could be treated successfully with inexpensive, widely available antimicrobial agents. The emergence of resistance to these agents has complicated the management of this serious condition.

Molecular Biology

Salmonella enterica subspecies *enterica* serovar Typhi is considered to be a clonal bacterium, and this has been confirmed in a recent study in which seven housekeeping genes in a collection of 26 isolates of *S.* Typhi were sequenced [2]. Only three polymorphic sites were found, and the isolates were categorized into four sequence types. This showed that *S.* Typhi is a recent clone, and its last common ancestor existed so recently that multiple mutations have not yet accumulated. Based on molecular clock rates for the accumulations of synonymous polymorphisms, the last common ancestor of *S.* Typhi was estimated to exist between 15,000 and 150,000 years ago.

Sequencing of the complete genomes of two isolates of *S. enterica* serovar Typhi, CT18 and Ty2, and one isolate of *S. enterica* serovar Typhimurium LT2 have been completed [3,4•,5]. Sequencing of 13 other *Salmonella* isolates is in progress [6]. *S.* Typhi CT18 is a multidrug-resistant (MDR) strain isolated from a child with typhoid in southern Vietnam in 1993 [3]. This strain carries a large molecular weight plasmid containing the antimicrobial resistance determinants and a smaller cryptic plasmid, closely related to the pMT1 plasmid of *Yersinia pestis*. *S.* Typhi Ty2 was isolated before the emergence of drug resistance in the 1970s and contained no plasmid [4•]. The strain has been the foundation for vaccine development and was the parent of mutant strains TY21a and CVD908 and their derivatives. The two genomes have been compared and show that 29 of the 4646 genes in Ty2 are unique to this strain, whereas 84 genes are unique to CT18 [4•]. Both genomes contain more than 200 pseudogenes. There are clear differences in prophages, insertion sequences, and island structures between the two genomes.

DNA microarray technology has been used to compare the genomic content of a diverse set of isolates of serovar Typhi from different locations and time periods [7•,8•]. These studies show that even in a highly clonal bacterial population, *S.* Typhi possess a large amount of horizontally acquired genetic information in the form of prophages and pathogenicity islands. For example, the SPI-7 pathogenicity island, which contains the *ViaB* locus-encoding production of the Vi capsular polysaccharide, has a mosaic structure that may have evolved as a consequence of several independent insertion events [9]. Identifying which of the many acquired genes confer virulence traits and which of the inactivated pseudogenes may result in host restriction represents a future challenge.

Significant genetic diversity has been demonstrated in *S.* Typhi using the technique of pulse field gel electrophoresis (PFGE). This technique, as well as the more traditional phage typing, was used to examine isolates from patients in the highlands of Papua New Guinea [10•]. Typhoid first appeared in the highlands during the 1980s. Between 1992 and 1994, 52 isolates comprised only one phage type and two predominant PFGE profiles. Between 1997 and 1999, the 81 isolates included four new phage types and new PFGE patterns. The two original PFGE patterns remained stable and dominant, and the new patterns probably were derived from mutations of these types. Examination of paired blood and fecal isolates from 23 patients revealed similar PFGE patterns in 12 patients but different patterns in 11 cases. In three of those cases, the phage types also were different between the paired isolates. This is an important observation, indicating that infection can occur with multiple strains.

Pulse field gel electrophoresis and phage typing may lack sufficient discrimination to study local epidemiology. An alternative method has been developed in Singapore and may be more suitable for this role [11]. A multiplex polymerase chain reaction (PCR) amplifies variable-number tandem repeat (VNTR) loci identified on the CT18 genome. The multiplex PCR can be performed on crude cell lysates and produces easily visualized VNTR banding profiles. A high level of VNTR heterogeneity was identified in isolates from within the same country and between countries. The profiles also remained stable after repeated laboratory subcultures.

