Local Article

Enteric Fever in South China: Guangxi Province

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Abstract
Guangxi is a province of China endemic for enteric fever. *Salmonella enterica* serovar Paratyphi A has been found to be causing more and more enteric fever episodes in the last 10 years, evident not only from routine surveillance but also from prospective population-based surveillance. The prevalent pattern of paratyphoid seen was different from typhoid since it mainly occurred in outbreaks. Almost all strains collected from different areas and years in Guangxi were resistance to nalidixic acid, which is an indicator of reduced efficacy of ciprofloxacin treatment. The emergence of epidemic paratyphoid fever occurred after large-scale use of the typhoid Vi vaccine, but little is know about why it emerged. This is of particular concern in the post Vi vaccine era due to the emergence and worldwide spread of multi-drug resistant *S.* Paratyphi A strains and the lack of a vaccine.

Key Words: Enteric fever, multidrug resistance, Vi vaccine, outbreak, *S.* Paratyphi A

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Introduction

Enteric fever is a major public health problem in countries where sanitary conditions are poor and it is the most frequent cause of community acquired septicaemia in several Asian countries [1]. Enteric fever is a clinical syndrome caused predominantly by human-restricted *Salmonella enterica* serovar Typhi (*S.* Typhi), and *S.* Paratyphi A, and may be caused rarely by *S.* Paratyphi B and C. Globally, the most common cause is *S.* Typhi [2], but across East and South Asia, *S.* Paratyphi A is becoming increasingly common [3]. The occurrence of large outbreaks and the emergence of multidrug resistant (MDR) isolates of *S.* Paratyphi A [4] has highlighted the importance of paratyphoid A fever and has led to concerns that *S.* Paratyphi A could replace *S.* Typhi under the selective pressure of typhoid-specific vaccination [3]. In India, an increase in paratyphoid as a cause of enteric fever from 6.5% in 1994 to 44.9% in 1998 was caused by an increase in the absolute number of paratyphoid cases [5]. Guangxi, the southern province of China, with a total population 48 million, is one of the provinces with the highest incidence of enteric fever and *S.* Paratyphi A infection has been recognised for several years. In this region there has been an apparent shift in the aetiology of enteric fever from *S.* Typhi to *S.* Paratyphi A such that *S.* Paratyphi A is currently the most common cause of enteric fever. Its implications are profound since the development of a vaccine against *S.* Paratyphi A may be several years away.

Epidemiology of enteric fever in Guangxi

The latest published figures for the estimated number of typhoid cases by Crump JA is around 22 million per year with an estimated 200,000 deaths [2]. Paratyphoid estimates correspond to between 1/10 and ¼ of those for typhoid [2,6]. However, these estimates have important limitations. The typhoid and paratyphoid incidence is mainly extrapolated from 22 population-based studies before the year 2000 and for the countries where this matter has been studied. In the last 10 years, many studies from Asia show that paratyphoid fever caused by *S.* Paratyphi A can contribute to more than 25% of all cases of enteric fever[7-12].

Over this period, re-emergence of *S.* Paratyphi A has also been reported widely in China. Since these two diseases are clinically indistinguishable, typhoid fever and paratyphoid fever were reported as one disease in The National Notifiable

Infectious Disease Reporting System (NIDR) in China before 2004. During 1980-1995, the incidence of typhoid fever in Guangxi province, southwest China, fluctuated between 3.2-13.4/100,000 (1000-6000 cases) per year. All of the strains isolated from patients were *S.* Typhi. Paratyphoid fever was a neglected disease. However, *S.* Paratyphi A was first isolated from patients in San Jiang county in 1995 [13] and Quanzhou county [14] in 1996 and gradually became widespread in Guangxi province. At the same time, increases of the proportion, as well as the absolute number, of *S.* Paratyphi A was reported from other enteric fever endemic areas of China [15-19], The first *S.* Paratyphi A outbreak in Jiangxi province was also reported in 1995 [13]. *S.* Paratyphi A is the prominent serotype of *Salmonella* responsible for paratyphoid fever in most endemic areas in China [20]. Due to the reported increase of paratyphoid fever, typhoid and paratyphoid fever have been reported separately in the NIDR since 2004. During 2004-2006, annual incidence of typhoid and paratyphoid in Guangxi was 3.0 per 100,000 and 2.5 per 100,000 respectively from NIDR and the incidence of typhoid was still higher than paratyphoid. However, the laboratory findings present a different picture. There were 1,855 strains of *S.* Paratyphi A and 401 strains of *S.* Typhi isolated from patients during 1994-2006 in Guangxi province Center for Disease Prevention & Control (GXCDC); 96.6% were from blood samples, the rest from stool and urine. Since 1999, *S.* Paratyphi A became predominant over *S.* Typhi in Guangxi and more than 90% of the strains isolated every year from patients were *S.* Paratyphi (Figure 1). Not only has the proportion of *S.* Paratyphi A in enteric fever increased, but the absolute number of *S.* Paratyphi A isolates has also increased while the isolation of *S.* Typhi still remains relatively constant.

