CONSIDERATIONS REGARDING MASS VACCINATION AGAINST TYPHOID FEVER AS AN ADJUNCT TO SANITATION AND PUBLIC HEALTH MEASURES: POTENTIAL USE IN AN EPIDEMIC IN TAJIKISTAN

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Abstract. We report on the ongoing epidemic of typhoid fever in Tajikistan that started in 1996. It has involved more than 24,000 cases to date, and is characterized by multiple point sources, overflow of sewage, contaminated municipal water, and person-to-person spread. Of the Salmonella typhi isolates available for testing in western laboratories, more than 90% are multidrug-resistant (MDR). Most recently, 28 (82%) of 34 isolates are resistant to ciprofloxacin, representing the first reported epidemic of quinolone-resistant typhoid fever. In the past, mass immunization during typhoid fever epidemics has been discouraged. A review of this policy is recommended in light of the alarming emergence of quinolone-resistant strains of S. typhi, the availability of improved vaccines, and the ongoing epidemic in Tajikistan. Mass immunization may be a useful measure for the control of prolonged MDR typhoid fever epidemics, as an adjunct to correction of municipal infrastructure and public health intervention.

Typhoid fever remains a serious problem in areas of the world with inadequate control of drinking water and sewage disposal, and where chronic carriers are not identified. Worldwide, 30 million cases and 600,000 deaths are estimated to occur each year.\(^1\)\(^2\) Mortality has been limited based on presumptive diagnosis and early antimicrobial treatment, the strategy currently recommended by the World Health Organization (WHO). With the widespread emergence of multidrug-resistant (MDR) typhoid fever during the past decade, adequate control now requires third-generation cephalosporins or quinolones.\(^3\) These drugs are expensive and not easily available in many countries. In addition, reports of quinolone-resistant strains of Salmonella typhi have begun to emerge recently.\(^4\)

We report here on the first epidemic of ciprofloxacin-resistant S. typhi. This started in Tajikistan in 1996, in the setting of poor sanitation, inadequate purification of drinking water, crowding, and the disruption of the public health infrastructure as a result of civil warfare. After more than 2 years, these conditions have not been resolved, and the number of typhoid fever cases now exceeds 24,000. We review the use of typhoid fever vaccines for outbreak control, a purpose for which they have been used since they first became available in 1896. We suggest that mass vaccinations may be a relevant adjunctive measure for epidemic control and to limit the worldwide emergence and spread of MDR S. typhi.

REVIEW OF THE ONGOING TYPHOID FEVER EPIDEMIC IN TAJIKISTAN

Tajikistan is in central Asia, a part of the Commonwealth of Independent States, which has gone through massive socioeconomic restructuring and civil war. It contains a remote, mountainous region, Pamir; a relatively wealthy industrialized region, Leninbad; a fertile valley region around the capital city of Dushanbe; and a region adjacent to the Afghanistan border, Khatlon (Figure 1). The population is 6 million of which 2 million live in the Dushanbe region and 170,000 live in Kulyab in Khatlon. The major civil disturbance ended in 1994, but hostilities continue in several parts of the country. Funds have been lacking for the usual government support of public health, roads, and the antiquated water and sewage systems. Funds have not been available for patient care and diagnostic procedures in hospitals and there has been a shortage of electricity. Water chlorination was discontinued after 1995 due to inadequate supplies, soap is not easily available, and many people do not have facilities to boil water. In some districts, more than 50% of the population only have available water from the open canalization, with water pipes non-existent or in poor repair.

