Financial Barrier as a Determinant of Getting Definitive Diagnosis and the Clinical Fate of Suspected Enteric Fever Patients in the Endemic Areas of Yunnan Province, China

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ABSTRACT

Background

Yunnan province has the highest incidence of typhoid and paratyphoid fever (enteric fever) in China. The definitive diagnosis of enteric fever depends on a hemoculture test. The test dictates adequate treatment of patients and the results are essential for burden estimating, priority setting, planning and evaluation of various public health measures.

In Yunnan, 40-50% of reporting cases do not have haemoculture done despite the fact that 80% of enteric fever cases are reported from hospitals at county level or above, where the test is available. Approximately 30-40% of enteric fever patients in the endemic areas are treated as outpatients. Improper diagnosis and case management make it impossible to properly control endemicity of this fecal-oral communicable disease. There is

currently no public financial system that fully covers suspected enteric fever patients in China. To date, there have been no studies that have identified a link between cost of haemoculture and diagnosis accuracy as well as a good clinical outcome of the patient. No study in China has covered home visit to follow up living conditions of these patients. Thus proper public hygiene status is not documented. There is a need to document the relationship between financial difficulties, health insurance and lack of proper diagnosis. There is also a need to document the hygiene condition of these patients.

General objective

This research aims to document the financial barriers against access to diagnostic procedures among enteric fever suspects in highly endemic areas of China and to document clinical course, financial and hygiene conditions among convalescent patients with enteric fever.

Specific objectives and study setting

This thesis consists of two studies: "Financial Barrier against Access to Diagnostic Procedures among Enteric Fever Suspects in Highly Endemic Areas of China" and "Clinical course, financial and hygiene conditions among convalescent patients with positive haemoculture for *Salmonella paratyphi A* in an endemic area of southwest China". These two studies were

concurrently carried out from May 2007 to September 2008 in enteric fever endemic areas of Yunnan.

The first study was conducted in seven counties (Shizong, Luoping, Chengjiang, Mile, Jinghong, Menghai and Mengla) of Yunnan. Six study hospitals at county level and twelve at township level were used for detecting the level of access to definitive diagnostic procedures, especially haemoculture among the outpatient suspects. Two prefecture level hospitals (Yuxi City Hospital and Traditional Chinese Medicine Hospital-located in capital city of Yuxi city - Hongta district) were involved in the second study which focused on clinical course, financial and hygiene conditions of enteric fever patients during their admission to hospital and within one month after discharge.

Study design and methodology

The first study is a hospital-based cross-sectional survey with face-to-face interview using a structured questionnaire and data extraction form. In the outpatient department of the study hospitals, laboratory investigations (haemoculture) were ordered by a doctor for their patients and the real payment of the patient was recorded. A total of 714 subjects were recruited. Predictors for financial barrier against

access to the test were analysed using Chi-square tests and logistic regression.

The second study is a prospective study in which 260 inpatients with *S. paratyphi* A hemoculture positive were followed up after two weeks and again at one month after discharge from hospital. Information was obtained from questionnaire, medical records, and observation of household environmental conditions using a check list. Two stool sample cultures from each patient were taken at the second follow up visit.

Results

From the first study, only 57% (407) of the outpatient suspects could afford haemoculture routinely ordered by their doctors. Of these, 30% (123) had haemoculture positive for *S. typhi*. After adjustment for income, not getting haemoculture was marginally associated with percentage of reimbursement from the insurance (P value for trend=0.047). Illiteracy was also an independent risk factor for this outcome.

From the second study, 66% of patients had fifteen days of illness, 56% had twelve days of hospitalization, while 75% had more than one week of persistent fever. No deaths occurred. Complications, relapses and carriers were rare. The average hospital charge was approximately 18% of the average annual family income. Three quarters of the patients had health insurance which paid for an average of one-third of the hospital charge.

23 (9%) patients were found to be in absolute financial hardship, such as borrowing money results in getting into debt. One fifth and one quarter of the study households had an open sewer and non hygiene latrine, respectively. Waste management problems as well as poor water supply (39%) were markedly higher in the rural areas, as were the number of low education and low income families.

Conclusions and recommendations

Poor coverage of haemoculture for patients suspected of having enteric fever in this endemic area was due to financial barrier. The current health insurance system inadequately relieved the problem. Better financial management is needed to improve the situation.

S. paratyphi A in this district poses a significant public health problem and economic burden. Although full hospitalization and antibiotic usage produced relatively good clinical results, hygiene conditions, which were very poor, needs to be improved for better prevention and control.

Key words: Enteric fever, haemoculture, access to care, health insurance, *Salmonella paratyphi* A, clinical course, financial hardship, hygienic problem, China

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BMIUE	Basic Medical Insurance for Urban Employees
CDC	Centre for Disease Control and Prevention
CI	Confidence interval
INR	Indian Rupee
IQR	Inter-quartile range
LR	Likelihood ratio
MDR strains	*S. typhi* resistance to Ampicillin and trimethoprim-sulfamethoxazole
NARST strains	Nalidixic-acid-resistant *S. typhi*
NRCMS	New Rural Cooperative Medical Scheme
OR	Odds Ratio
RMB	Renminbi (Yuan)
SD	Standard deviation
S. paratyphi	*Salmonella paratyphi*
S. typhi	*Salmonella typhi*
USD	United States Dollar
WHO	World Health Organization

TCMH	Traditional Chinese Medicine Hospital

STRUCTURE OF THE THESIS

The thesis consists of five chapters.

Chapter one provides the background information of the study area, the current situation of prevalence of enteric fever in Yunnan that generated the research questions in this study.

Chapter two contains findings of previous studies relevant to definitive diagnosis, financial barrier for diagnosis and treatment, clinical course and hygienic conditions.

Chapter three presents manuscript 1 "Financial Barrier against Access to Diagnostic Procedures among Enteric Fever Suspects in Highly Endemic Areas of China" which has been accepted for publication in the Journal of Heath, Population and Nutrition on 30 August 2009. This chapter fulfils the first objective of this thesis.

Chapter four presents manuscript 2 "Clinical course, financial and hygiene conditions among convalescent patients with positive haemoculture for *Salmonella paratyphi A* in an endemic area of southwest China". This chapter answers the research question related to the last objective of the thesis.

In chapter five, an integrated discussion for the two studies of the thesis is presented. General conclusions and recommendations are given, together with the strengths and limitations of both studies.

Chapter 1 Introduction

1. Background

Nowadays, typhoid and paratyphoid fever (both called enteric fever) is rare in developed countries with the provision of clean water, good sewage systems and sanitation since the last century. However, it remains a serious health problem in developing countries where sanitation conditions are inadequate and access to clean water is limited. According to the best global estimates, at least 16 million new cases occur each year, resulting in 600,000 deaths. Areas where the incidence reaches more than 100 cases per 100,000 population per year are considered as endemic. The cases occurring in Asia (south-central and southeast sub-regions) account for 59% of the total global cases, 24% occur in Africa, 16% in Latin America, and 1% in Europe [1].

Enteric fever is a systemic infection with a prolonged febrile period. It is caused by the bacterium *Salmonella enteric* serovar (*S. typhi* and *S. paratyphi*), transmitted by the fecal-oral route via contaminated food and water. Poor outcomes, including death, can occur without effective antibiotic treatment. Enteric fever is an important cause of economic burden since it leads to absenteeism from work.

The absence of specific symptoms or signs makes the clinical diagnosis of this disease inaccurate. Definitive diagnosis of enteric fever depends on the isolation of *S.typi* or *S.Paratyphi* from blood or

bone marrow. Definitive diagnosis dictates adequate treatment of patients. From a public health point of view, accurate data are essential for priority setting, planning and evaluation of various public health measures [2].

In many developing countries, many patients cannot acquire definitive diagnosis due to limited facilities. It has been reported that 90% of patients are treated as outpatients and not notified, especially in rural hospitals [3]. Thus, the real magnitude of the disease burden is difficult to estimate. However, implication of an Indian study conducted in a slum, patients without haemoculture performed and treated as an outpatient could not attribute to lack of facilities. The costs of treatment for patients with enteric fever as an outpatient and inpatient were USD 101 and USD 500, respectively. Only 3%-11% of all culture-confirmed patients were hospitalized. That study also showed that the laboratory test costs USD 3.5 [4]. These facts hint that accurate diagnosis may have a strong linkage with out of pocket money and also depends on the ability to pay.

Although many articles mentioned that enteric fever contributes to a big disease burden, data are very scarce. Three prior follow-up studies have been done, but they focused on different parts, such as clinical manifestations and costs of illness [4, 43, 57]. None have integrated the clinical course and financial problem, and thus not have led to any policy changes.

The high incidence of enteric fever in endemic areas is due to unsafe water drinking, inadequate sanitation, and poor hygiene. In developed countries, the incidence of enteric fever has declined greatly with

provision of safe water and good sewage systems in the general population [5]. Waterborne and foodborne outbreaks occurring in endemic areas have been identified by many studies [6-12]. Several studies which singly focused on poor food hygiene and housing sanitation as risk factors for enteric fever have been conducted in Indonesia and Vietnam. These studies showed that poor hygiene and sanitation were associated with enteric fever [13-14, 68]. However, all of these studies did not link clinical course, financial status and hygiene of enteric fever together at same time. In China and Yunnan province, there is not enough data to show the linkage for high incidence of enteric fever with poor sanitation and hygiene condition in enteric fever endemic areas.

2. Background of Yunnan province

2.1 Geographic background of Yunnan province

Yunnan is the most southwestern province of China, with the Tropic of Cancer running through its southern part. It shares a border of 4,060 km with Myanmar in the west, Lao PDR in the south, and Vietnam in the southeast.

The province has an area of 394,100 km^2, 4.1 % of the nation's total. Mountainous areas account for 94 percent of the province's total land. The population was 44,830,000 in 2006, including 31,157,000 rural people and 13,673,000 urban people. There are 16 prefecture-level divisions, 129 county-level divisions, 1,565 township-level divisions and 13,428 administrative villages in Yunnan [15].

2.2 Economic-demographic characteristics of Yunnan province

Yunnan is one of the least developed provinces of China, with more poverty-stricken counties than the other provinces. In 2006, the GDP per capita of Yunnan was approximately USD 1,000 while the average GDP of China was USD 2,060. The net annual per capita income of farmers is approximately USD 281, whereas the average annual salary of civil servants is USD 2,338. About 6.7 million (15%) people live below the poverty line of less than an annual average income of approximately USD 119 per capita [15].

3. Enteric fever specific information

3.1 Enteric fever burden in Yunnan

In contrast to the recent decline in incidence of enteric fever in China, Yunnan is still one of the provinces with the highest rate of this disease. The number of cases and incidence reported from Yunnan are shown in Table 1.

Table 1 Reporting case and incidence in China and Yunnan 2001-2007

Year	China		Yunnan			
	Cases*	Incidence (/100,000)	Cases*	Rank in China	Incidence (/100,000)	Rank in China
2001	64461	5.07	9683	2	22.26	2
2002	59796	4.47	8992	2	18.91	2
2003	56288	4.17	9316	2	21.73	2
2004	49332	3.79	11142	1	25.59	1
2005	34696	2.65	9375	1	21.07	1
2006	25986	1.99	8172	1	18.36	1
2007	20455	1.55	5946	1	13.26	1

* Clinical case and confirmed case

3.2 Endemic characteristic of enteric fever in Yunnan

3.2.1 Location

The data (46,997 reporting cases) from 2002 to 2006 showed that the prefectures with higher than average incidence in Yunnan were Banna, Dehong, Yuxi, Honghe and Kunming. Endemic counties include Hongta distrct (Yuxi), Chengjiang county (Yuxi), Menghai county (Banna), Kaiyuan city (Honghe) and Luxi city (Dehong) at county level (Table 2). In Hongta district and Chengjiang County, the incidence of enteric fever reached 375 per 100,000 population per year.

Table 2 Top five prefectures and counties with highest incidence* per 100,000 per year, 2002-2006

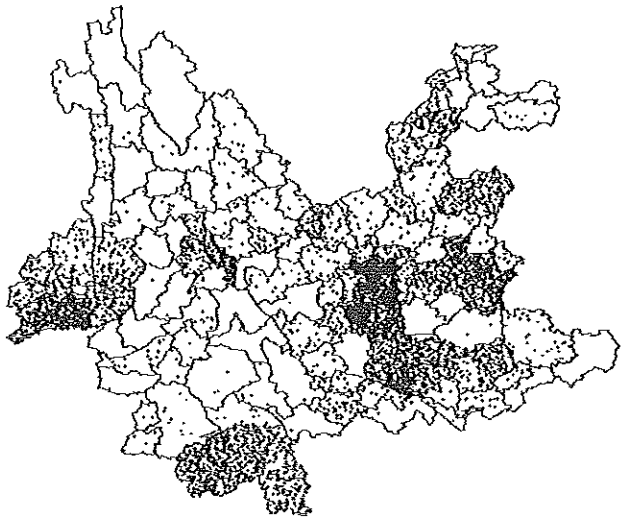
Rank	Prefecture	County
1	Banna (96.0)	Hongta (189.3)
2	Dehong (76.6)	Chengjiang (177.9)
3	Yuxi (68.6)	Menghai (117.8)
4	Honghe (41.7)	Kaiyuan (110.2)
5	Kunming(29.5)	Luxi (108.1)

* Average annual incidence

Case distribution with spot map is shown in Figure 1.