Two prospective population-based disease surveillance studies were conducted in Guangxi recently. The case definition and laboratory procedures of these two studies were the same. Table 1 summarises the findings of the two studies and demonstrates that *S.* Paratyphi A caused most enteric fever episodes.

Table 2 shows the distribution of age, sex and occupation between enteric fever cases caused by *S.* Paratyphi A and *S.* Typhi in Guangxi.

In Guangxi, the prevalent pattern of paratyphoid was different from typhoid as it occurred mainly in outbreaks [13,14, 21-26]. During 2000-2005 there were 93 outbreaks in Guangxi, and out of these 93, sixty occurred in schools. The number of paratyphoid patients in outbreaks accounted for more than 50% of all paratyphoid patients in the years 2000 to 2005. The outbreaks and incidence reported varied by different geographical areas. Paratyphoid outbreaks seemed more likely to occur in the counties where the typhoid polysaccharide Vi vaccine (Vi vaccine) was introduced early; in addition, the more doses of Vi vaccine used in the county, the more outbreaks occurred [22].

Figure 1. Number of isolated strains of *S.* Typhi (ST) and *S.* Paratyphi A (SPA) collected by GXCDC from 1994-2006.

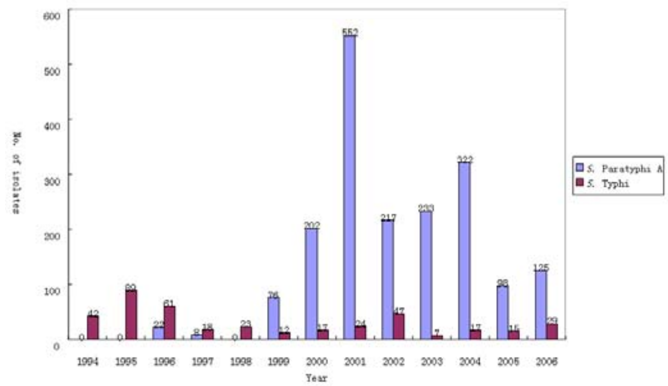

Table 1. Enteric fever episodes in two cities of Guangxi, China.

Study site	Hechi city*	Quanzhou city#
Surveillance period	Aug 01-Jul 02	April 06-Dec 07
Age group survey(y)	5-60.9	7-18
Population under surveillance(no.)	98,376	22,453
Total enteric fever cases	42	33
No. of *S.* Typhi cases(%)	15(36)	0(0)
No. of *S.* Paratyphi A cases(%)	27(64)	33(100)

* data from the Diseases of the Most Impoverished (DOMI) Program implemented by the International Vaccine Institute and funded by the Bill & Melinda Gates foundation[3].
# unpublished data from the School Intervention Program for Typhoid & Paratyphoid (SIT) implemented by GXCDC and funded by National CDC and GXCDC.