Typhoid fever has been endemic at a low level in Tajikistan for many years, and became epidemic in February 1996. A moderate increase had occurred in the industrialized north (Leninbad) during 1995, which is now under control. During 1995, the Tajikistan Ministry of Health recorded a total of 154 cases in the Dushanbe region, 18 cases in Pamir, and 52 cases in Khatlon. During the first four months of 1996, the number of cases in Leninbad and in remote Pamir remained unchanged, whereas there was a greater than 5-fold increase in typhoid fever in Dushanbe and Khatlon, heralding a major epidemic. Heavy rains at the end of April, and again at the end of May were associated with an increase in the number of typhoid fever cases recorded 10 to 20 days later. Since then, more than 24,000 cases have been officially registered in these two regions, and as of April 1998, the epidemic continues. During the period of 1996 for which information is available, there was only a slight increase (less than 50%) in other water-borne diseases such as hepatitis A and shigellosis, and an approximately 3-fold increase in infections caused by S. paratyphi.

The city of Kulyab was particularly affected during the civil war. The government infrastructure was destroyed, and there was an exodus of middle and upper class business. Sanitation and water purification were neglected. In several instances, open sewage drainage ditches were observed to be located next to the water pipe system, of which valves for the regulation of pressure were immersed in contami-
nated sewage each time heavy rain led to overflowing of the drainage ditches.

There were no cases of typhoid fever recorded in Kulyab during 1995. In February 1996, 2 cases were identified, in March 18 cases, and in April 26 cases. Figure 2 shows the number of cases that occurred each day during May and June 1996. A total of 1,706 cases occurred in May and 1,621 occurred in June. There were two epidemic peaks, one near the end of April, and one in June, both occurring after the heavy rain. After the flooding at the end of May, between 50 and 105 new typhoid fever cases were admitted to the main hospital per day. Many of the cases came from an area approximately 100 to 200 meters from the main hospital where two open toilets, which served as the only sanitary facility for the entire hospital, had been noted to overflow during the flooding. A logical link thus exists between hospitalized patients with typhoid fever in May and the nearby epidemic.

During the months for which data are available (May and June 1996), more than 60% of the cases in Kulyab and Yavan, a town just south of Dushanbe, occurred in those 4–19 years of age. The reported case fatality rates ranged from 1.2% to 8.2% in the same time period. Information recorded on the causes of death suggested intestinal perforation and/or hemorrhage in most cases.

Chloramphenicol was generally the first-line antimicrobial agent used during the epidemic. For numerous reasons, quinolones were administered to only a minority of patients. The
available data regarding the relationship between clinical outcome and administered antimicrobial agent(s) is incomplete to draw any firm conclusions.

**Diagnosis of MDR typhoid fever.** In Kulyab, approximately half of the suspected typhoid fever cases in May and June 1996 were confirmed by culture. The extent of the epidemic overwhelmed the capacities of local microbiology laboratories and the supply of media and reagents was exhausted by the end of June. Thereafter, diagnosis was made clinically, based on the presence of prolonged fever in an epidemic setting without another cause identified.

Several blood culture specimens from clinically suspected typhoid fever cases were sent to different laboratories in western Europe or the United States for bacterial isolation and susceptibility testing: 7 of 7 specimens sent by WHO were positive for *S. typhi* (June 1996), as were 7 of 8 specimens collected by the Federation of the Swiss Red Cross (July 1996, Renz T, unpublished data) and 24 of 26 specimens collected by Medical Emergency Relief International (MERLIN, London, United Kingdom, February 1997).5 In approximately half the suspected typhoid fever cases in Kulyab Widal serology was performed locally. Forty-six percent of the blood samples were positive in May 1996, and in 93% of those with positive Widal tests, *S. typhi* was cultured. Standard methodology (single antibody titer to the O and/or H antigen ≥ 1/80) was used, but paired Widal specimens (acute and convalescent) were not obtained.