Figure 1 Distribution of enteric fever cases in Yunnan Province, 2006

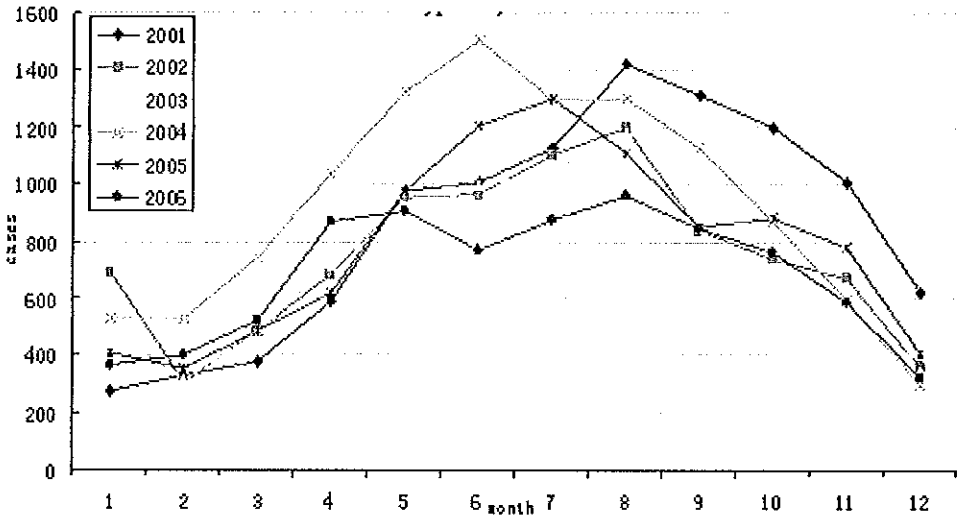
(1 Case = 1 Dot)



3.2.2 Seasonality

The distribution of cases has a very similar pattern each year. The peak occurs from May to November (Figure 2).

Figure 2 The monthly trend of enteric fever cases in Yunnan Province, 2001-2006



With this information, our study data were collected in Yuxi, Banna, Honghe and Qujing from May 2007 to September 2008 when the incidence would be high.

3.2.3 Person

Data from Yunnan communicable disease register reveal that cases which occur in the 10-50 age group account for 86.7% of total cases. Males account for 52% of the total. The most common occupation of the patients was farmer (38%), followed by student (23%) and worker (9%).

3.3 Enteric fever surveillance in Yunnan

3.3.1 Reporting system

There are 1898 health units which can report enteric fever cases to Disease Information System Network in Yunnan.

From the report, 40% of reporting cases do not have blood culture taken, despite the fact that 80% of enteric fever cases are reported from hospitals at county level or above, where the test is available. This inconsistency leads to the research questions of this study.

3.3.2 Implementation of sentinel surveillance

In 2005, Hongta District and Chengjiang County had been determined as two sentinel surveillance sites of national enteric fever surveillance system in Yunnan due to the high incidences in recent years. The task of this sentinel surveillance system is as follows:

(1) Suspected enteric fever case surveillance.

(2) Surveillance of carriers in public health concern population.

(3) Antimicrobial resistance surveillance.

There were 734 enteric fever suspected cases detected from June 2005 to December 2006 in the city first hospital of Yuxi. *S. paratyphi* A was isolated from 176 of the 734 suspected patients (24% positive rate). No *S. typhi* was detected.

The percentages of drug resistant isolates were 100% for rifampicin and 99.4% for nalidixic acid. Unfortunately, there was no information

on resistance to common antibiotics used for enteric fever cases in Honghe, Xisuangbanna and Dehong.

From January to December 2006, 525 cases of enteric fever suspected cases had been detected in Chengjiang county hospital and township hospitals. Twenty two cases were caused by *S. paratyphi* A. None was from *S. typhi*.

3.3.3 Control of enteric fever

There is no special intervention program involved to prevent and control enteric fever in this endemic area. Enteric fever cases are not followed up by any agent with an exception of the outbreak which is usually under the responsibility of the county CDC.

3.4 Medical insurance and seeking medical care of enteric fever

Medical insurance is one important issue in this thesis as it is hoped that the insurance will reduce financial difficulty when the patient gets the disease.

In China, as well as in the study area, there are two leading types of medical insurance.

The first is Basic Medical Insurance for Urban Employees (BMIUE) covering a population of 3,315,900 or 7.3% of total population of 45 million in Yunnan.

The other is New Rural Cooperative Medical Scheme (NRCMS) which began in 2005 to improve the health security of farmers in rural areas. The coverage of NRCMS reached 85% in 2006. However, NRCMS does not cover medical examinations and other service fees. Only prescription drugs

can be reimbursed. The maximum liability of reimbursement is relatively low and varies in different areas (from 10% to 20%) [16].

Urban employees, including civil servants, public service staff and the state enterprise workers are covered by BMIUE. Other urban residents, including students, are generally not covered by any type of medical insurance.

The costs in RMB for laboratory investigation are 80-220 for blood culture, 10-40 for Widal test, 5-25 for routine blood count, 5-10 for routine urinalysis, and 25-50 for chest x-ray. The patient may or may not get these laboratory investigations depending on their financial background.

Our pilot study (the registers of enteric fever in outpatient department were checked with list of inpatients), conducted in five county hospitals in 2006, showed that 30%-50% of enteric fever patients were treated as outpatients, and there was a big difference between outpatient expense (RMB 1000) and inpatient expense (RMB 1500-3500) for the medical care costs.

These financial barriers for not getting haemoculture test and admitting to hospital also lead to our research questions.

3.5 Situation of safe drinking water and sanitation

In 2007, the proportion of qualified safe drinking water in rural areas was 24%, and 76% in urban area of Yunnan province (data source: Yunnan CDC). The rate of utilization for sanitation latrine reported by CDC was 49.1% in rural areas and 70.29% in urban areas [6, 17], but

the study from Yunnan CDC showed that the respective rates were 27% and 72%.

There are 42 sewage treatment plants constructed in Yunnan, but only 20 have been completed. The capability of treatment for sewage is 1 million tons per day. The rate of sewage disposal of the city is 51.4 % which is lower than the average levels of the whole country (60.1%). Only 41.9% of the garbage in cities of Yunnan is properly disposed.

Conclusion of local situation, enteric fever remains a serious public health problem in some parts of Yunnan where sanitation and economic conditions are inadequate, most case are teenagers or young adults, nearly forty percent and approximately one quarter are farmers and students who are not covered by NRCMS for outpatient laboratory examination service or hospitalization. However, more than one quarter of reporting cases lack laboratory diagnosis. Thus, patients may suffer from a lingering illness and some of them face financial barrier.

Chapter 2 Literature Review

This chapter reviews international knowledge and focuses on the definitive diagnosis of enteric fever and ability of the patient to pay for treatment. The follow up study, clinical course, and survivorship of *S. typhi* and latrine sanitation is also explained. The knowledge gap identified from this review will guide current research. At the end of the chapter, the objective of the research and structure of the thesis are explicated.

1. Definitive diagnosis of enteric fever

The definitive diagnosis of enteric fever depends on the isolation of *S. typhi* or *S. paratyphi* from blood, bone marrow or stool. In practice, blood culture is the mainstay of diagnosis.

Bone marrow culture has the highest sensitivity (90-95%). This method has several advantages, one being that the sensitivity of isolation is not influenced by prior antibiotic therapy even in persons who have already received up to 5 days of antibiotic use or who have a long history of illness with a negative blood culture of the recommended volume blood. Bone marrow culture provides the best bacteriologic confirmation and is therefore the gold standard for diagnosis of enteric fever [18-20]. However, this method is painful and not easily accepted by patients.

Blood culture has a sensitivity of 50-80% and is influenced by duration of illness, volume of blood inoculated and prior use of antibiotic. Blood culture can be performed within two weeks of illness

duration, but the sensitivity is higher during the first week of illness, increased volume of blood culture and the ratio of blood to broth can be useful. Prior use of antibiotic reduces the sensitivity of blood culture [20-26].

Stool culture is less useful, and is positive in only 30% of patients with acute typhoid fever. The sensitivity of stool culture depends on the amount of feces cultured, and the positive rate increases with the duration of the illness. For the detection of carriers, several samples should be examined because of the irregular nature of shedding [27].

The Widal test has been a suggestive test for typhoid fever but the test is not definitive. The role of this test is controversial, because the sensitivity and specificity of this widely used test vary among geographic area. In 1991, Thelma, et al reviewed the clinical application of Widal test in different areas and concluded that the sensitivity and specificity of the test is unsatisfactory (Table 3) [28]. The test can be negative in up to 30% of culture-proven cases.

Enterica serotype *typhi* shares these antigens with other *salmonella* serotypes and shares cross-reacting epitopes with other enterobacteriaceae, and this can lead to false-positive results. Such results may also occur in other clinical conditions, such as malaria, typhus, bacteraemia caused by other organisms, and cirrhosis [29]. An Indian study conducted in 2004 showed that the sensitivity and specificity of Widal test was 74% and 83%, respectively [30].

Table 3 Sensitivity and specificity of Widal test done in developing countries endemic for typhoid fever

Country	Agglutinin	Cut-Off Titer	Sensitivity (%)	Specificity (%)	Reference
I. Tube agglutination					
Philippines	O	1:20	61	88	Aquino
Philippines	O	1:80	64	100	Buck et al
Hong Kong	O and H	1:50	84	99	Chow et al
Jordan	O and H	1:160	92	-	Shehabi
Peru	O	1:160	58	-	Levine
	H	1:160	82	-	
Ceylon	O and H	1:160	85.7	88	Senewiratne
II. Slide agglutination					
Philippines	O	1:160	72.5	57.5	Roxas et al
		1:320	57.5	100	
Jakarta	O and H	1:20	53	98	Hoffmann et al
Ethiopia	O and H	1:160	82	-	Abraham et al
South Africa	O and H	1:200	75	92.5	Somerville et al

Source: Thelma E. Phil J Microbiol Infect Dis 1991.

A previous study showed that a fourfold rise of agglutinin titer was rarely demonstrated whereas two- to three-fold rises of agglutinin titer were more common [31]. However, a latest study showed inconsistent results. Sensitivity of the test was 52% and the specificity was 88% for a cut-off of >1:200 for the O antigen test performed on acute-phase serum, and 90% sensitivity and specificity when the convalescent-phase serum was tested [32].

Since results of Widal test were inconsistent in different studies, we consider blood culture as a necessary diagnostic test for the suspects with having enteric fever in this thesis.

2. Financial barrier and definitive diagnosis of enteric fever

There have been no studies showing a linkage between financial barrier and lack of definitive diagnosis of enteric fever. Two studies have emphasized that up to 90% of enteric fever patients who were treated as outpatients without having a blood culture was due to a shortage of facilities, experts and equipments in hospitals [3, 33]. Only one qualitative study conducted in Cambodia reported that the test of diagnosis for dengue fever for poor people is too expensive to afford [34].

3. Follow-up study and financial barrier

In 1990, an American study paid attention to carrier, chronic carrier, and contact screening as well as frequency and time of follow-up. 185 cases were followed up. Thirty per cent of these were discharged by 51 days, 60 per cent by 88 days and 90 per cent by 238 days [35].

A prospective surveillance was carried out in an urban slum community in Delhi, India, to estimate the costs of illness for cases of typhoid fever. Non-patient (public) costs included costs of outpatient visits, hospitalizations and laboratory tests. Medicines were provided free of charge to the families. The mean cost per episode of blood culture-confirmed typhoid fever was 101 USD; hospitalization increased the costs by around five fold (510 USD) [4]. Therefore the rate of hospitalization was low, despite blood culture (cost USD 4.6) being free of charge, the study indicated that there was a strong linkage between hospitalization and ability to pay (table 4). The study also

described duration (days) of fever and few of patient's house sanitation conditions. A limitation of the study was that duration (days) of illness and outcome of illness were not mentioned.

Table 4. Mean (SD) duration of fever, hospitalization rate, and mean total costs of illness by diagnosis (1996 INR 35.5=USD1)

Feature	Blood culture-confirmed typhoid (n=98)	Blood culture-confirmed paratyphoid (n=31)
Total duration (days) of fever	14.2 (8.7)	10.4 (5.4)
% of cases hospitalized	11.1	3.1
Mean total cost	3,597 (5,833)	1,785 (1,331)
Mean total cost if hospitalized	18,131 (11,218)	_†
Mean total cost if not hospitalized	2,111 (1,375)	1,785 (1,331)

† Only 1 of 31 cases hospitalized

Source: Bahl et al. Journal of health, population, and nutrition 2004 [4].

Another follow-up study from Nepal, which mainly focused on clinical symptoms, tried to identify indistinguishable clinical syndromes between patients with infection of *S. typhi* and *S. paratyphi*. Infections with *S. typhi* and *S. paratyphi* were clinically indistinguishable and had equal severity. However, the limitation of that study was a lack of follow up of the patients. The information about hygiene conditions was about prior to admission, and there were no home visits. Thus the clinical course studied was incomplete.