Case ascertainment and laboratory diagnosis

Confirmation of typhoid or paratyphoid fever requires isolation of *S.* Typhi or *S.* Paratyphi A, respectively, from blood, bone marrow, stool, or duodenal fluid. The Widal test identifies the agglutinating antibodies against the O (somatic) and H (flagellar) *S.* Typhi antigens, which appear a week to 10 days after disease onset. The high number of false-positive and false-negative Widal test results limits its clinical usefulness. In Guangxi, due to a lack of laboratory capacity in first-line and second-line health facilities, most of the cases reported in NIDR were diagnosed by clinical experience or the Widal test. Culture-confirmed cases only accounted for 17.8% of the total reported cases [27], so typhoid and paratyphoid fever reported from NIDR cannot usually be distinguished. However, this was not necessary for control and treatment of these diseases before the typhoid Vi vaccine was introduced in China in 1995. Some simple, inexpensive and rapid serological diagnostic tests for typhoid fever are available [28-33]. In an evaluation of three commercial kits, the sensitivity and specificity of Typhidot® (Malaysian Bio-Diagnostics Research Sdn. Bhd.,Selangor, Malaysia) and the Tubex® test (IDL Bideh, Solletuna, Sweden) in identifying blood-culture-positive cases of typhoid fever was higher than that of the Widal test. The sensitivity and specificity among the Widal test, Typhidot-M® and the Tubex® test were also evaluated in Guangxi [34], but these rapid tests have not been introduced into routine practice due to feasibility and their low sensitivity.

Table 2. Comparison of age, sex and occupation for patients with enteric fever in Guangxi, China.

Characteristic	*S.* Paratyphi A infected patients N=1603	*S.* Typhi infected patients N=293	P value
Mean age ± SD(yrs)	24.8 ± 12.7	25.0 ± 13.6	>0.5
Median age	20.7	19.5	>0.05
% aged < 10 yrs	2.37	5.8	<0.002
% aged > 50 yrs	4.93	4.43	>0.5
Sex ratio (M: F)	1.43:1	1.16:1	>0.1
Occupation:			
% student	56.39	47.3	<0.005
% peasant	21.05	36.15	<0.001

Antimicrobial resistance

In late 1987, there was an outbreak of typhoid fever in China, caused by strains resistant to all the first-line antimicrobials (ampicillin, co-trimoxazole, and chloramphenicol) [35]. Such multi-drug resistant typhoid is now reported from many parts of the world [36]. Along with the emergence of epidemic *S.* Paratyphoid A in Guangxi, multidrug resistant paratyphoid is also found. In the DOMI program conducted in Hechi, Guangxi, China, during 3 years of disease surveillance, 28 *S.* Typhi and 70 *S.* Paratyphi A were isolated. While the *S.* Typhi were sensitive to all antibiotics tested, except for one case resistant to nalidixic acid, the *S.* Paratyphi A isolates had varied antibiotic resistance profiles. All 70 *S.* Paratyphi A isolates were resistant to nalidixic acid [37]. In the Guangxi CDC laboratory, 338 *S.* Typhi strains collected from 1994 to 2005 in Guangxi were tested using the K-B method. All *S.* Typhi isolates were sensitive to norfloxacin, amoxicillin, ciprofloxacin, cefotaxime, ceftazidime and ofloxacin. One (0.3%) strain was resistant to chloramphenicol, 3 (0.89%) strains to tetracycline, 6 (1.78%) strains to ampicillin, 36 (10.3%) strains to nalidixic acid, and 108 (31.95%) strains were resistant to sulfonamide. From 1999 to 2005, there were 1,414 *S.* Paratyphi A strains collected in Guangxi. All *S.* Paratyphi A isolates were sensitive to amoxicillin, ciprofloxacin, ceftazidime and ofloxacin, while 0.15% of *S.* Paratyphi A strains were resistant to norfloxacin, 0.35% to chloramphenicol, 1.70% to sulfonamide, 6.22% to ampicillin and 86.79% were resistant to nalidixic acid. Fourteen *S.* Paratyphi A strains collected from several cities in 2006 were all found to be resistant to nalidixic acid. From this data, it seems that multidrug resistance is more common in paratyphoid than typhoid and there is one common phenotype: almost all *S.* Paratyphi A strains collected from different regions of Guangxi, in different years, are resistant to nalidixic acid. Nalidixic acid resistance is a marker for predicting low-level resistance ciprofloxacin among *S.* Typhi and *S.* Paratyphi A and also an indicator of treatment failure with ciprofloxacin [38-40]. Multi-drug resistance as well as reduced susceptibility to many commonly used antibiotics has also been reported for *S.* Paratyphi A in many countries [8, 9, 11, 41].