Epidemiology

Salmonella enterica subspecies *enterica* serovar Typhi and Paratyphi A (*S.* Paratyphi A) are exclusively human pathogens and principally transmitted by the fecal-oral route. They are common in areas of inadequate sanitation or where clean drinking water is in short supply. In endemic areas, established risk factors for disease include eating food prepared outside the home (*eg*, ice cream or flavored ice drinks from street vendors), drinking contaminated water, inadequate sanitation, having a close contact or relative with recent typhoid fever, and recent use of antimicrobials [1]. Host factors, such as achlorhydria, also are important. Because acute and chronic *Helicobacter pylori* infection cause hypochlorhydria, infection with *H. pylori* is a potential risk factor for typhoid. In a nested case-control study, 83 patients with culture-proven typhoid were identified during the course of a 1-year surveillance of febrile persons aged 0 to 40 years in an urban slum in Dehli, India [12•]. The presence of serum anti–*H. pylori* antibodies was significantly associated with typhoid fever (adjusted odds ratio = 2.03; 95% confidence interval = 1.02–4.01). Additional risk factors identified included illiteracy, being part of a nuclear family, not using soap, and consumption of ice cream. The estimated etiologic fraction attributed to *H. pylori* was approximately 34%. If confirmed in other studies, this is an additional impetus to develop strategies to prevent *H. pylori* infection in children in developing countries.

The true burden of disease in developing countries is difficult to estimate. Microbiologic facilities often are unavailable and epidemiologic studies with active surveillance are difficult and expensive to perform. An alternative method to estimate the incidence of typhoid was examined in a study in Egypt [13]. A household survey to determine the patterns of persons with fever seeking health care was conducted in a district near Cairo with a population of 664,000. A 4-month period of surveillance was then established among health care providers who treated febrile patients. These health care providers collected epidemiologic information and blood for culture and serologic testing from patients aged 6 months or older with fever of 3 or more days duration. After adjustments for the provider sampling scheme, test sensitivity, and seasonality, the incidence of typhoid fever was estimated to be 13 per 100,000 persons per year. The authors propose this as a suitable surveillance tool for the evaluation of typhoid fever and other febrile illnesses in endemic areas.

An important trend in some areas of the Indian subcontinent has been the increasing proportion of cases of enteric fever caused by *S.* Paratyphi A [14]. In a small study from a hospital in Nagpur, central India in 2001 to 2002, 46% of 39 *Salmonella* isolates were *S.* Paratyphi A [15]. In this study, multidrug resistance was rare. A similar increase in *S.* Paratyphi A isolates has been seen in Bombay, India [16]. Many of these patients had received typhoid immunization with the oral Ty21a or injectable capsular Vi polysaccharide vaccine, suggesting that widespread vaccination against *S.* Typhi could be followed by an increase in *S.* Paratyphi A.

Most cases of typhoid fever in developed countries (*eg*, the United States) are related to foreign travel [17]. However, some cases are home grown. In a review of outbreaks of typhoid fever occurring in the United States during the past 30 years, 60 reported outbreaks were identified. Exposure occurred within the United States in 54 of these outbreaks [18]. These 54 outbreaks accounted for 957 total cases (median 10) and four deaths. The median incubation period was 2 weeks. The average frequency of outbreaks decreased from 1.85 per year during 1960 to 1979 to 0.85 per year during 1980 to 1999 (P = 0.0001). The route of transmission was identified in 36 (67%) outbreaks. In 16 (62%) of the 26 foodborne outbreaks, an asymptomatic carrier was identified by culture or serology. The authors conclude that although the average size of outbreaks was small, they caused significant morbidity and often were foodborne.

An unusual outbreak occurred in Ohio in 2000 [19]. A cluster of men with typhoid, who denied having traveled abroad, was reported to the public health authorities. An epidemiologic investigation revealed seven men in

Ohio, Kentucky, and Indiana with culture-confirmed typhoid fever and two men with probable typhoid. All but one reported having sex with an asymptomatic male *S*. Typhi carrier. He had probably contracted typhoid after a trip to Puerto Rico earlier that year. The outbreak represents apparent sexual transmission of typhoid by oral or anal sex.