4. Clinical course and outcome of enteric fever

Fever, initially low grade, rises progressively, and by the second week is often high and sustained (39-40°C). Untreated, the fever persists for two weeks or more and defervescence occurs slowly over the following 2-3 weeks. Convalescence may last for 3-4 months. If an appropriate antibiotic is given, then the fever gradually falls over 3-4 days [36]. Two studies reported a median of fever about 5-7 days with a range of 3 to 6 days [37-39], but could be as long as 10 days even when the patient is receiving appropriate therapy and does not have complications [40]. However, there is no any published study describing the whole duration of illness with antibiotic therapy.

Traditionally, clinical features of paratyphoid fever are similar to those of typhoid fever but are usually milder with a short incubation period [36, 41]. However, three recent Nepalese studies show inconsistent results. *Salmonella enterica* serovar *paratyphi* A and *S. enterica* serovar *typhi* cause indistinguishable clinical syndromes [42-44]. Household hygiene was not assessed.

Complications occur in 10 to 15% of patients and are particularly likely in patients who have been ill for more than two weeks. Gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy are the most important serious complications [36].

Gastrointestinal bleeding is more common, occurring in up to 10% of patients. In 1-2% of cases, bleeding is significant, and can be rapidly fatal if a large vessel is involved.

Perforation is now a rare occurrence with modern therapy. It was less than 1% in a recent report [37].

The incidence of neuropsychiatric presentations varies among countries. It ranges from 10 to 40% among hospitalized patients with typhoid in Indonesia [45, 46] and Papua New Guinea [47] but is less than 2% in Pakistan [48] and Vietnam [49]. This geographic variation is unexplained.

Many data report relapses which occur in 5-10% of patients, and usually 2 to 3 weeks after defervescence [3, 36, 41]. In Israeli, the rate is as low as 2% [37]. The relapse is usually milder than the original attack.

The overall mortality of enteric fever with proper treatment is less than 1%. In developing countries higher rates are reported, 30 to 50% in some areas of Papua New Guinea and Indonesia [36, 50- 52]. However, the most important contributor to a poor outcome is probably a delay in instituting effective antibiotic treatment.

The organisms may be by multi-drug resistant. Simultaneous resistance to ampicillin and trimethoprim-sulfamethoxazole *(MDR strains)* and nalidixic-acid-resistant *S. typhi (NARST)* have often been reported in previous studies, but resistance to ceftriaxone has rarely been mentioned. Ceftriaxone has been the antibiotic of choice recently for enteric fever suspects although a few resistances have been reported [53].

5. Survival of *S. typhi and* latrine sanitation

Humans are the only natural host and reservoir for *S. typhi* and S. *paratyphi* A. *S. typhi* (and generally, *S. paratyphi* serogroups A-C) as they only infect humans. In an exceptional outbreak of paratyphoid fever

in England, dairy cows excreted paratyphoid B organisms in milk and feces [54].

The pathogens can survive for days in groundwater, pondwater, or seawater, and for months in contaminated eggs and frozen oysters [41]. *S enterica* survive a period of 4 weeks in shady fresh water. If the stream is polluted with raw sewage, then the organism can survive over 5 weeks. Within solid faecal material, it can survive up to 1-2 months [42, 55-57].

6. Synthesis of the research problem

The above reviews show that enteric fever in Yunnan is serious in certain pocket areas, with poverty, incomplete coverage of health insurance and poor sanitation. It is likely that the population in the affected area will suffer from the disease both physically and socio-economically. There is a need for a study to link these two together. This information can be useful for planning of local health security packages as well as public health interventions.

7. Overall objectives of this thesis

This thesis aims to document financial barrier against access to diagnostic procedures among enteric fever suspects in highly endemic areas of China and to document clinical course, financial and hygiene conditions among convalescent patients with enteric fever.

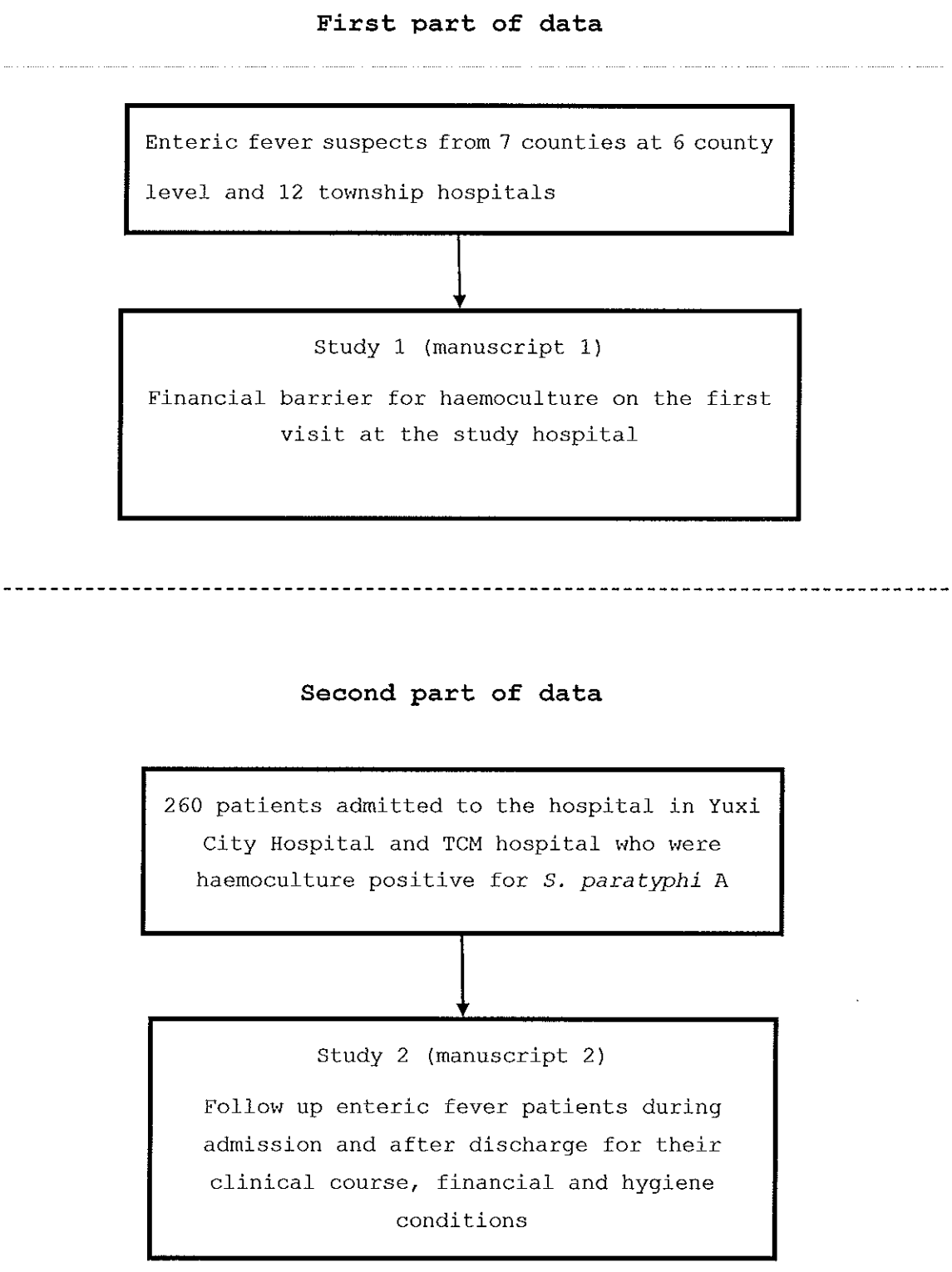
8. Composition of the research work in this thesis

The research work was conducted in an area where endemicity of enteric fever was superimposed with poverty and poor coverage of health

insurance in Yunnan. All data collected from 7 counties (Chengjiang, Luoping, Shizong, Mile, Menghai, Menla county and Jinghong city) were used to document financial barrier issue against access to diagnostic procedures among enteric fever suspects in highly endemic areas, which is presented as a manuscript 1 and accepted in a peer-reviewed journal in chapter 3.

The second part (manuscript 2, chapter 4) involves follow up of the inpatients to document their clinical course, financial and hygiene conditions (Figure 3). The patients were from Yuxi City Hospital and Yuxi City Traditional Chinese Medicine Hospital (TCMH).

Figure 3 Flow chart of the thesis



Chapter 3 Financial Barrier against Access to Diagnostic Procedures among Enteric Fever Suspects in Highly Endemic Areas of China

This manuscript has been accepted for publication in the Journal of Heath, Population and Nutrition on 30 August 2009.

Manuscript 1

Financial Barrier against Access to Diagnostic Procedures among Enteric Fever Suspects in Highly Endemic Areas of China

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ABSTRACT

There is currently no public financial system that fully covers enteric fever suspects in China. We aimed to document the level of access to definitive diagnostic procedures, especially haemoculture, for these patients and examine the effect of health insurance on access to such care. A hospital-based cross-sectional study was conducted in six counties of Yunnan province, using a structured questionnaire and data extraction from medical records. A total of 714 subjects were recruited. Chi-square test and logistic regression was employed for data analysis. The majority of subjects were young adult (52%), farmers (55%) from low income families (49%). Only 57% (407) could afford haemoculture routinely ordered by their doctors. Of these, 30% (123) had haemoculture positive for *S. typhi*. After adjustment for income, not getting haemoculture was marginally associated with percentage of reimbursement from the insurance (P value for trend=0.047). Illiteracy was also an independent risk factor for this outcome. Poor coverage of haemoculture for patients suspected of having enteric fever in this endemic area was due to financial barrier. The current health insurance system inadequately relieved the problem. Further financial reform to help patients suspected with enteric fever is required.

Key words: Cross-sectional studies; Typhoid fever; Enteric fever; Haemoculture; Health insurance; Healthcare; China

INTRODUCTION

Nowadays, typhoid fever and paratyphoid (enteric fever for short) are rare in industrialized countries, but they remain a serious health problem in the developing world. According to the best global estimates, at least 16 million new cases are diagnosed each year, with 600,000 deaths occurring. Areas where the incidence reaches more than 100 cases per 100,000 population per year are considered to be endemic [1].

China has a relatively low incidence of enteric fever, ranging between 2 and 5 cases per 100,000 population per year. Yunnan, an under-developed province of southwestern China (GDP per capita of Yunnan was 1273 US$ while average GDP of China was 2280 US$ in 2007) has the highest incidence of approximately 25 per 100,000 population per year in the nation [2]. In 8-9 endemic counties of Yunnan, the rates rank the highest in China, reaching 100 to 375 per 100,000 population per year, and contributing from 5 to 10 thousand cases annually.

The absence of specific symptoms or signs makes the clinical diagnosis of this disease inaccurate. The definitive diagnosis of enteric fever depends on the isolation of *S. typhi* or *S. paratyphi* from blood, bone marrow or a specific anatomical lesion [3]. In practice, blood culture (haemoculture) is considered as minimum standard. Definitive diagnosis dictates adequate treatment of patients. Confirmed cases of enteric fever must be treated with efficacious antibiotic for at least 10 days to avoid relapse and carrier status. From a public health point of view, accurate data are essential for priority setting, planning and evaluation of various public health

measures. Proper diagnosis and treatment prevent carriers and promote public safety [4].

In developing countries, diagnoses of enteric fever are often made without cultures, especially in rural hospitals, due to the lack of necessary facilities [5, 6]. From the Disease Information System of Yunnan, 40-50% of reported cases did not have blood culture done, despite the fact that 80% of enteric fever cases were reported from hospitals at county level or above, where the test is available. The underlying cause of this problem is expected to be the health finance system. Provincial price bureau fixes the hospital charge for haemoculture at 80 RMB (or approximately 11 US$) but the patient must pay this fee.

In 2007, Yunnan province had 129 counties with a total population of 44.8 million, 70% of whom were farmers. There are three main health insurance schemes in China: the New Rural Cooperative Medical Scheme (NRCMS), the Urban Worker Medical Insurance (UWMI) and private insurance. In rural areas, NRCMS is the most popular. It is a voluntary scheme with a 10 RMB annual premium collected from each farmer participating and a 20 RMB subsidy obtained from the provincial and the central government. This scheme began in 2005, and the coverage was 85% in 2007. The scheme does not cover any diagnostic procedures for outpatients [7]. Persons in the same family share the same family reimbursement account, which has a fixed limit for outpatient services. The scheme usually reimburses 10% of outpatient drug fees at village clinics and township hospitals, with a maximum limit equal to the family premium. Reimbursement at the outpatient department of the county

hospital is not possible. The Urban Worker Medical Insurance (UWMI), which is a government subsidy added to a small amount of premium deducted from staff salary, covered only 7.8% of Yunnan's population in 2007 [8]. This scheme reimburses a high percentage of the costs of diagnostic procedures and drugs. Private medical insurance is rare, and usually does not have reimbursement for outpatient services. In practice, any reimbursement from the insurance will be directly paid to the hospital and deducted from the patient's bill.

Under the local circumstance that enteric fever is endemic and laboratory tests are available but not fully utilized, it is important to know the proportion of suspected patients not getting the proper test and to examine to extent of financial constraints of the patients family, as well as the effect of insurance on access to diagnostic procedures.

The objectives of this study were 1) to document the proportion of enteric fever suspects who did not receive haemoculture. 2) to examine the effect of health insurance on access to this diagnostic procedure after adjustment for income and other confounders.

We expect that the results of the present study will provide evidence to the policy makers for decision on control measures and insurance planning to modify the scheme to improve such care.