In June 1996, all seven blood culture samples collected by WHO grew *S. typhi* that was sensitive to chloramphenicol but resistant to ampicillin and trimethoprim/sulfamethoxazole (TMP/SMX). However, 7 of 8 blood culture specimens collected by the Swiss Red Cross in July 1996 grew MDR *S. typhi*, defined as resistant to chloramphenicol, ampicillin, and TMP/SMX (Renz T, unpublished data). Furthermore, 74 of 80 *S. typhi* isolates collected in January and February 1997 by the Centers for Disease Control and Prevention (CDC) (Atlanta, GA)6 and MERLIN5 were MDR. Of great concern, 28 of the 34 MDR isolates collected by MERLIN, but none of the WHO or CDC isolates, were also resistant to ciprofloxacin (minimum inhibitory concentration = 0.5–1.0 mg/L).5 It is not clear whether these findings represent a trend during this epidemic from initial drug susceptible to MDR strains; the concurrent presence, at least early in the epidemic, of chloramphenicol-sensitive and MDR strains;7 or whether prolonged incubation of blood culture specimens resulted in preferential growth of a susceptible strain of *S. typhi* in the samples collected by WHO in June 1996 that had been stored in a hospital incubator. The epidemic in Tajikistan, to our knowledge, represents the first reported epidemic of ciprofloxacin-resistant typhoid fever, which together with population displacements associated with the civil war, raises serious concerns about spread of these organisms to wide areas. Further data about the geographic distribution and the clonality of the epidemic strains are urgently needed.

**Potential indication for typhoid fever vaccination during the epidemic.** The clustering of typhoid fever cases in different regions of Tajikistan and within certain parts of the cities is consistent with multiple point sources of the epidemic. The association of the two major peaks of the epidemic in Kulyab with flooding, and the state of the drinking water pipes suggests contamination of the communal water supply as the major cause. In early 1997, testing by the CDC identified that 97% of drinking water samples in Dushanbe were contaminated with coliform organisms and a case control study suggested that the epidemic there was caused by contaminated drinking water.6

In addition, a complexity of factors is likely to have facilitated secondary transmission of typhoid fever to contacts. These factors include the large number of cases, the probable ineffectiveness of chloramphenicol, the lack of facilities for handwashing and adequate excreta disposal, and frequent visitors to hospitalized patients. Hospital-related acquisition of typhoid fever is well documented in the literature.6,10 Many of the typhoid fever patients in Dushanbe in June and July 1996 were thought by the local physicians to have acquired the disease during residence or visit to Kulyab, suggesting that multiple modes of disease acquisition occurred.

Overall, the data summarized above suggest that since 1996 Tajikistan is having a large-scale, prolonged typhoid fever epidemic that has overwhelmed the public health infrastructure. Water, sanitation, and personal hygiene deficiencies are extensive and have created multiple point sources of disease acquisition as well as opportunities for secondary spread. For these reasons, and in view of epidemic MDR *S. typhi* strains, mass vaccination may be useful for epidemic control. The feasibility of this strategy is suggested by preliminary data from a mass vaccination campaign involving a contingent of Russian soldiers stationed in Dushanbe (Aparin PG, unpublished data). After 174 cases of typhoid fever, including 2 deaths, occurred during January and February 1997, a total of 18,362 soldiers 18–21 years of age received a dose of Vi vaccine in March 1997. Fifty-one typhoid fever cases of generally mild severity were recorded among the vaccinated group until December 1997. This decrease in new cases suggests efficacy of the mass vaccinations among individuals who were affected by inadequate food, water, and general living conditions in the setting of the Tajikistan epidemic.

**HISTORY OF THE USE OF MASS VACCINATION FOR THE CONTROL OF ENDEMIC AND EPIDEMIC TYPHOID FEVER**

**Early vaccination campaigns.** In most areas of Europe and North America, the incidence of typhoid fever greatly decreased during the second half of the 19th century, in association with widespread water and sanitation installations, and effective public health programs.8,11 However, occasional localized epidemics continued to occur since drinking water filtration was not yet optimized, early communal water systems were susceptible to contamination, and widespread water chlorination did not begin until around 1910.