Diagnosis

Differentiating typhoid fever from other common infections that cause fever in endemic areas is difficult. Many of the symptoms are nonspecific and overlap with other infections. The principal method for the diagnosis of typhoid fever is culture of blood or bone marrow [1]. However, culture facilities usually are unavailable in the areas where the disease is endemic. The Widal test measures agglutinating antibodies against the somatic (O) antigen and flagellar (H) antigen of *S*. Typhi or *S*. Paratyphi A. This test is easier and less expensive to perform than culture and is more widely available. However, it suffers from a lack of sensitivity and specificity, particularly when used as a single screening test for patients with fever.

Several alternative serologic tests have been developed [1]. One such test, developed at the Royal Tropical Institute in the Netherlands, is a rapid dipstick assay for the detection of *S*. Typhi–specific immunoglobulin M (IgM) antibodies in serum and whole blood [20•,21]. The test requires 3 to 4 hours to perform and has the potential to be useful in areas that lack laboratory facilities. This assay was evaluated in South Sulawesi, Indonesia, an area endemic for typhoid fever [20•]. Culture of blood and serology was performed for 473 patients admitted to the hospital with clinically suspected typhoid fever. The diagnosis was confirmed by culture in 205 (65%) of 314 patients with a final clinical diagnosis of typhoid fever. In 159 patients, a diagnosis other than typhoid was made. The sensitivity of the dipstick was 58% in patients with a final diagnosis of clinical typhoid, with a specificity of 98%. The sensitivity of the dipstick was higher in culture-positive patients compared with culture-negative patients and increased with the duration of illness. A significant proportion of initially negative patients became positive when tested later in the course of illness. In a smaller study in Egypt, the typhoid dipstick was evaluated with a *Brucella* dipstick in 85 plasma samples from febrile patients with culture- or serologically proven typhoid, culture- or serologically proven *Brucella* infection, and patients with negative culture and serology [21]. The typhoid test was determined to have a sensitivity of 90% and specificity of 96%. However, the observation that four of 25 (16%) patients with culture-proven brucellosis reacted with the typhoid dipsticks is of concern.

Another available serology test is Typhidot M (Malaysian Bio-Diagnostics Research, Kuala Lumpur, Malaysia). This is a dot enzyme immunoassay (EIA) that detects IgM antibodies against an outer membrane protein of *S*. Typhi. A dot EIA and blood/bone marrow culture was concurrently performed in 128 patients with suspected typhoid fever in Karachi, Pakistan [22]. The EIA was positive in 71% of the 69 culture-positive cases. An alternative approach was used by a study in Sri Lanka. An enzyme-linked immunosorbent assay was developed to measure anti–*Salmonella* Typhi lipopolysaccharide salivary immunoglobulin A levels [23]. The assay was most sensitive in the second and third weeks of fever. The ease of collecting salivary samples makes this an interesting approach to diagnosis.

There have been previous small studies of the value of PCR for the detection of *S*. Typhi in blood, although the method has not been widely adopted. In a study from New Dehli, India [24], a nested PCR protocol was developed for the detection of the flagellar gene of *S*. Typhi. The PCR was positive in 100% of 20 culture-positive typhoid cases and 60% of 20 culture-negative but clinically suspected cases. None of the 20 patients with bacteremia caused by bacteria other than *S*. Typhi was PCR positive. Although diagnosis by DNA amplification is unlikely to become an inexpensive method of diagnosis in endemic areas, it may have a role in research studies in which a variety of different tests could be used to provide a confirmed diagnosis in study patients.

Multidrug Resistance

The emergence of resistance to multiple antimicrobial agents in *S*. Typhi and *S*. Paratyphi A has been a major problem in Asia in the past 15 years [1]. MDR isolates with resistance to chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole, and with reduced susceptibility to fluoroquinolones (indicated by resistance to nalidixic acid [Na^R]), have caused epidemics and become endemic in the Indian subcontinent, Southeast Asia, China, and some countries of central Asia. A report from Myanmar (Burma) shows that this country should be added to the list of those affected [25]. In a 1-year study from 1998 to 1999, blood cultures were performed in febrile children attending the Medical Unit (III), Yangon Children's Hospital. A bacterium was isolated from blood cultures in 65 of 120 children. The most common isolate, found in 28 children, was *S*. Typhi. All the *S*. Typhi were resistant to chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole but susceptible to ceftriaxone and nalidixic acid.