MATERIALS AND METHODS

This study was approved by the ethics committees of Yunnan Provincial Centers for Disease Control and Prevention (Yunnan CDC), and the Faculty

of Medicine, Prince of Songkla University. Permission was also obtained from the hospital.

Study design

This is a hospital-based cross-sectional study with face-to-face interview using a structured questionnaire and data extraction from medical records.

Study setting

The study was conducted in six counties in Yunnan where the incidence of enteric fever is high. According to recent demographic data, there were approximately 4 million people residing in these areas [8]. The incidence rates in these areas ranged between 100 to 375 per 100,000 population per year. Six study hospitals at county level and twelve at township level were selected based on the fact that their total contribution of reported enteric fever cases was around 80% of the whole province. All hospital administrations agreed to participate in the study. They also had facilities for examination of enteric fever, including haemoculture, the results of which are under a quality control process checked by prefecture clinical laboratories.

Definition of an enteric fever suspect

According to WHO and Chinese national guidelines, an enteric fever suspect is a patient with fever (38°C and above) which has lasted for at least three days, with symptoms of headache, malaise, disturbances

of bowel function (constipation in adults, diarrhea in children) and residing in endemic areas during an endemic season [3, 9].

Study population and sample

The study population is all suspected cases of enteric fever in endemic areas of Yunnan province.

Case ascertainment: All patients presenting with fever were screened at the outpatient department for eligibility. To be eligible for the study subjects must have been a native resident who had fever for at least three days before coming to the hospital without any specific symptom or sign of localized infection. Patients attending for their second or subsequent visit for the same episode of fever were excluded.

Sample size

Based on the Disease Information System of Yunnan, around 50% of the enteric fever patients had no haemoculture confirmed. We assumed that half of our subjects would not be able to pay for the test. Among those who did pay, the prevalence of insurance would be 80% compared to 60% among those not paying. With a significance level of 0.05 and a power of 90%, the total sample size required was calculated to be 238. However, as the enteric fever control programme required to have a broader picture of Yunnan province, the sample size was increased to 700 so that more than 100 cases were selected from each of the six study county.

Variables and data collection

The main outcome variable is whether the patients received haemoculture. The main explanatory variable is percentage of medical expense reimbursable from insurance system. Family income is the key adjustment factor. Other variables include type of hospital and demographic characteristics, such as age, sex, education and occupation. Data were collected from May 2007 to September 2008. Before data collection, a pilot study was conducted in a hospital. Twenty suspected enteric fever cases were interviewed. The questionnaire was discussed with clinic doctors and CDC staff, and then revised. Two full-time research assistants were employed for each study hospital. All 36 research assistants from the 18 study hospitals were trained to be familiar with the definition of suspected enteric fever case, criteria of inclusion and exclusion, data collection procedures and interview methods. The outpatient services were arranged so that the attending physician took the clinical history and physical examination of the patient. If the patient was eligible for the study, he/she would be given an explanation by the doctor about the necessity of the haemoculture before he/she decided to pay or not pay to have the test done. After the patient had decided to have or not to have haemoculture, the research assistant then approached the patient for informed consent, and interviewed them about all medical fees which may or may not include the haemoculture test. The patient then paid the cashier, and the haemoculture test was done (if paid for). The research assistant who followed the patient recorded the real payment of the patient from the bill, and conducted a further interview, obtaining information such

as insurance type, and reimbursement status, before the patient proceeded to the next section (ie. laboratory or ward) of the hospital.

Data Analysis

Background characteristics of the patients were described by frequency, percentage, median and interquartile range, for each type of hospital. Access to blood culture, total median expense incurred from the current illness and percentage of the medical expense reimbursable from the insurance were similarly tabulated. To assess the effect of income and insurance, the fraction and percentage of access to blood culture was computed for each combination of income and insurance reimbursement category. Finally, to adjust for other possible confounders, logistic regression predicting no access to blood culture was carried out with these two main factors and other significant covariates in the model. The final significance level was set at 0.05.

RESULTS

During the study period, 714 subjects were recruited. Of these, 234 were from county hospitals and 480 from township hospitals.

Table 1 presents the background characteristics of the subjects by type of hospital. The sample was preponderant by young adults, males, Han ethnicity, farmers with a relatively low level of education and 46.55 of the subjects were not covered by any type of insurance for the current medical service. The overall median value for annual per capita income of the family was 2500 RMB, which was close to that of local farmers. Compared to patients from county hospitals, those from

township hospitals were more likely to belong to a minority ethnic group, live in a rural area, have a larger family size, a lower level of education, and lower annual per capita income of family, but covered by medical insurance.

Table 2 presents receipt of blood culture and the financial situation of subjects at the current hospital. Only slightly more than half (57%) of the suspects received haemoculture. The median value of medical expenses was 264 RMB, which was higher than 10% of the median of annual per capita income of the study families (2500 RMB). While the median medical expense for the current illness was similar in the subjects from the two types of hospitals, the percentage of reimbursement was much lower at the county hospital where the percentage of receiving blood culture was contradictorily higher.

Altogether, 407 patients had their haemoculture taken. Among these, 123 (30%) had positive results for *S. typhi*. Among the haemoculture positive patients, 98 were hospitalized, 24 were treated as outpatients, and one patient ran out of money, so he bought medicine at a drugstore. Out of 284 patients who had a negative haemoculture results, 28 were hospitalized, and 256 were treated at the outpatient service.

Table 3 presents the number of patients not getting haemoculture / total (percentage) by per capita family income quartile and percent of medical expense reimbursable from the insurance. Patients from a low-income family and those having a low percentage of reimbursement were less likely to get haemoculture. Of these two factors, family income had a stronger effect. Among the 168 subjects in the top income quartile,

all received haemoculture. In contrast, as much as a quarter of the 64 subjects who could get more than half of the medical expenses reimbursed did not receive such care.

Table 4 presents the univariate analysis of predictors for access to haemoculture. Of nine independent variables showing significant association with the outcome in the univariate analyses, only three were included in the final logistic regression model. Factors which were not significant in logistic regression were age, sex, family size, ethnicity, occupation, and family residence. Family income had the strongest independent effect. Using the lowest quartile as the reference group, the second quartile had less than one-fifth the odds of having the problem of not receiving haemoculture. The third quartile further had only six in a thousand times the risk among the poorest. Since none of the richest group had the problem of not receiving haemoculture, the odds ratio was too low to be computed. Education level was also a significant independent predictor. Illiterate subjects had the highest odds of not getting haemoculture. There was no dose-response relationship among the remaining education groups. The percentage of reimbursement was not significant (P=0.13) but was marginally so when a test for linear trend was applied (P=0.047). This suggests that insurance has a marginally important role in helping the patient to receive haemoculture.

DISCUSSION

In these endemic areas for enteric fever, potential enteric fever cases were young adult farmers from low income families. Unfortunately,

only about a half could have haemoculture routinely ordered by the doctors. The problem of not having this test was more serious at the township hospital despite the higher percentage of insurance coverage. Among the subjects tested, as much as 30% had the organism detected. Despite this seriousness, a large proportion of subjects were treated without admission. After adjustment for family income, the effect of insurance reimbursement was only marginal. Of all other demographic variables, literacy of the patient also had an independent effect on not having the test done.

Our findings that enteric fever suspects were farmers from poor families are similar to those in previous a report in India [10], Indonesia [11] and Bangladesh [12]. Enteric fever is transmitted through contamination of food and water, and is associated with poverty and poor hygiene. The poor who are at higher risk than the rich also received less complete diagnostic care when they were suspected to have enteric fever from the communicable disease.

Medical care and financial burden to the patients at township and county hospitals are quite different. The popular health insurance (NRCMS) partly reimbursed medical fees only when the service was at the township hospital. Patients at a county hospital were therefore less likely to be assisted by the insurance. However, the percentage of patients having a blood culture test done was higher in the county hospital. This was due to the higher income of patients served by this level of hospital. The difference in income confounded the effect of the hospital. After adjustment for income, the effect of hospital was

not significant. The implication of this finding was that this diagnostic care is differently accessed by the patients mainly due to the patient limitation of income, not due to the hospital setting.

Lack of haemoculture test among 43% of the subjects is a serious finding. Obtaining a definitive diagnosis of enteric fever is more cost-effective than providing empirical treatment because it can cut down unnecessary treatment given to non-cases and emphasize proper antibiotic use, which needs to be as long as 10 days [9, 13]. However, 30% of those not having the test might also have Salmonella in their blood. With inadequate treatment, a patient may end up with antibiotic resistance, become a chronic carrier, develop severe complications and consequently die [14].

The very steep slope of dose-response relationship between family income and the chance of having blood culture elaborates the financial barrier from the out-of-pocket fee for service system. Economists have developed a technique to evaluate worth for money of various health services based on interviews with a sliding scale of willingness to pay [15-24]. Ability-to-pay, another economic term comparing the medical expense incurred with annual family expenditure, has also been used to access financial burden [25]. Our study did not include those variables since we considered that blood culture is a life-saving process for serious infection, and should not have a monetary value attached to the poor patient. The cost of this service (80 RMB) is not going to cripple the family. Access to this care is therefore more a humanitarian than financial concern. However, there must be a suitable

financial management system to enable the service. Health insurance is almost universally adopted as a financial safety net for most illnesses. Unfortunately, it was shown in this study that health insurance in the study area had poor coverage and inadequate reimbursement, which has only a marginal effect on access to blood culture. The insurance system therefore does not guarantee full access to this necessary care. Moreover, our results indicate that the illiterate tended not to get the service. Leaving the decision to the poor who are sick and inadequately educated is therefore not justifiable.

Inability to have definitive diagnostic tests of communicable disease is not uncommon in developing countries. A study in India showed that blood culture for enteric fever was also expensive [26]. In Cambodia, citizens are reported as being too poor to afford the fee of blood test for a diagnosis of dengue [27].

Inability to receive hospital services in China has recently become an important public health and social problem. Hospital costs rose from 20% of total health expenditure in 1980 to 59% in 2000, and slightly dropped to 49% in 2006 [28]. More than 35% of urban households and 43% of rural households have difficulty affording health care costs [29].

Our study was conducted at county and township level hospitals where rural medical insurance is involved. It provides a good illustration of the financial pitfalls on communicable disease control. However, the study areas are in enteric fever endemic, the conclusion may not be generalized to areas where epidemiological settings are different.

In conclusion, patients affected by febrile illness in this study face a financial barrier to obtain proper diagnosis for the endemic enteric fever. Existing health insurance is inadequate. Better financial management is needed to improve the situation.

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Table 1: Background characteristics of the subjects (n=714)

Characteristic Frequency (%) & Median (IQR)	County hospital (n= 234)	Township hospital (n= 480)	Total (n=714)
Age, median *(IQR)	29.7 (19.7,39)	27.2 (12.6,40.2)	28.3 (15.6,40)
Gender			
Male	122 (52.1)	266 (55.4)	388 (54.3)
Female	112 (47.9)	214 (44.6)	326 (45.7)
Ethnicity			
Han	184 (78.6)	217 (45.2)	401 (56.2)
Dai/Hani/Yi/Hui/others	50 (21.4)	263 (54.8)	313 (43.8)
Occupation, frequency (%)			
Farmer	115 (49.1)	280 (58.3)	395 (55.3)
Worker/Staff/Business	48 (20.5)	31 (6.5)	79 (11.1)
Student	47 (20.1)	97 (20.2)	144 (20.2)
Preschool	11 (4.7)	69 (14.4)	80 (11.2)
Others (housewife/Jobless)	13 (5.6)	3 (0.6)	16 (2.2)
Patient family residence			
Urban	70 (29.9)	29 (6)	99 (13.9)
Rural	164 (70.1)	451 (94)	615 (86.1)
Family size , median(IQR)	4 (3,4)	4 (4,5)	4 (4,5)
Education achieved (%)			
None	19 (8.1)	54 (11.2)	73 (10.2)
Preschool	11 (4.7)	69 (14.4)	80 (11.2)
Primary school	68 (29.1)	177 (36.9)	245 (34.3)
Middle school	74 (31.6)	139 (29)	213 (29.8)
High school/ Vocational	45 (19.2)	36 (7.5)	81 (11.3)
University	17 (7.3)	5 (1)	22 (3.1)
† Annual per capita income of family (RMB), median (IQR)	2250 (1400,3750)	2106.7 (1000,5000)	2225 (1250,4733.3)
133-1250	36 (15.4)	165 (34.4)	201 (28.2)
1251-2500	51 (21.8)	77 (16)	128 (17.9)
2501-6000	65 (27.8)	94 (19.6)	159 (22.3)
6001-45000	82 (35)	144 (30)	226 (31.7)
Covered by any type of medical insurance, frequency (%)	43 (18.4)	289 (60.2)	332 (46.5)

* IQR: Inter-quartile range † Quartile of the whole data set

Table 2: Receipt of blood culture and the financial situation of subjects at the current hospital*

Characteristic Frequency (%) & Median (IQR)	County hospital (n= 234)	Township hospital (n= 480)	Total (n=714)
Access to blood culture	150 (64.1)	257 (53.5)	407 (57.0)
Medical expense for the illness† (Median, IQR)	263.9 (190.8,389)	264 (176.7,460.5)	264 (180.1,424.2)
Percentage of reimbursement for all types of payment (%)			
0-10	193 (82.5)	196 (40.8)	389 (54.5)
11-50	21 (9)	240 (50)	261 (36.6)
51-100	20 (8.5)	44 (9.2)	64 (9)

* All financial values are in RMB.