The first typhoid fever vaccines contained a heat-killed broth culture of whole typhoid organisms. After the first human experiments in England in 1896,13–16 the successful use of these vaccines for the control of an epidemic was first documented in 1900.14 Since then, there have been many reports suggesting the effectiveness of mass vaccination campaigns for the rapid termination of epidemics and for the prevention of clinical disease in those vaccinated.14,16–20 However, the evaluation of whether the use of vaccines was effective left many unresolved questions since early vaccines
were of unstandardized quality, the studies were uncontrolled, and most reports did not address issues such as the means of diagnosis (inclusion of culture proven cases only), the duration of exposure of vaccinated and nonvaccinated groups, and concurrent sanitary and public health interventions.16,21 Nevertheless, when more than 10,000 British soldiers were vaccinated between 1904 and 1908, a 6-fold reduction in new cases was reported in this population.16,20

The incidence of typhoid fever in the U.S. Army was recorded as greater than 14% of the population annually during the last years of the 19th century.17,18,20 After 1911, when immunization was made compulsory, the incidence of new cases was reported to decrease more rapidly and to a greater degree (to less than 1 annual case per 10,000 soldiers after 1920) than in the general population.17 Similar observations were reported from civilian campaigns. Typhoid fever essentially disappeared in the vaccinated populations, whereas similar incidence reductions in non-immunized persons were not recorded until several years later, as sanitary conditions were improved.17,20,22,23

Limited civilian epidemics continued to occur in the first half of this century. In Hannover, Germany in 1926, 117,000 inhabitants of the city were immunized within 3 weeks of the onset of an epidemic involving 2,200 cases (0.5% of the population).24 However, this massive immunization campaign was criticized as unnecessary since the source of contamination of the municipal water supply had been rectified and the number of new cases was already decreasing by the time the vaccinations were initiated.25

Apart from such outbreaks, the incidence of typhoid fever in western Europe had stabilized at fewer than 5 cases per 100,000 population annually by 1939. With the disruption of the community infrastructure and large population movements, a dramatic resurgence of typhoid fever occurred during World War II,26 and enthusiasm for mass vaccination was revived. Public Health authorities suggested that: "...where a lack of money or of coordinated effort still prevents the procurement of a safe water supply, mass vaccinations could at least limit the epidemics, and such campaigns should certainly not present insuperable difficulties".26 In the following years, adequate drinking water and sanitation were restored in many parts of western Europe, and the incidence of typhoid fever decreased to prewar levels. Mass immunizations were never conducted.

Mass vaccination campaigns since World War II. Since World War II, typhoid fever vaccines have been used in three situations: 1) high incidence, prolonged epidemics with multiple point sources of disease transmission; 2) low incidence, prolonged epidemics with multiple point sources (endemic disease); and 3) single point-source epidemics. Table 1 summarizes use of typhoid vaccination during prolonged epidemics that have occurred recently.

Mass vaccination appears to have been associated with the control of typhoid fever in Bangkok, Thailand after 1977.27 In Bangkok, typhoid fever was endemic at a low level with fewer than 100 cases yearly in 1970 and 1971 recorded in two main hospitals. The number of cases began to increase for unclear reasons in 1972, and more than 800 cases occurred in the peak year of 1976. In 1977, annual mass vaccination of all school children 7–12 years of age was initiated since this was the most heavily affected age group. The number of new cases seen in the same two hospitals subsequently was approximately 400 in 1978, 300 in 1979, and fewer than 100 in 1984 and 1985. No decrease occurred in the number of paratyphoid cases, suggesting that the degree of typhoid fever control achieved was likely to have been linked to mass immunization, and not to concurrent improvements in sanitation. Significant decreases in typhoid fever cases also occurred among the nonvaccinated age groups, indicating that reductions in the secondary spread of the disease played a role in the overall effectiveness of the vaccination programs.27

Another experience with mass typhoid fever vaccination in a Kurdish refugee camp in Iran28 supports the findings in Bangkok. In 1991, an increase to approximately 15 new cases per week of typhoid fever was recorded in the camp. In conjunction with sanitary improvements and hygiene education, at least one dose of the oral Ty21a vaccine was administered during a 6-week period to approximately 12,000 of 15,000 refugees who were registered in the camp. Over the next three months, a more than 5-fold decrease in new cases was reported, and no cases were reported from those with a history of vaccination28 (and Reisinger EC, personal communication).