In some regions, the incidence of MDR isolates appears to have decreased. A hospital in Bombay, India, reports that the incidence of MDR *S*. Typhi isolates decreased from 40% in 2000 to 17% in 2002 [16]. Unfortunately, the proportion of Na^R isolates was 82% in 2000 and 88% in 2002. In a study of children in Calcutta, India, from 1990 to 1992, all isolates were MDR [26]. In 2000, 50% were susceptible to chloramphenicol and 40% to cotrimoxazole and ampicillin. A similar downward trend in the proportion of MDR isolates also has been seen in Cairo, Egypt [27]. Between 1987 and 2000, 853 patients with suspected

typhoid fever were culture positive for *S.* Typhi. The proportion of MDR isolates peaked at 100% in 1993 but declined to 5% in 2000. Recent isolates were susceptible to ciprofloxacin and ceftriaxone, but susceptibility to nalidixic acid was not tested in this study. The authors propose that chloramphenicol may be reintroduced as the first-line treatment for typhoid in these areas.

There is more limited information from Africa concerning the distribution of drug-resistant isolates. A report from Ghana characterizes 58 *S.* Typhi strains isolated from patients with typhoid fever [28]. Ten of the 58 (17%) isolates were MDR and 34 were resistant to at least one of the antibiotics tested. In contrast, in Dakar, Senegal, the level of resistance to chloramphenicol, ampicilin, and trimethoprim/sulfamethoxazole in 232 *S.* Typhi isolates was less than 1% [29]. This difference in the level of drug resistance occurred despite easy access to commonly used antimicrobials without prescription in both areas. The reason why *S.* Typhi remains drug sensitive in some areas but MDR in adjacent areas is unclear. Indonesia, where chloramphenicol remains an effective drug for treating typhoid fever despite the unregulated and widespread use of antimicrobials, is a good example of this apparent paradox.

The multidrug resistance pattern is invariably born on a large molecular weight transferable plasmid. Analysis of *S.* Typhi CT18 reveals an incHI1 plasmid, pHCM1, of 218 kbp (kilobase pairs) that encoded transferable multiple antibiotic resistance [3,30•]. A core region of the plasmid showed significant DNA sequence similarity to R27, a plasmid isolated in 1961 from a *S. enterica* in the United Kingdom. Five regions of DNA in pHCM1 were found that were not present in R27. Two of these were potential acquisition regions. The larger included the sequences of several antibiotic resistance genes and several insertion sequences. The smaller region carried a trimethoprim-resistance gene and a class 1 integrase. Restriction analysis suggests that this R27-like plasmid has evolved by the serial acquisition of DNA on mobile elements encoding resistance to antimicrobials and heavy metals and other genes of unknown function, and has spread into several *S.* Typhi genotypes across southern Vietnam. There is considerable worry that these multiresistant isolates may acquire further resistant determinants. Class 1 integrons, demonstrated in *S.* Typhi from Korea [31], Vietnam, and India [30•,32], may assist in this process.

Low-level Fluoroquinolone Resistance

Isolates with reduced susceptibility (or resistance) to fluoroquinolones also have spread in many Asian countries [1]. Resistance to fluoroquinolones typically occurs by point mutations in the genes encoding the bacterial DNA gyrase and topoisomerase IV enzymes, which are the target for these agents, or in the genes controlling the transport of the drug into the bacterial cell. The newly identified plasmid-mediated mechanism of quinolone resistance has not been detected in *S.* Typhi or *S.* Paratyphi A [33]. Common single mutations in the *gyrA* gene can produce a ten-fold increase in the fluoroquinolone minimum inhibitory concentration (MIC) compared with the wild type. The MIC of such isolates is still within the susceptible range according to current guidelines, and they are reported as susceptible when using disc sensitivity tests. However, the reduction in susceptibility translates into an increased chance for clinical failure when infection with these isolates is treated with fluoroquinolones [34,35••, 36••]. The breakpoints need to be re-evaluated, and data are being collected to inform this decision. These strains usually are resistant to the first-generation quinolone, nalidixic acid, and this can be a useful screening test for the presence of such isolates, with the caveat that occasional isolates with reduced susceptibility to fluoroquinolones are nalidixic-acid susceptible [36••,37]. On the Indian subcontinent, there are sporadic reports of *S.* Typhi isolates fully resistant to ciprofloxacin, although the numbers are low [26].