† Current medical expense for current illness RMB (median)

Table 3: Number of patients not getting haemoculture / total (percentage) by per capita family income quartile and percent of medical expense reimbursable from the insurance

Percentage of reimbursement	Family per capita income quartile				Total
	1st	2nd	3rd	4th	
0-10	118/128(92.2)	64/98(65.3)	11/104(10.6)	0/59(0)	193/389(49.6)
11-50	60/65(92.3)	38/57(66.7)	0/60(0)	0/79(0)	98/261(37.5)
51-100	5/8(62.5)	11/17(64.7)	0/9(0)	0/30(0)	16/64(25.0)
Total	183/201(91.0)	113/172(65.7)	11/173(6.4)	0/168(0)	307/714(43.0)

Table 4: Predicting factors for not getting haemoculture among enteric fever suspects

Variable	Univariate analysis: Getting haemoculture (n= 407)	Univariate analysis: Not getting haemoculture (n= 307)	Univariate analysis: Chisq* P-value	Logistic regression: Adjusted OR(95%CI) †	Logistic regression: P(LR-test) ‡
Annual per capita income of family (RMB)			< 0.001		< 0.001
132-1250	18 (4.4)	183 (59.6)		1	
1251-2500	59 (14.5)	113 (36.8)		0.191 (0.106,0.344)	
2501-6000	162 (39.8)	11 (3.6)		0.006 (0.003,0.014)	
6001-45000	168 (41.3)	0 (0)		-	
Percentage of reimbursement for all types of payment			< 0.001		0.1324¶
0-10	196 (48.2)	193 (62.9)		1	
11-50	163 (40.0)	98 (31.9)		0.718 (0.42,1.228)	
51-100	48 (11.8)	16 (5.2)		0.416 (0.163,1.06)	
Education level achieved (%)			< 0.001		0.0019
Illiterate	23 (5.7)	50 (16.3)		1	
Primary school	132 (32.4)	113 (36.8)		0.169 (0.057,0.497)	
Middle	131 (32.2)	82 (26.7)		0.153 (0.051,0.453)	
High school+	121 (29.7)	62 (20.2)		0.197 (0.064,0.611)	
Age (years)			0.03	-	
0-19	133 (32.7)	101 (32.9)			
20-39	175 (43.0)	126 (41.0)			
40-59	84 (20.6)	53 (17.3)			
60-85	15 (3.7)	27 (8.8)			
Sex			0.103	-	
Male	220 (43.7)	284 (56.3)			
Female	233 (49.1)	242 (50.9)			
Family size			< 0.001	-	
1-4	289 (71)	172 (56)			
5-7	118 (29)	135 (44)			
Ethnicity			0.046	-	
Han	215 (52.8)	186 (60.6)			
Dai/Hani/Yi/Hui/others	192 (47.2)	121 (39.4)			
Occupation			< 0.001	-	
Farmer	203 (49.9)	192 (62.5)			
Urban employee	71 (17.4)	8 (2.6)			
Unemployed	133 (32.7)	107 (34.9)			
Family residence			< 0.001	-	
Urban	80 (19.7)	19 (6.2)			
Rural	327 (80.3)	288 (93.8)			

* Chi-squared test † OR=Odds Ratio † CI=Confidence interval
‡ Likelihood ratio test ¶ Value for linear trend= 0.047
- Not statistically significant and not included in the model

Chapter 4 Clinical course, financial and hygiene conditions among convalescent patients with positive hemoculture for *Salmonella paratyphi* A in an endemic area of southwest China

Manuscript 2

Clinical course, financial and hygiene conditions among convalescent patients with positive hemoculture for *Salmonella paratyphi* A in an endemic area of southwest China

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Abstract

Background

In Hongta district, Yunnan province of China, *S. paratyphi* A hold a dominating position with a high incidence. This study was conducted to document clinical course, financial and hygiene conditions among convalescent patients with *S. paratyphi* A.

Methods

A prospective study was conducted at two hospitals of Hongta district in Yunnan. 260 inpatients with *S. paratyphi* A hemoculture positive were followed up after discharge. Information was obtained from questionnaire, medical records, and observation of household environmental conditions using a check list. Two stool sample cultures from each patient were taken on the 30 th day after discharge.

Results

66% of patients had a half month of illness, 56% had twelve days of hospitalization, while 75% had more than one week of persistent fever. No deaths occurred. Complications, relapses and carriers were rare. The average hospital charge was approximately 18 % of the average annual family income. Three quarters of the patients had health insurance which paid for an average of one-third of the hospital charge. 23 (9%) patients were found to be in absolute financial hardship. One fifth and one quarter of the study households had an open sewer and non hygiene latrine, respectively. Waste management problems as well as poor water

supply (39%) were markedly higher in the rural area, as was low education and low income families.

Conclusions

S. paratyphi A in this district poses a significant public health problem and economic burden. Although full hospitalization and antibiotic usage produced relatively good clinical results, hygiene conditions, which were very poor, needs to be improved for better prevention and control.

Key words

Salmonella paratyphi A, clinical course, financial hardship, hygienic problem, China

Background

Enteric fever is a systemic infection caused by *Salmonella enterica* serovars *typhi* and *paratyphi*. Typhoid fever was estimated to cause 21.6 million illnesses and 216,500 deaths during 2000 and paratyphoid 5.4 million illnesses globally [1]. Currently, most of the burden of the disease occurs in the developing world, where sanitary conditions remain poor. Enteric fever is still a serious public health problem in some parts of China. Yunnan province of southwest China has the highest incidence of approximately 25 per 100,000 population per year. In some endemic counties of the province, the rate ranked the highest in China, reaching 100 to 375 per 100,000 population, and contributing more than 5 to 10 thousand cases annually.

From 2000 to 2006, in Hongta district of Yunnan, *S. paratyphi* A held a dominating position with a high incidence of approximately 280 per 100,000 population annually. *S. typhi* contributed 0% to 3.7% of all *Salmonella* isolated in hemoculture specimens from 2000 to 2006 [2]. In 2006, all of the local 1325 cases of enteric fever were due to *S. paratyphi* A making Hongta the highest endemic area of China.

Previous studies from Egypt [3], China [4], India [5] and Nepal [6, 7] described the clinical signs and symptoms of infection with *S. paratyphi* A. However, due to lack of follow up, none of these studies gave information on the long clinical course of the patients. Few studies have examined the financial situation before and during hospital admission. None have provided information at the convalescent phase. Enteric fever is a disease of the poor. The patient's financial situation

may link to the need of performing food handling jobs and to poor household hygiene condition.

The objective of the current study was to document the clinical course, financial and hygiene conditions among convalescent patients of *S. paratyhi* A in southwest of China. This information could be used in local control programmes and can also benefit endemic areas in other counties.

Methods

The study was approved by the ethics committees of Yunnan Provincial Centres for Disease Control and Prevention (Yunnan CDC), and the Faculty of Medicine, Prince of Songkla University. Permission to conduct the study was also obtained from the two study hospitals.

Study design of setting

This was a prospective study following up patients with *S. paratyphi* A hemoculture positive, who were admitted to two hospitals of Hongta district in Yunnan where enteric fever was highly endemic.

Sample size

We planned to have 250 cases in our study. This sample size would be adequate to describe continuous outcome variable, such as days of fever and amount of money spent, with 95% CI of the means being within 2 sd. For binary outcome variables, such as hygiene behaviours, it would be adequate to have 95% limits of the estimated proportion being within 5 % percent from the estimate of the prevalence, if the latter lies

between 30% to 70%. However, the prevalence estimate would be imprecise if the outcome was rare, such as complication or mortality.

Patients and data collection

The study was conducted during May 2007 to July 2008. Inclusion criteria was suspected enteric fever patients who were native residents, who were inpatient, diagnosed as having enteric fever with positive haemoculture of *S.* serovar *typhi or* serovar *paratyphi* A, B, or C.

Laboratory Methods

10 ml of venous blood (4ml for preschool children) was drawn and directly inoculated into a blood culture bottle (BioMérieux), and then put into a mini VITAL automated blood culture system within 7 days. Only bottles showing signs of positive growth were cultured on SS or Mac agar. Suspected colonies obtained on the media were screened by means of Kliger's iron agar, motility, indol urea and citral test. The strains were differentiated by serological identification of *Salmonella*. In parallel tube, Widal tests were performed. The serum sample was considered positive for *S. typhi*, if the titre against O and H were ≥ '1:80' and '1:160', respectively. For *S. paratyphi*, the cut off point were set 'O'≥1:80, for 'A', 'B' and 'C' ≥'1:160', respectively. All *Salmonella* isolates were confirmed at a reference laboratory (Chinese Centers for Disease Control and Prevention, Bejing).

Follow-up schedule

Full-time research assistants were employed to collect the data at each study hospital after being trained and tested on data collection procedures. Target patients were selected according to the above inclusion criteria and approached to obtain their consent. Demographic and socioeconomic details and general information about exposure (contact with other cases of enteric fever, behaviour on water drinking and food handling) were obtained when subjects were still in hospital. An appointment for home visit was made with the patients before they left the hospital. On the day of discharge, the study assistant interviewed each patient to check history record on the clinical course before and during hospitalization, co-morbidity record, the days of antibiotic use and hospital charge. A home visit was conducted within two weeks after discharge. Additional data were collected on non-medical expenses of patient and reimbursement from medical insurance, overall ability to pay and coping mechanisms of the patient for the illness. Information on food handling and personal hygiene practice was also obtained. The household environmental conditions were observed using a check list inspecting type of water supply, type of latrine and household sewage. A second blood sample for Widal test was taken at least two weeks after the first one. Two stool samples were taken on the 30^{th} day after the patient was discharged and at subsequent 48 hours.

Data analysis

Data was entered using Epidata software (Version 3.0) and analysed with R (Version 2.7.2). Chi-square test was used to identify the risk factors.

Results

During the study period, 1168 suspected enteric fever patients were investigated with haemoculture, of which 260 were confirmed to have *Salmonella paratyphi* A and were recruited into the study. One patient left the hospital on day 3 of admission due to financial problems. However, she and all other 259 patients completed the follow-up as planned.

Table 1 presents background characteristics of the subjects. Female participants exceeded the males. The subjects were mostly young adults living in urban areas with a wide range of occupations. Farmers contributed around one third. The education level was mostly middle school or above. A third had an annual family income of not more than 10,000 yuan, the local average. Few patients had recently been in contact with enteric fever patients in the family before falling ill. Approximately 15% of patients admitted to having a poor water drinking practice.

Table 2 shows the subject's financial status and expenditure for their illness. The average hospital charge was approximately 18% of the average annual family income. Around two-thirds of the charge was paid by the patients or their family. Three quarters of the patients had health insurance which paid for an average of one-third of the hospital charge. Approximately 9% of patients were found to have total financial hardship from this admission, whole quarter felt this partly. The amount

of borrowed money was relatively low in most of the cases. Non-medical costs were relatively small compared to the medical costs.

Table 3 presents the clinical course of the subjects. Most patients had approximately a half month of illness, twelve days of hospitalization, more than one week of persistent fever and over ten days of antibiotic use. Sensitivities of Widal test were lower on the acute serum (59%) than the convalescent serum (77%). Although more than 10% of patients had concomitant diseases, such as hypertension, emphysema, cor pulmonale, diabetes, bronchitis, pharyngitis, tonsillitis and cervicitis, only three cases had complications, namely intestinal perforation, myocarditis and pneumonia. Relapses and carriers were rare, being less than 1%. No deaths occurred.

Table 4 presents the behaviour on food handling and observations on house sanitation after discharge from hospital. Around 2% of patients were involved in the food business. Approximately one fourth of patients were a food handler in the family, cooking for their family members. At least 20% of patients lived in poor hygiene housing with a simple pit latrine and open sewage or without drainage. Although, more than 90% of patient families could get access to public water supply, only 60% had chlorinated tap water.

Table 5 shows information the behaviours on food handling and home sanitation from the home interview and observed after discharge from hospital. On the average, about a quarter of the convalescent patients handled foods, especially in the cooking process. This behaviour varied minimally across demographic characteristics. One fifth and one quarter

of the study households had open sewer and non hygiene latrine, respectively. The waste management problems as well as poor water supply were markedly higher in rural area, low education and low income families.

Discussion

This paper investigated various outcomes of one of the largest series of patients infected with *S. paratyphi* A. Despite prolonged high fever, only a few cases (<1%) was developed serious complications. Amidst financial difficulties among these poor patients, health insurance, which covered three quarter of the patients, was helpful. Inadequate hygiene conditions were prevailing, especially in rural areas, among the low income family and the poorly educated.

The trend of increasing isolation rates of *S. paratyphi* A in Asia is interesting. Reports in 2004 and 2005 revealed that among enteric fever episodes, the percentage caused by *S. paratyphi* A were 34% in Nepal [7], 14% in Indonesia, 15% in Pakistan, 24% in India and 64% in China [8]. In GuangXi province of China, the proportion of *S. paratyphi* A strains isolated accounted for 91.4% of all *Salmonella* isolated in 2002 [9]. The explanation for these high proportions of paratyphoid A among enteric fever patients is unclear.