Substantial efficacy of typhoid fever vaccination has also been reported in numerous studies of its use to reduce endemic disease. Controlled field trials were conducted since the 1950s and involved more than 100,000 persons, and they demonstrated the efficacy of the inactivated whole cell vaccines,29–33 the Vi parenteral vaccine,34,35 and the oral Ty21a vaccine.36–40 A substantial decrease in typhoid fever cases in unvaccinated persons was repeatedly demonstrated after
these mass vaccination campaigns. Detailed reviews of the development of these vaccines and the results of the mass trials in endemic areas are available. In contrast to the examples listed earlier, the control of epidemics associated with contamination of a single common source (usually water or food) and a relatively explosive onset is rapidly achieved by carrier identification and/or purification of the water supply. There are numerous reports of epidemics controlled by these methods in the literature. Therefore, vaccinations were not necessary. Epidemics where evidence of a single source was not obvious initially led to mass vaccination campaigns in Hanover, Germany in 1926 (as discussed earlier) and in two contiguous towns in Romania in 1974. In these towns, where no typhoid fever had occurred for several years, a rapid increase in cases was reported in June 1974. Beginning in July 1974, 39,670 inhabitants of these two towns were immunized with a heat/phenol-inactivated vaccine. A total of 137 cases occurred, and the epidemic was thought to be foodborne, traced to a single chronic carrier. After August 4, 1974, during a 10-year period, no additional typhoid fever cases were reported in the vaccinated groups compared with 4 cases in nonvaccinated individuals. The epidemic ended within a month, once the carrier was identified. Mass vaccination may not have been necessary.

Currently available typhoid fever vaccines. The heat-phenol-killed and the acetone-dried whole cell vaccines had a protective efficacy of 51±66% and 79±88%, respectively, in controlled trials in endemic areas. The need for two doses approximately one month apart and poor tolerability have limited the usefulness of these vaccines as a public health tool; thus, their production has been discontinued by major vaccine manufacturers.

Enthusiasm for development of improved vaccines waned after the introduction of chloramphenicol as effective therapy in 1948 and was only revived by the first outbreaks of MDR typhoid fever in Mexico in 1972–1973. Two typhoid fever vaccines are currently available. A live oral vaccine consisting of an attenuated strain (Ty 21a) of S. typhi was licensed in the United States in 1989 (Vivotif Berna; Berna, Coral Gables, FL). The Ty21a vaccine is generally well tolerated, and 3–4 doses, each taken 48 hr apart, are required for 50–90% efficacy in endemic areas.

In 1994, purified Vi (virulence) polysaccharide capsular antigen, prepared without the cell wall components responsible for the adverse effects of the old whole cell vaccines, was licensed as typhoid vaccine in the United States (Typhim Vi; Pasteur-Merieux-Connaught, Swiftwater, PA). The Vi vaccine is generally well tolerated, seroconversion occurs within a week, and maximal protection is achieved after approximately one month. In two randomized trials in endemic areas, this vaccine was 75% and 55% protective against clinical typhoid fever over 17 and 36 months of follow-up, respectively. Serum antibody titers above a presumably protective level (1 μg/ml) may persist for 10 years in individuals who receive this vaccine (Klugman KP and others, unpublished data).

Coexisting infectious disease and malnutrition may attenuate the antibody response to vaccination, and protection against typhoid fever in early experiments using whole cell vaccines was overcome by a large inoculum of S. typhi. These factors may explain the limited efficacy of typhoid fever vaccines in areas with a high intensity of disease transmission.