Treatment

In areas where MDR isolates are common, fluoroquinolones (*eg*, ciprofloxacin or ofloxacin), third-generation cephalosporins (*eg*, ceftriaxone and cefixime), and azithromycin have proven to be effective alternatives [1,38]. For Na^R typhoid, third-generation cephalosporins and azithromycin remain effective, and fluoroquinolones administered in maximum dosage for 7 to 10 days work in a proportion of patients. The disadvantage of these drugs in endemic areas is that they are expensive and may be unavailable.

In many Asian countries where MDR typhoid is common, fluoroquinolones are the most affordable treatment option. However, these agents can cause lesions of the cartilage in juvenile animals, although the relevance of this laboratory observation to treatment of children is unclear. Evidence based on compassionate use suggests these agents can be used safely in children, but there is still concern. In a retrospective observational study in Canada, an automated database was searched to identify patients aged younger than 19 years who had been prescribed levofloxacin, ofloxacin, ciprofloxacin, or azithromycin and had developed a tendon or joint disorder within 60 days of the prescription of one of these drugs [39•]. Cases were verified by a blinded review of the medical records. The incidence of verified tendon or joint disorders was 0.82% for ofloxacin (13 of 1593) and ciprofloxacin (37 of 4531) and 0.78% for azithromycin (118 of 15,073). The distribution at the time of onset was comparable for all groups. This study suggests that the incidence of tendon and joint disorders in children was less than 1% and was comparable to a reference group of children treated with the nonfluoroquinolone agent azithromycin.

In certain areas of the world, chloramphenicol-susceptible typhoid is still common or has reappeared after a period of MDR epidemics. Whether chloramphenicol, or one of the newer drugs such as ciprofloxacin, is the best treatment in these areas is debated. In a randomized, controlled trial in Indonesia, ciprofloxacin and chloramphenicol were compared in 55 adults with typhoid fever [40]. An interesting feature of this study was that patients were randomized to have a blood and bone marrow culture performed after 3 or 5 days of treatment. After 5 days of treatment with chloramphenicol, 14 of 14 (100%) of the bone marrow cultures and four of 11 (36%) blood cultures were still positive. In the ciprofloxacin-treated patients, 10 of 15 (67%) bone marrow cultures and two of 11 (18%) blood cultures were positive. Despite this, there were no significant differences in the clinical cure rates (92% for chloramphenicol and 96% for ciprofloxacin), and the mean (range) time to defervescence was 5.7 (3 to 12) days for the chloramphenicol-treated patients and 5.1 (2 to 8 days) for patients treated with ciprofloxacin. The authors do not report nalidixic-acid sensitivity of the isolates, although the rapid defervescence seen with ciprofloxacin suggests that most isolates were nalidixic-acid sensitive. The study was too small to show if either regimen was more or less effective than the other. There was no follow-up after discharge from hospital; thus, important data concerning relapse and convalescent fecal carriage were unavailable.

There also is debate concerning the optimum duration of therapy with ceftriaxone. In some studies, courses of 7 days or less have been associated with increased rates of clinical failure or relapse [1]. In a randomized treatment study in Sanliurfa, Turkey, a standard 14-day regimen of chloramphenicol was compared with ceftriaxone administered for 5 days after defervescence [41]. Clinical cure without complications was achieved in both groups. Mean (range) fever clearance was 5.4 (3 to 7) days with ceftriaxone and 4.2 (2 to 6) days with chloramphenicol. Four (14%) chloramphenicol-treated patients relapsed, but no patients treated with ceftriaxone relapsed. The average duration of ceftriaxone administered in this study was 10 days with a range of 8 to 12.