Paratyphoid fever is traditionally perceived to be a milder disease [10, 11]. This has led to neglect of this important pathogen. Recent studies have shown that no significant difference exist in the

presenting symptoms between infections due to *Salmonella Paratyphi* A and *S. Typhi* [7, 12].

The total duration of fever in our series (9.2 days) was slightly shorter than that (10.4 days) reported from India [17]. The median body temperature of our patients (39.2℃) was close to a previous local report of 39.3℃ [4] but higher than 38.3℃, which was the median of the Katmandu series [7]. There has been no evidence of a relationship between the level of temperature and other aspects of severity.

Complications of *Salmonella Paratyphi* A infection have rarely been reported. We found only three cases with serious complications.

Widal test is easy to perform, inexpensive and widely used in China. The sensitivity of 59% reported in our study for the first test was similar to one reported in Egypt [3]. Using this test without hemoculture may miss as many as 40% of the cases. Amidst no previous report on sensitivity of the test in convalescent-phase, our reported sensitivity of 77% was still far from ideal. These facts point to the strong need of using hemoculture in the suspected enteric fever patient [13, 14].

Our patients were hospitalized for a median of 12 days. This was 5 days longer than the American series of typhoid fever in 1996 to 1997 [15]. The difference may be due to hospital policy. In China, the Ministry of Health recommends at least 10 days admission to ensure full treatment with antibiotic [16]. Our study could find only a few carriers. This result could be biased by the fact that all our patients were fully

treated with antibiotic. Carrier rates may be higher among outpatients who are not hospitalized and not fully treated due to financial limitations [10].

Financial burden from enteric fever has rarely been examined. A study carried out in an urban slum community in Delhi, India, in 2004 estimated the mean cost per episode of blood culture-confirmed cases to be USD101 for outpatients and USD 510 for inpatients [17]. The latter value is slightly higher than costs incurred to our patients (RMB 3000 or USD 440). In both instances, enteric fever poses quite a heavy financial burden to patients and their family. Insurance in China can reduce, but not diminish, this difficulty and the coverage is still far from universal.

Our follow up activities revealed underlying causes of endemicity of enteric fever in the area. Shortage of safety water supply and poor management of excreta were serious problems. A report in 2006 showed that the rate of sanitary latrine use was only 49% in rural areas of Yunnan [21]. *Salmonella*, like many enteropathogenic organisms, can survive as long as 5 weeks in the sewage system [18]. The open sewage [19] and unsafety water [7, 20] are important sources for enteric fever. A study conducted in India similarly indicated that patients with typhoid fever had lower literacy rates and a low economic status with poor water supply, sanitation, and hygiene [5]. A similar result from a study in Indonesia, emphasized that typhoid fever cases tended to be in the lower soci-economic group, lived in houses without proper water supply and hygienic sewage system.

Conclusions

S. paratyphi A in this district poses a significant public health problem and economic burden. Although full hospitalization and antibiotic usage produced relatively good clinical results, hygiene conditions, which were very poor, needs to be improved.

Competing interests

There are no competing interests in this study from the authors.

Authors' contributions

WX and VC jointly conceived the idea of the study, while WX, XQF and LL performed the study. Under VC's instruction, WX designed the study, analyzed and interpreted the data, and drafted the manuscript. All authors revised the paper and approved the final version of the manuscript.

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Table 1: Background characteristics of subjects (n=260) by hospital

Characteristic Frequency (%) & Mean (SD)	City hospital (n=192)	TCMH* (n=68)	Total (n=260)
Age	33.2 (14)	27.6 (11)	31.8 (13.5)
Sex			
Male	89 (46.4)	26 (38.2)	115 (44.2)
Female	103 (53.6)	42 (61.8)	145 (55.8)
House location			
Urban area	114 (59.4)	48 (70.6)	162 (62.3)
Rural area	78 (40.6)	20 (29.4)	98 (37.7)
Occupation			
Farmer	61 (31.8)	23 (33.8)	84 (32.3)
Blue-collar	33 (17.2)	9 (13.2)	42 (16.2)
White-collar	44 (22.9)	11 (16.2)	55 (21.2)
Student	38 (19.8)	21 (30.9)	59 (22.7)
Unemployed	6 (3.1)	0 (0)	6 (2.3)
Preschool children	0 (0)	1 (1.5)	1 (0.4)
Other	10 (5.2)	3 (4.4)	13 (5)
Education achieved			
No education	3 (1.6)	1 (1.5)	4 (1.5)
Primary school	26 (13.5)	4 (5.9)	30 (11.5)
Secondary school	66 (34.4)	26 (38.2)	92 (35.4)
High school/Vocational college	42 (21.9)	10 (14.7)	52 (20)
University	55 (28.6)	27 (39.7)	82 (31.5)
Annual family income (RMB)			
≤10,000	59 (30.7)	21 (30.9)	80 (30.8)
10,001-15,000	41 (21.4)	22 (32.4)	63 (24.2)
15,001-25,000	68 (35.4)	19 (27.9)	87 (33.5)
>25,000	24 (12.5)	6 (8.8)	30 (11.5)
Family member with fever more than 3 days within 10 days	3 (1.6)	3 (4.4)	6 (2.3)
Contact with another affected within 15 days	4 (2.1)	5 (7.4)	9 (3.5)
Drinking unboiled/unfiltered water	32 (16.7)	5 (7.4)	37 (14.2)

* TCMH: Traditional Chinese Medical Hospital

Table 2 Financial status of subjects (n=260) by hospital

Financial status (%), mean (SD)	City hospital (n=192)	TCMH (n=68)	Total n (percentage, 95% CI)
Hospital charge for the illness*, mean (SD)	3.1 (1.9)	2.6 (1.1)	3.0 (1.7, 2.7-3.2)
Annual family income*, median(IQR)	15.0 (10.0,25.0)	15.0 (10.0,20.0)	17.0 (7.9, 16.1-17.9)
Hospital charge to the patient*, median(IQR)	1.56 (1.14,2.47)	1.45 (0.95,2.13)	1.9 (1.5, 1.7-2.1)
Hospital charge to the insurance*, median(IQR)	0.8 (0.20,1.79)	1.0 (0.20,1.46)	1.0 (1.0, 0.9-1.1)
Covered by medical insurance	150 (78.1)	51 (75.0)	201(77.3, 71.7-82.2)
NRMCS**	59 (39.3)	20 (39.3)	79 (39.3, 32.5-46.4)
BMIUE#	74 (49.3)	18 (35.3)	92 (45.8, 38.7-52.9)
Others	17 (11.4)	13 (25.4)	30 (14.9, 10.3-20.6)
Perceived payment difficulty for the illness			
Total	13 (6.8)	10 (14.7)	23 (8.8, 5.6- 12.9)
Partial	51 (26.6)	14 (20.6)	65 (25, 19.8-30.7)
Payment impact to normal/near future life	43 (22.4)	17 (25)	60 (23.1, 18.0-28.6)
Number of people borrowed money for payment	8 (4.2)	1 (1.5)	9 (3.5, 1.5-6.4)
Money borrowed for payment, mean (SD)	67 (337.3)	36.8 (303.2)	59.1 (328.4, 19.0-99.2)
Days family members visited hospital , mean (SD)	8.7 (6.6)	7.1 (6.9)	8.2 (6.7, 7.4-9.0)
Relative's transportation cost, mean (SD)	59.5 (67.1)	48.5 (73.7)	56.6 (68.9, 48.2-65.0)
Relative's food cost, mean (SD)	81.7 (91.8)	49.4 (79.3)	73.2 (89.7, 62.2-84.1)
Relative's other cost ,mean (SD)	23.1 (60.4)	24.1 (61.1)	23.4 (60.5, 16.0-30.7)

* × 1000 RMB

** New Rural Cooperative Medical System

Basic medical insurance for urban employees

Table 3 Clinical course of the subjects (n=260) by hospital

Clinical characteristic	City hospital (n=192)	TCMH (n=68)	Total (n=260)
Days of illness, median (IQR)	17 (12,21)	16 (14,19)	16 (13,20)
Days of hospitalization, median (IQR)	12 (8,15)	13 (10,15)	12 (9,15)
Highest temperature ℃, median (IQR)	39.2 (38.9,39.6)	39.5 (39,39.8)	39.2 (38.9,39.7)
Days of persistent fever in whole illness, median (IQR)	8 (6,11)	9 (7,11)	9 (6,11)
Days of antibiotic use, median (IQR)	11 (8,14)	13 (10,14.2)	11 (8,14)
Widal test* 1 ≥1:160 (%)	115 (59.9)	39 (57.4)	154 (59.2)
Widal test* 2 ≥1:160 (%)	146 (76)	54 (79.4)	200 (76.9)
No. of concomitant diseases			
1	28 (14.6)	3 (4.4)	31 (11.9)
2	7 (3.6)	0	7 (2.7)
Complications (%)			
Intestinal perforation	1 (0.5)	0	1 (0.4)
Myocarditis	1 (0.5)	0	1 (0.4)
Pneumonia	1 (0.5)	0	1 (0.4)
Relapses (%)	1 (0.5)	1 (1.5)	2 (0.8)
Positive stool culture 30 days after leaving hospital (%)	0	1 (1.5)	1 (0.4)

* The titers are for H based on Chinese national guidelines.

Table 4 Behaviour on food handling and household sanitation observation after discharge from hospital (n=260)

Hygiene factor (%)	City hospital (n=192)	TCMH (n=68)	Total (n=260)
Patient involved in food business	3 (1.6)	2 (2.9)	5 (1.9)
Patient as a food handler in family after leaving hospital	56 (29.2)	8 (11.8)	64 (24.6)
Cooking frequency per day			
1	13 (6.8)	1 (1.5)	14 (5.4)
2	28 (14.6)	5 (7.4)	33 (12.7)
3	15 (7.8)	2 (2.9)	17 (6.5)
Open sewage or without drainage	35 (18.2)	14 (20.6)	49 (18.8)
Type of latrine			
Simple open pit	11 (5.7)	5 (7.4)	16 (6.2)
Simple pit inside the house	33 (17.2)	11 (16.2)	44 (16.9)
Public latrine	58 (30.2)	39 (57.4)	97 (37.3)
Water flush toilet	90 (46.9)	13 (19.1)	103 (39.6)
Water supply of house			
Chlorinated city public water supply	112 (58.3)	48 (70.5)	160 (61.5)
Non-chlorinated public water supply	66 (34.4)	14 (20.5)	80 (30.8)
Pond	3 (1.6)	0	3 (1.2)
Well	11 (5.7)	5 (7.4)	16 (6.2)
Other	0	1 (1.5)	1 (0.4)

Table 5 Percentage of risky behaviours among the study convalescence patients

Predictors	n	Food handling %	Open sewage %	Non-hygienic latrine %	No-chlorinated water supply %
Total	260	24.6	18.8	23.1	38.5
House location					
Urban	162	24.7 [a]	4.3	16.0	1.2
Rural	98	24.4 [a]	42.8	35.7	98.9
Education					
Primary school	30	20.0 [bc]	36.7	23.3	66.7
Secondary school	92	28.2 [ac]	33.6	35.8 [a]	63.1
Higher than secondary school	134	23.9 [ab]	4.5	13.4 [a]	11.9
Family income-RMB					
≤10,000	80	21.2 [bcd]	37.5	36.2	65.0
10,001-15,000	63	28.6 [acd]	28.6	25.4	60.3
15,001-25,000	87	23.0 [abd]	1.1	12.6	8.0
>25,000	30	30.0 [abc]	0	13.3	3.3

a,b,c Figures with the same superscript are not significant with different ($p>0.05$) from one another by chi-square test.

Chapter 5 Discussion and Conclusions

The above two chapters provide results from two studies. This chapter integrates them into the thesis by arguing about the linkages and drawing conclusions and recommendations.

1. General discussion

1.1 Linkage between the results of our two studies

The first study, which looked at suspected outpatients, revealed that they were facing financial difficulties that prevented them from getting haemoculture. Existing medical insurance had poor coverage on these patients and the reimbursement rate strongly influenced the chance to get haemoculture. The second study involved inpatients who had positive haemoculture for *S. paratyphi* A. One-tenth of them had financial hardship despite the insurance.

Both studies confirm that a significant proportion of these patients were in financial difficulties.

In addition, the follow up component of the second study reveals poor housing hygiene and poor compliance to food handling despite the advice given to patients and their family during the admission.

1.2 Implication of uncertain diagnosis

Approximately half of suspects could not afford haemoculture, resulting in uncertainty of definitive diagnosis. Thus, the results

of the treatment and control of transmission would be difficult. The medical insurance did not cover laboratory investigation, therefore failed to help low income families who could not pay for the test.

1.3 Hospitalization and follow up of enteric fever patients

Based on the clinic's decision, at least one third of enteric fever patients were not hospitalized but instead treated as outpatients. There were several financial barriers. The cost of treatment was high and the reimbursement rate was low (maximal liability only up to 30% of hospital charge). Some subgroups, such as students, are not covered by medical insurance. In India, few patients are hospitalized. This status might be due to the big difference of charge between outpatient (USD 100) and inpatient (USD 510) [4]. In Thailand, hospitalized patients who suffer from shigellosis only account for 5.8% of all episodes despite patients being covered by 3 insurance schemes (civil servants medical benefit scheme, social security scheme and universal health coverage scheme). Patients who were not admitted probably had less serious disease [58]. In our study, most patients had approximately 15 days of illness, 12 days of hospitalization, more than 7 days of persistent fever and over ten days of antibiotic use. This disease is not less serious than shigellosis.