CURRENT WHO APPROACHES TO EPIDEMIC CONTROL AND SUGGESTED STRATEGY FOR THE FUTURE

During the past 30 years, expert scientific groups have recommended to WHO a strategy of epidemic typhoid control that is based on antimicrobial treatment of acute cases as a supplement to improvements in water and sanitation, the mainstay of long-term typhoid fever control. This strategy does not rely on vaccination as a means to control epidemics, based on the requirement for multiple doses and the frequent occurrence of adverse reactions. Another consideration was that vaccination campaigns would divert resources away from attention to the source, be it drinking water or sewage improvements. Today, a re-evaluation of this strategy may be indicated, according to the following reasoning.

1) Multidrug resistance has greatly increased the cost of treatment: Quinolones are now required for acute MDR typhoid fever and for the eradication of chronic carriage. These drugs are expensive and not easily available in many countries. Short courses of quinolones (2–3 days) appear to be effective only in mild cases with fully sensitive strains.

2) The ongoing ciprofloxacin-resistant epidemic in Tajikistan and the potential spread of these strains raises serious concerns regarding the effectiveness of treatment of typhoid fever in the future; at present, quinolones are the only safe and reliable oral treatment. The intravenous third-generation cephalosporins are significantly less effective and no new class of antimicrobials is on the therapeutic horizon. Individuals with resistant strains may remain infectious for extended periods, and our ability to eradicate chronic S. typhi carriage with extended courses of quinolones may become compromised, creating increased opportunity for secondary spread of these organisms. Increased international travel and population movements in relation to civil war may further disseminate resistant strains.

3) Newer vaccines, such as the Vi vaccine, are effective, protection is provided by a single injection, and adverse reactions are minimal.

4) Areas disrupted by civil disturbance, such as in Tajikistan, may lack the immediate resources for the necessary water and sewage constructions, and for the implementation of an effective public health infrastructure. While it is not clear that mass vaccination campaigns could successfully be performed in such settings, the sanitation repairs needed for control of this multiple source epidemic are extensive, and would require an estimated 10–15 years to be accomplished. This is unacceptable in face of an uncontrolled MDR typhoid epidemic. While sanitation intervention undoubtedly remains a high priority, further extension of the outbreak may be limited after a single round of mass vaccinations.

For these reasons, it is concluded that mass immunization may be a valuable adjunct for the control of typhoid fever during a sustained, high incidence epidemic. Unresolved civil disturbance has currently led to the suspension of plans by WHO for a mass vaccination campaign in Tajikistan.
Choice of vaccine and target groups for immunization. Controlled trials in areas with different attack rates for typhoid have shown efficacy of both presently available vaccines, although these have never been directly compared.\textsuperscript{61} The oral Ty21a vaccine may have a slightly longer duration than the Vi vaccine and a broader spectrum of protection in that it may also provide immunity against \emph{S. paratyphi} B.\textsuperscript{36} Disadvantages of the Ty21a vaccine include potential risks in the presence of immunosuppression, and reduced efficacy if antibiotics or mefloquine are co-administered. For urgent immunization in the epidemic setting, the Vi vaccine appears preferable because of its stability at ambient temperature and the need for only a single injection.

In the future, a conjugate Vi vaccine,\textsuperscript{62} (Szu SC and others, unpublished data) or a single dose, oral vaccine may become available. Although a conjugate vaccine may be immunogenic in infants and young children, it will likely be costly and require a cold chain for maximum efficacy.

Typhoid fever in endemic and epidemic situations is particularly prevalent in persons between 5 and 25 years of age.\textsuperscript{29–40} Mass vaccination campaigns should be targeted at these age groups: they have already been successfully conducted in school children.\textsuperscript{27,34,36–38,40} The scientific advisory group of experts to the Children’s Vaccine Initiative and the Global Program for Vaccines and Immunization of WHO now recommends vaccination for school-age children in typhoid-endemic areas and areas with high prevalence of MDR \emph{S. typhi}, in coordination with school-based administration of tetanus-diphtheria vaccine.\textsuperscript{63} Adolescents and young adults may be more difficult to reach, but target groups may include military personnel, factory workers, and people at communal markets. Vaccination should also be considered for older adults because they are more likely to become chronic \emph{S. typhi} carriers,\textsuperscript{64} thus potentially prolonging an epidemic. Finally, differences in the age-specific attack rates need to be evaluated with some caution since the majority of cases may be asymptomatic or have a mild non-specific illness,\textsuperscript{65} especially young children and infants.\textsuperscript{66,67} However, in one study, the highest case fatality rate from typhoid fever was seen in young children,\textsuperscript{68} who also have the highest all-cause death rates in refugee and civil war settings.\textsuperscript{69} In the United States, the Vi and Ty21a vaccines are licensed for use in children more than 2 and 5 years of age, respectively.