One of the principle and life-threatening complications of typhoid fever is intestinal perforation. Forty-two children with intestinal perforation were reviewed in a study from Turkey [42•]. The average age was 10.5 years. Twenty-three of the children had multiple perforations. The operative procedure chosen was primary closure in 55%, ileostomy in 26%, and resection with anastomosis in 19%. Twenty-two patients received parenteral nutrition for an average of 9 days. Postoperative complications were more common if admission was delayed, with a prolonged perforation to operation interval, and/or if there was severe peritonitis, but were less common in patients receiving parenteral nutrition or those who underwent an ileostomy. The authors conclude that children with severe abdominal contamination and delayed diagnosis benefited from treatment with an ileostomy and parenteral nutrition. Two (4.8%) of the children died of overwhelming sepsis. Mortality rates from typhoid perforation usually are higher in developing countries. In a study of 105 patients managed in Nigeria between 1988 and 2001, the mortality rate was 16.2% [43]. The principal complications in this study were wound infections (26.7%), intra-abdominal abscesses (9.5%), and wound dehiscence (7.6%).

Vaccines

There are two licensed typhoid vaccines [44]. They are well-tolerated and moderately protective. The Vi polysaccharide vaccine usually is administered by deep subcutaneous or intramuscular injection to individuals aged older than 2 years. The vaccine confers protection within 7 to 10 days of inoculation and requires boosters every 3 years. The oral attenuated *S. enterica* var Typhi strain Ty21a was developed by chemical mutagenesis, and therefore, the attenuating mutations are not fully defined. The vaccine usually is administered orally as three to four doses of the bacteria, in an enteric-coated capsule or liquid formulation, on alternate days. It provides protection 10 to 14 days after the last dose. Protection persists for approximately 3 to 5 years for those living in endemic areas with repeated exposure to *S.* Typhi, whereas travelers require a repeat course at 1-year intervals. It is not recommended for children aged younger than 5 years or in immunosuppressed individuals. It is inactivated by concomitant administration of antibacterials, which should be avoided 1 week before and 1 week after the vaccination series. For similar reasons, mefloquine, proguanil, and chloroquine should not be administered until 3 days after the last dose.

Promising new vaccine candidates are in development. The Vi polysaccharide-protein conjugate vaccine, a conjugate of the Vi capsular polysaccharide with nontoxic recombinant *Pseudomonas aeruginosa* exotoxin (rEPA), has been evaluated in Vietnam [45,46]. Two doses of the Vi-rEPA vaccine were safe and had an efficacy of 89% (95% confidence interval, 76% to 97%) after 46 months of follow-up in children aged 2 to 5 years [45,46]. Several attenuated strains of Ty2 with defined mutations such as CVD 906-*htrA* (*aroC aroD htrA* mutants), Ty800 (*phoP phoQ* mutants), and χ4073 (*cya crp cdt* mutants) are in phase I or II clinical trials [44]. In each case, the intention is that they will be effective when administered as a single oral dose.

Conclusions

The long-term solution for the prevention of typhoid in endemic areas is the provision of clean water and adequate sanitation. Unfortunately, this is beyond the current resources of most countries where typhoid is common. The main use of the licensed vaccines is in travelers to endemic areas and microbiologists. Mass vaccination programs in endemic areas rarely have been used outside of epidemics [47–49]. In view of the increasing morbidity, mortality,

and costs associated with drug-resistant typhoid fever, the cost effectiveness of mass vaccination as a public health measure to control this growing problem is being re-examined. The most recent recommendations of the World Health Organization are that school-based immunization programs should be employed in areas where typhoid is a recognized public health problem and MDR strains are particularly prevalent [50••]. In highly endemic countries, where typhoid cases are commonly reported in children aged younger than 5 years, immunization should be initiated in nursery school children. Vaccination also should be considered an effective tool for the control of typhoid outbreaks. It remains to be seen whether endemic countries will be able to adopt these recommendations.

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