1.4 Sanitation, hygiene and the chance of disease spreading

In developing countries, most patients were treated as outpatients without follow-up and strict isolated regulation, such as those reported in Nepal and Indonesia. This condition may probably contribute to the spread of organisms into the environment [42, 43]. In Britain and

America, over 80% of enteric fever patients are treated in hospital, the remaining patients treated under home isolation [59, 60]. Patients are not allowed to work, especially in the food handling and daycare industries. Patients are followed up by health bureau officers until 3 consecutive negative stool specimens, each taken no less than 48 hours apart are obtained [60-62]. In New Zealand, enteric fever patients are restricted to visiting places where the sanitation system is not perfect [63]. This restriction cannot work in our study area mainly due to inaccurate diagnosis for the above reasons and the necessity of the patients to earn a living.

Sanitation and hygiene are the critical measures that can be taken to prevent enteric fever. In developed countries, the impressive control of this once predominant disease has been achieved without special eradication programs, through improvements in water supplies, sanitation, and food hygiene [64]. In recent years, the most infections with *S. typhi* and *S. paratyphi* in developed countries were attributable to foreign travel where safe water and sanitation condition were poor [65, 66]. In rural areas of Yunnan, sanitary conditions are still poor. Coverage of sanitary latrines was only 49% and tap water coverage was 56% in 2007. In most of the cities, there is no good sewage system and no sewage treatment plant. Sewage from the city is discharged directly into the suburbs. Farmers use sewage to water vegetables. Open pit latrines are breeding grounds for flies. Poor sanitation, poor drinking water and poor hygiene behaviour, such as drinking unboiled water, eating unheated food with raw vegetables fertilized by night soil [67], probably contribute to the high incidence of enteric fever.

1.5 Special financial policy on communicable diseases control

There are not enough specific financial policies on communicable disease control in the hospital system. These patients who suffer from communicable disease cannot get waivers or subsidies, and have to pay out of pocket. Only a few special communicable disease control programs implemented by the CDC have special financial policies, such as HIV/AIDS, TB, Malaria, Schistosome and Leprosy (Table 5).

In endemic areas of enteric fever of China, a special financial policy should be established in order to provide suspects with free diagnostic and therapeutic services. This would lead to improvement of the enteric fever control program.

Table 5 Financial policy on priority of communicable disease control in Yunnan

Disease	Mass screening covered by program*	hospitalization	Special therapy covered by program
HIV/AIDS	waiver	Depends on patient's status of insurance	Subsidy for patients with low income, not covered by insurance
TB	waiver	Depends on patient's status of insurance. Target patients of program be transferred to CDC	Waiver
Malaria	waiver	Depends on patient's status of insurance	Waiver
Schistosome	waiver	Depends on patient's status of insurance	Waiver
Leprosy	waiver	-	Waiver
Enteric fever	waiver only at rural level in two counties	Depends on patient's status of insurance	-

* Programs conducted by CDC

1.6 Achieving the goal of control enteric fever control in endemic areas of Yunnan province

The control of enteric fever needs more than effective antibacterial treatment. Improvement of basic sanitation, safe drinking water,

education about safe drinking water and food preparation is important in reducing the rate of enteric fever in endemic areas. There is a need to advocate a hygiene policy [68]. In tandem with the development of the economy, water and sanitation projects aimed at rural population health improvements are widely conducted in China. At present, the technical program for improvement of water supply and toilet facilities has been developed. Some projects for improvement of drinking water and toilet facilities have been implemented in Yunnan. The surveillance system of drinking water quality in rural areas was set up in 2007. Central government currently subsidies local public health funds for improvement of water supply and waste disposal in rural areas. The coverage of rural tap water increased from 30% in 1990 to 61% in 2007 and the coverage of sanitary latrine improved from 44% in 1990 to 55% in 2007 [17]. In Yunnan, the water and sanitation were also improved. In rural areas, the coverage of tap water and sanitary latrine reached 63% and 53%, respectively [17], but this level of improvement is still considered as inadequate.

2. Summary of findings and recommendations

These findings and implications for recommendation are shown in Table 6.

Table 6 Summary of findings and recommendations

Summary of findings	Recommendations
1. The suspects of enteric fever were preponderant by farmers with relatively low levels of education and most were not covered by any type of insurance for the current medical service.	Prevention programs and insurance schemes covering investigation of suspected enteric fever should focus on this high-risk group.
2. Approximately half of suspects could not afford haemoculture, especially the low income and the lower education groups. The percentage of reimbursement was marginal.	Financial schemes to overcome this barrier should be established.
3. The popular health insurance (NRCMS) partly reimbursed medical fees only when the service was at the appointed township hospital.	Fees of service care at the outpatient department of the county hospital, especially haemoculture, should be reimbursed.
4. Three quarters of the patients had health insurance which paid for an average of only one-third of the hospital charge.	The percentage of reimbursement for admission of enteric fever should be increased.

Table 6 Summary of our recommendations

Summary of findings	Recommendations
5. All admitted patients with positive haemoculture were eventually cured without being a carrier.	The antibiotic was effective and should be further used.
6. Sensitivity of Widal test was lower, especially for the acute serum (59%)	Haemoculture should replace Widal test for the definitive diagnosis of enteric fever.
7. Some patients had poor water drinking practice, directly handled foods, lived in poor hygiene housing with a simple pit latrine and open sewage or without drainage and had no-chlorinated tap water, all of those were likely to contribute to the prevalence in endemic areas.	Health promotion program about safe drinking water and food preparation, and sanitation should be accelerated.

3. Strengths and limitations of the study

3.1 Strengths of the study

This study was conducted at county and township level hospitals in different areas where rural medical insurance is available. The finding linked financial conditions, clinical pattern, a home condition of the patients thus providing strong evidence for the improvement of this related system.

3.2 Limitations of the study

Those who did not get haemoculture test were not followed up. The second study was over-represented by those who could pay for the test. The poor patients who could not afford haemoculture may have a different financial situation and disease progression from the existing study group.

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Appendix

Appendix I: Invitation to Participate Form

Project name: Ability to pay as a determine of accuracy of diagnosis and the clinical fate of suspected enteric fever patients in Endemic Area, Yunnan

Dear Sir or Madam:

We are inviting you to voluntarily join this study. The decision to participate is entirely yours. If you decide to take part in the study, you will be interviewed and required to respond some sensitive questions, such as family income, medical insurance, your ability to pay for expenditure of current illness, difficulty to pay and source of money for payment, type of medicine you taken. Second Widal test and stool culture in duration of follow-up will be done if you volunteer.

Some of the questions we will ask may be embarrassing but we will try our best not to confuse you. You may refuse to answer any question you do not want to. You can refuse Widal test and stool culture when participant this study.

Your decision to participate or refuse will not affect the diagnosis and treatment of current illness.

Your decision, you name, and your content of answer will be maintained in confidence by the staff directly involved within The District Centre for Disease Control and Prevention and will not be released to anyone outside.

If you fully participate in the study, it will contribute to the disease control and medical equity information provided for policy reform.

If you have any questions about this study, please contact the person who explained this or the doctor in charge of typhoid and paratyphoid at CDC at any time.

Thank you very much

Research team

Appendix II: Consent Form

Project name: Ability to pay as a determine of accuracy of diagnosis and the clinical fate of suspected enteric fever patients in Endemic Area, Yunnan

I am (Miss, Mr, Mrs)..... (Participant's name) agree to join the project about which the researcher (name)..... (Position)....., has already explained the detail to me as in the invitation to participate form.

If I have any queries with respect to the procedures in the research project, I can ask research team at any time. If I am not satisfied with the performance of the research team, I have the right to notify Lulin (Director of Yunnan provincial CDC), telephone number (0871-3611746) or the president of the Ethics Committee (Dean of the Faculty of Medicine, Prince of Songkla University, Thailand: telephone number +66 74-451100). If I am still not satisfied with the project, I have the right to discontinue participation in this project at any time without any consequences.

I have read and understood all details of the project provided by the researcher, and that I can change the consent at any time if I wish. I voluntarily participate in the study.

.....(Signature of the participant).....(Date of signature)

.....(Signature of the researcher) .....(Date of signature)

.....(Signature of the witness) .....(Date of signature)

Appendix III: Questionnaire for definitive diagnosis

Name of hospital: ..... Department: .....

Date of recording (patient first visit hospital):

___/___/___ □□□□ □□ □□

Name of patient: .....

Sex: .....

If children under 14 year old, parent's name .....

Address in detail: County (District) .....

Township (Street) .....

Village (Community) .....

Telephone number: .....

Site of employment/work or self-employed/school:

.....

Section 1. General information

A. Socio-demographic characteristics

Respondent data

1. Who is the respondent, in relation to the patient? □

(1) patient him/herself (2) father (3) mother

(4) spouse (5) children (6) other,.....

2. What is your education? □

(1) No education (2) Primary school (3) Middle school

(4) High school (5) Vocational (6) University/College

(7) Other.....

Family data

3. Where is family's residence (determine by ID card)? □

(1) Urban (2) Rural

4. Ethnicity (determine by ID card): □

(1) Han (2) Yi (3) Hani (4) Hui (5) Dai (6) others: .....

5. How many person stay with your family since the last 12 month

(including patient)? □

(1) one (2) two (3) three (4) four (5) five (6) six

(7) more than six

6. How many persons are employed/self-employed (generating

family income)? □

(1) one (2) two (3) three (4) four (5) five or more

Patient data

7. Age (birthday) ___/___/___ □□□□ □□ □□

8. Sex ☐

(1) Male (2) female

9. Education ☐

(1) No education (2) Primary school (3) Middle school

(4) High school (5) Vocational (6) University/College

(7) Other.....

10. Occupation ☐

(1) Farmer (2) Worker (3) Officer (4) Housewife/keep house

(5) Student (6) Jobless (7) Preschool children

(8) Other .....

Section 2. Current illness and health care expenditure

11. Have you ever sought care elsewhere for current illness since sick?

(1) Yes (2) No, go to 16 ☐

12. Where did you seek care prior to this seeing doctor?

a. Village clinic (1) Yes (2) No ☐

b. Small private clinic (1) Yes (2) No ☐

c. Private hospital (1) Yes (2) No ☐

d. Township hospital (1) Yes (2) No ☐

e. County (or district) hospital (1) Yes (2) No □

f. Prefecture (or city) hospital (1) Yes (2) No □

g. Other ..... (1) Yes (2) No □

13. Why did you change to seek care at this hospital? □

(1) Not cure, not improve (2) Not cure, need further treatment

(3) Money is exhaustive now (4) Other reason

14. Medical expenses incurred for current illness prior to seeing doctor.

..... yuan □□□□

15. For prior to seeing doctor, non-medical expenses by yours family member?

(1) Days spent for visiting hospital ..... □

(2) Traveling cost

..... yuan □□

..... day □□

(3) Food costs

..... yuan □□

..... day □□

(4) Other costs

..... yuan □□

..... day □□

(i.e. opportunity cost)

16. Have you ever taken any antibiotic for current illness since sick?

(1) yes (2) no □□

17. Where did you get this antibiotic from? □□

(1) Prescribed by doctor in hospital

(2) bought from pharmacy

18. The name of antibiotic you got. □

□

(1) Chloramphenicol (2) Trimethoprim-Sulfamethoxazole

(3) Ampicillin/Amoxycillin (4) Ciprofloxacin

(5) Norfloxacin (6) Pefloxacin (7) Ofloxacin

(8) Ceftriaxone (9) Cefotaxime (10) Cefoperazone

(11) Cefixime (12) Aztreonam (13) Azithromycin

(14) Other

19. How many days the antibiotic had been used? □

.....

20. How many times has been used in per day? □

.....

21. For this seeing doctor, non-medical expenses by your family member?

(1) Day spent for visiting hospital ..... □

(2) Traveling cost/day ..... yuan □□

(3) Food costs / day ..... yuan □□

(4) Other costs / day .....yuan □□

(i.e. opportunity cost)

22. For short time observation or supportive therapy eg in the hospital, non-medical expenses by yours family member?

(1) Days spent for observation or supportive therapy..□

(2) Traveling cost/day .....yuan □□

(3) Food costs / day ..... yuan □□

(4) Other costs / day .....yuan □□

Section 3. Family's ability to pay and coping strategies to the cost of illness

23. Is there any paying difficulty for the bill in this current illness? □

(1) yes, absolutely (2) yes, partially (3) no

24. What is the money used to pay for current illness? □

(1) cash money	(1) Yes (2) No	□
(2) saving	(1) Yes (2) No	□
(3) insurance claims	(1) Yes (2) No	□
(4) borrowing	(1) Yes (2) No	□
(5) sell of properties	(1) Yes (2) No	□
(6) sell of earning material	(1) Yes (2) No	□
(7) other, ...	(1) Yes (2) No	□

25. Did the payment for current illness used have any impact to your normal & near-future life? If yes, how?

.....

.....

.....