Advantages and disadvantages of mass vaccinations. No conclusions about the exact prevalence of quinolone-resistant strains in Tajikistan, their \emph{in vivo} susceptibility, and their relationship to the clinical outcome are currently possible due the deficiencies in local microbiology facilities and clinical data collection. Such data will be central to the evaluation of the cost-effectiveness of preventive and therapeutic interventions in the future.

More studies are also needed to determine the exact impact of vaccination on prevention of the carrier state, but the best assessment at present is that vaccine-induced systemic antibodies may be sufficient to inactivate the inoculum, and reduce the likelihood of systemic infection and temporary and chronic carriage, and, thus, secondary spread.\textsuperscript{41,70} This is the most likely explanation for the observation of the large decrease in typhoid fever cases in unvaccinated persons after mass vaccination campaigns.\textsuperscript{27,41} Substantial reductions in endemic and hyperendemic disease have been achieved with mass vaccinations in multiple, large clinical trials, whereas the availability of clean water, adequate sewage removal, and control of other waterborne diseases has not been associated with the concomitant eradication of endemic typhoid fever as long as chronic carriage is widespread.\textsuperscript{71}

In areas where endemic typhoid fever has been controlled in the long term, large investments were necessary for identification of chronic carriers and sanitation improvements. Given the alarming emergence of MDR typhoid fever, we suggest that the addition of mass vaccinations to public health programs in endemic areas\textsuperscript{63} merits discussion. Economic barriers will require the targeting of such programs in priority to 1) areas with current large-scale outbreaks, 2) areas with the highest rate of endemicity or MDR, and 3) areas with limited success in implementing effective infrastructure changes to solve underlying sanitation and public health deficiencies. The long-proven benefits of preventing typhoid fever by vaccination in terms of quality of life, reductions in the cost of hospitalization, and gains in productive time for patients and caregivers\textsuperscript{11,27} are likely to be amplified in areas with epidemic and hyperendemic disease.

In addition to the cost, potential disadvantages of mass vaccination campaigns include adverse reactions to the vaccine, which are generally mild. Early observations of occasional rapid development of illness following vaccination in endemic areas (provocation disease\textsuperscript{19,21,25,72,73}) were not substantiated in any of the large controlled trials.

Concerns that a vaccination campaign may interfere with the institution of concurrent sanitation and public health measures, and that it could even provide a false sense of security in the vaccinated population have also been raised in the setting of cholera epidemics in refugee settings,\textsuperscript{74,75} but remain controversial.\textsuperscript{76}

CONCLUSIONS

The global typhoid fever situation has steadily worsened since the emergence and spread of MDR strains of \emph{S. typhi} since 1989.\textsuperscript{3,63} The occurrence of a massive epidemic in Tajikistan raises alarming prospects for the spread of quinolone-resistant \emph{S. typhi} strains to widespread areas. The present paper was intended to initiate a review of current typhoid vaccination policies to include the control of epidemic and endemic disease. Since no suitable alternatives to quinolones for the treatment of MDR typhoid fever are currently available, a redefinition of the importance and cost-effectiveness of preventive approaches,\textsuperscript{77} including novel vaccination strategies and augmentation of vaccine effects with adjuvants,\textsuperscript{78} in comparison with treatment-based intervention appears justified.

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