Risk factors associated with typhoid and paratyphoid fever outbreak

Enteric fever is an oral-faecal transmitted disease and therefore is primarily a disease where overcrowding, poor sanitation and untreated water are the norm. Ice cream is also recognised as a significant risk factor for the transmission of typhoid fever [6]. Two studies from Japan and Singapore indicated paratyphoid outbreaks caused by *S.* Paratyphi A were associated with consumption of contaminated oysters and coconuts [42,43]. A recent study by Vollaard indicated that typhoid and paratyphoid fever are associated with distinct routes of transmission. Factors within the household (e.g. poor personal hygiene and housing) were more important risk factors for typhoid, whereas factors outside the household (e.g. food from street vendors and flooding) were more important for paratyphoid fever [44]. In Guangxi, the epidemiological field investigations showed major causes of typhoid and paratyphoid outbreaks in 14 schools during 1996-2002 might be due to drinking unboiled well water, misdiagnosis, and improper treatment schemes [45]. Some case-control studies conducted to investigate the causes of outbreaks of paratyphoid fever in recent years in Guangxi suggested that the outbreaks might be associated with hand washing, drinking contaminated well or river water, and/or contact with patients [21,46]. But still, little is known about the current causes of paratyphoid in Guangxi.

Vi vaccination

Two vaccines for typhoid fever, one based on the Vi polysaccharide and the other on whole-cell live attenuated bacteria, are currently licensed. The live oral vaccine Ty21a is available in an enteric-coated capsule [47] or liquid formulation. The vaccine is moderately effective for up to about 3 years after vaccination [48,49]. The Vi polysaccharide vaccine has a protective efficacy ranging from 55% to 72% for 3 years after vaccination [50-53]. Neither vaccine protects against infections caused by *S.* Paratyphi A; indeed, no licensed vaccine protects against *S.* Paratyphi A. However, a new vaccine against *S.* Paratyphi A composed of surface-O-specific polysaccharide conjugated with tetanus toxoid has proved safe and immunogenic [54].

In China, an immunisation program against typhoid fever was initiated in the 1980s. Both vaccines (killed whole cell injection and live orally administered Ty21a) were administered. The use of the former vaccine was stopped due to severe local side effects. The latter vaccine had limited application due to its high cost. In 1990, scientists from the US National Institutes of Health introduced the technology for production of the Vi vaccine to The Ministry of Health in China. This locally produced Vi vaccine, formulated in 30μg doses, was then tested in Jiangsu [51] and Guangxi provinces [50] in 1994 and 1995 respectively. These two individually randomised placebo-controlled trials showed that the locally produced Chinese Vi vaccine confers a protection of 70% in school-aged children and adults up to 19 months after vaccination. The Ministry of Health, through a joint research program with six institutes of biological products, produced around 10 million doses of Vi per year before 2004.

Since July 1996, following the locally produced Vi trial results, the Vi vaccine has been used routinely and nationwide in China. The implementation of Vi immunisation in Guangxi includes vaccination in areas and vicinities of outbreaks and general immunisation in school-aged children in endemic areas. Since Vi is a non-EPI vaccine and no central government or local government funds it, the decision to establish a vaccination program is up to the city or county. Hence the large-scale use of Vi was usually in high typhoid endemic areas of Guangxi. From 1995 to 2006, more than 4.2 million doses were used in Guangxi. The average coverage of the first doses of Vi in students varied from 0% to 90% between counties. In the Guilin region, the highest endemic area of Guangxi, Vi vaccination took place each year from 1995, and between 1995 and 2006, more than 1.4 million doses were administered, peaking in 2000 and 2001. Overall, seventy-seven percent of the vaccine was given to students [55]. Introduction of Vi vaccines in Guangxi led to a fall in typhoid in all age groups in the endemic area. However, it is apparent that the causal agent of enteric fever has shifted from *S.* Typhi to *S.* Paratyphi A in endemic areas after the introduction of the Vi vaccine [22].

Conclusions

Enteric fever remains a major public health problem in Guangxi. *S.* Paratyphi A has been causing more and more enteric fever episodes in this region over the past 10 years. The emergence and worldwide spread of multidrug resistant *S.* Paratyphi A strains results in the treatment of enteric fever becoming more difficult. As there is no licensed vaccine to control enteric fever caused by *S.* Paratyphi A, high attention should be paid to the emergence of epidemic paratyphoid fever in the post Vi vaccine era. Since little is known about the emergence of epidemic paratyphoid, understanding the risk factors, epidemiology, diagnosis and treatment of paratyphoid fever and some specific aspects of its pathogenesis are essential for control of the disease.

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