Section 4. Data on income

26. Income of all family members (in yuan per year)

..... (yuan) □□□

Section 5. data transferred from medical chart and financial record

27. Date of onset ___/___/___ □□□□ □□ □□

28. Date of examination ___/___/___ □□□□ □□ □□

29. Primary diagnosis □

(1) Enteric fever

(2) Other

30. Body temperature:

Measured temp (℃) ..... □□

31. Financial record: (total) hospital Charge

..... yuan □□□

32. Total paid money ..... yuan □□□

(1) Money the patient or the related family give to the hospital(out of pocket)..... □□□

(2) Money supported by insurance ..... □□□

33. Breakdown of Charge: (in yuan) ..... □□□

(1) Blood routine examination

Required by doctor (1)Yes (2)No □

Completed by patient (1) Yes □

..... yuan □□

(2)No □

(2) Urine routine examination

Required by doctor (1)Yes (2)No □

Completed by patient (1) Yes □

..... yuan □□

(2)No □

(3) Chest x-ray

Required by doctor (1)Yes (2)No □

Completed by patient (1) Yes □

..... yuan □□

(2)No □

(4) Widal test

Required by doctor (1)Yes (2)No □

Completed by patient (1) Yes □

..... yuan □□

(2)No □

(5) Culture:

① Blood

Required by doctor (1)Yes (2)No □

Completed by patient (1) Yes □

..... yuan □□

(2)No □

② Stool

Required by doctor (1)Yes (2)No □

Completed by patient (1)Yes □

..... yuan □□

(2)No □

(6) To observation ward for observation or supportive therapy eg. iv fluid and specific therapy eg. antibiotic:

1)Yes □

.....yuan □□

(2)No □

(7) Drug (name): □

□

(1) Chloramphenicol

(2) Trimethoprim-Sulfamethoxazole

(3) Ampicillin/Amoxycillin (4) Ciprofloxacin

(5) Norfloxacin (6) Pefloxacin (7) Ofloxacin

(8) Ceftriaxone (9) Cefotaxime

(10) Cefoperazone

(11) Cefixime (12) Aztreonam (13) Azithromycin

(14) Other

.....yuan □□

(8) Other: Other form of diagnostic and treatment procedure eg. Ultrasonography, surgery etc.

(1)..... .....yuan □□

(2)..... .....yuan □□

(3)..... .....yuan □□

(4)..... .....yuan □□

(5)..... .....yuan □□

Investigators: ..... **Inspector:** .....

Date of investigation: **Date of inspection**:

___/___/___ □□□□ □□ □□ ___/___/___ □□□□ □□ □□

Appendix IV: Follow-up Investigation Form

Hospital name of Pervious visiting: ..... Department: .....

Date of follow-up: ___/___/___ □□□□ □□ □□

ID: .....

Name of patient: .....

Sex: .....

If children under 14 year old, parent's name .....

Address in detail: County (District) .....

Township (Street) .....

Village (Community) .....

Telephone number: .....

Site of employment/work or self-employed/school:

.....

Section 1 Environmental observation of the house

1. Area where the house was situated □

(1) Good urban area (2) Poor urban area (3) Good rural area

(4) Poor rural area

2. Cleanliness of the kitchen □

(1) Clean (2) Moderately clean (3) Dirty

3. Kitchen floor made from □

(1) Tile (2) Ground or cement

4. Sewage system □

(1) Closed with gutter (2) Open with gutter

(3) Closed without gutter (4) Open without gutter

5. Sewage system of house □

(1) Closed drainage system (2) Open or without drainage system

6. Living- room floor made from □

(1) Tile (2) Ground or cement

7. Water supply of house □

(1) Public water supply (2) river (3) pond (4) well

Section 2 Health care expenditure and non-medical expenses for current illness

1. Financial record: (total) hospital Charge

..... yuan □□□

2. Total paid money..... yuan □□□

(1) Money the patient or the related family give to the hospital (out of pocket) ..... □□□

(2) Money supported by insurance ..... □□□

3. For current illness, non-medical expenses by yours family member?

(1) Days spent for visiting hospital ..... □

(2) Traveling cost/day ..... yuan □□

(3) Food costs / day ..... yuan □□

(4) Other costs / day .....yuan □□

Section 3 Family's ability to pay and coping strategies to the cost of illness

1. Is there any paying difficulty for the bill in this current illness? □

(1) yes, absolutely (2) yes, partially (3) no

2. What is the money used to pay for current illness?

(1) cash money (1) Yes (2) No □

(2) saving (1) Yes (2) No □

(3) insurance claims (1) Yes (2) No □

(4) borrowing (1) Yes (2) No □

(5) sell of properties (1) Yes (2) No □

(6) other, ... (1) Yes (2) No □

3. Did the payment for current illness used have any impact to your normal & near-future life? If yes, how?

.....

.....

.....

Section 4 Remaining unmet need after receiving free hemoculture among suspect enteric fever patients

1. Financial record: Total hospital Charge at end of whole illness course.

..... yuan □□□

2. Total paid money at end of whole illness course ..... yuan □□□

(1) Money the patient or the related family give to the hospital (out of pocket) ..... □□□

(2) Money supported by insurance ..... □□□

3. Financial source of expense

(1) Cash and saving ..... yuan □□□

(2) Insurance claim ..... yuan □□□

(3) Borrowing or loan ..... yuan □□□

(4) Selling property ..... yuan □□□

4. Do you consider that your current health problem is not well taken care of by the hospital due to your financial shortage?

(1) yes (2) no □

5. If the answer is yes according to above question, in what aspect?

□

(1) Inadequate investigation

(2) Inadequate medication

(3) Unmet need for hospitalization

Section 5 Duration of treatment

Name of antibiotic: □

□

(1) Chloramphenicol (2) Trimethoprim-Sulfamethoxazole

(3) Ampicillin/Amoxycillin (4) Ciprofloxacin

(5) Norfloxacin (6) Pefloxacin (7) Ofloxacin

(8) Ceftriaxone (9) Cefotaxime (10) Cefoperazone

(11) Cefixime (12) Aztreonam (13) Azithromycin (14) Other

Adult dosage/day(mg): ..... □□□

Children dosage/day(mg): ..... □□

Duration: .....days □□

Starting: ___/___/___ □□□□ □□ □□

End: ___/___/___ □□□□ □□ □□

Section 6 Dispose of patient feces

1. Feces and urine were excreted into a special container; it had been disposed in a sanitary manner with choric disinfector.□

(1) Yes (2) No

2. How did you dispose Feces and urine in a sanitary manner?

.....

3. Feces and urine were excreted into latrine directly. □

(1) Yes (2) No

4. Type of latrine for excretion (Feces and urine) □

(1) Simple pit latrine in open

(2) Simple pit latrine in household

(3) Public latrine

(3) Flush toilet connected to sewage system

Section 7 Behavioral data on food handling and household contact information

7.1 Food handling and contact

7.1.1 Are the patient a food handler?

(1) yes (2) no □

7.1.2 If yes, dose he/she also cook for other people?

(1) yes (2) no □

7.1.3 How often did the patient need to cook after coming back from hospital?

..... day □□

7.1.4 Is your family running any business related with food?

(1) yes (2) no □

(If yes, detail .....)

7.1.5 Is the patient involved in process of food preparation in that business? □

(1) Buy raw material

(2) Preparing raw material

(3) Cooking

(4) Transferring and storing

7.2 Is there anybody in your family got fever for more than 3 days within 10 days before the onset of the patient? □

(1) yes (2) no

7.3 The patient contact with same illness person □

(1) Yes (2) No

7.3.1 Date of contact: ___/___/___ □□□□ □□ □□

7.3.2 Location of contact: .....

7.4 Family water drink

7.4.1 Drinking unboiled / untreated water □

(1) Yes (2) No

7.4.2 Type of unboiled / untreated water □

(1) Well water (2) River water (3) Pool water

(4) Pipe water (5) Other .....

Section 8 Laboratory and examination results

8.1 Culture

Date of sample collection	Type of sample	Date of test	Date of result reporting	Result

8.2 Widal test

Sequence of sample	Date of sample collection	Type of sample	Date of test	Date of result reporting	Result (Titer)		
					O	H	A
First time							
Second time							

Section 9 Clinic information

9.1 Onset date: ___/___/___ □□□□ □□ □□

9.3 Illness duration: _____ days □□

9.3.1 Fever (1) Yes (2) No □

9.3.2 Continuous fever duration: _____ days □□

9.3.3 Highest measured temp (℃): _____ □

9.3.4 Final diagnosis:

1. ..... □

2. ..... □

3. ..... □

Investigators: ..... **Inspector:** .....

Date of investigation: **Date of inspection:**

___/___/___ □□□□ □□ □□ ___/___/___ □□□□ □□ □□

Appendix V: Check list card

Name of patient: Sex: Male Female Age: (year)

Name of hospital:

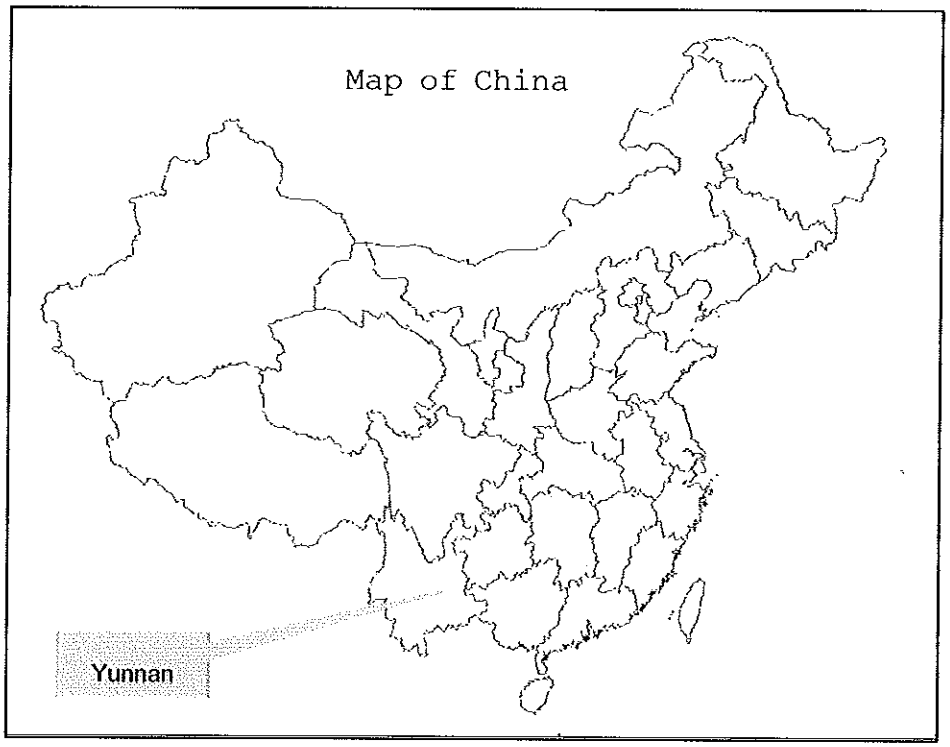
Date of admission: year month day

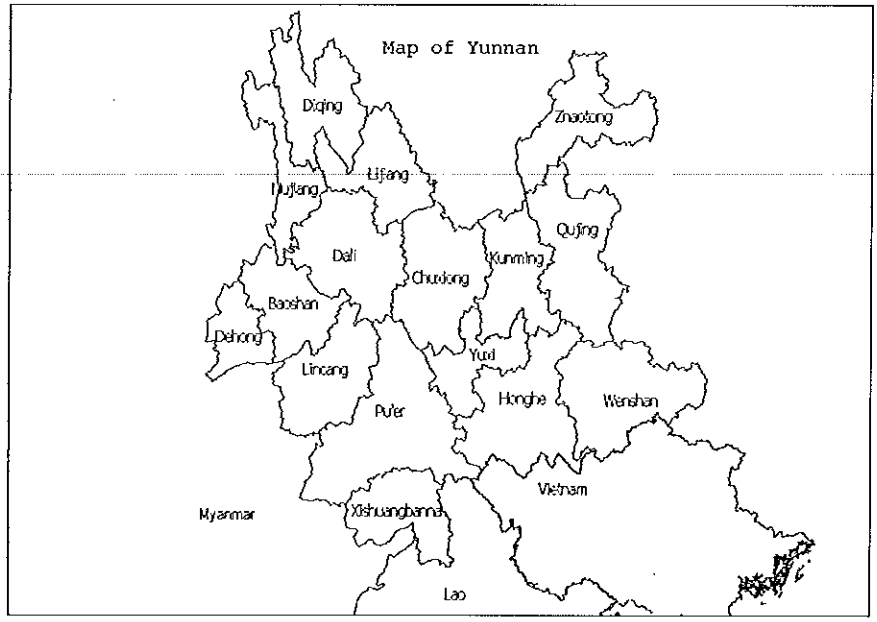
No. of item	Item of test	Ordered by doctor	Completed by patient	remark
1	Blood routine examination			
2	Urine routine examination			
3	Stool routine examination			
4	Chest X-ray			
5	Widal test			
6	Blood culture			
7	Stool culture			
8				
9				

Note: 1. Completeness mark '√', Non completeness mark'×'.

2. Other item ordered, .add more to next blank.

Appendix VI: Map of China and Yunnan province




Map of Yunnan
Diqing
Zhaotong
Lijiang
Nujiang
Qujing
Dali
Kunming
Chuxiong
Baoshan
Dehong
Yuxi
Lincang
Honghe
Wenshan
Pu'er
Vietnam
Myanmar
Xishuangbanna
Lao