Local Article

Enteric fever in endemic areas of Indonesia: an increasing problem of resistance

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Abstract

Reported levels of antibiotic resistance in *Salmonella* Typhi from South Sulawesi, Indonesia were very low (< 1%) before 2001 and chloramphenicol remained the treatment of choice. Since 2001 however resistance has been rising and in 2007 6.8% of isolates were resistant to all three first line drugs: Ampicillin, chloramphenicol and co-trimoxazole. Ciprofloxacin resistance is currently at 3.90 %. At the same time there has been an increase in the number of reported cases. This may be because of improved diagnostics or it may be a genuine outbreak of drug resistant *S.* Typhi. In conclusion drug resistant typhoid fever will become a serious problem in Indonesia in the future, requiring the use of expensive drugs for the treatment of typhoid. A concerted effort is needed by the medical services to implement reliable diagnosis so that treatment or vaccination can be used to control the spread of drug resistant typhoid fever.

Key Words: Antibiotic resistance, *Salmonella*, Typhi, Indonesia.

J Infect Developing Countries 2008; 2(4): 279-282.

Received 27 June 2008 - Accepted 23 July 2008

Indonesia has a population of 224,904,900 in an area of 8.3 million km2 within 17,504 islands. Sulawesi Island is one of the five largest islands in the Indonesian archipelago and has a population of 42,708,400. Typhoid fever is still a major health problem in Indonesia and the prevalence in South-Sulawesi is one of the highest in the archipelago [1]; the case detection rate for 1991 was 257/100,000 population which had risen to 386/100,000 population by 2007 [1]. Published figures for Indonesia as a whole estimated a prevalence of 358-810/100.000 in 2007, with 64% of enteric fever in 3 to 19 year olds [2]. The mortality rate varies from 3.1-10.4% among hospitalised patients [2] with cases occurring throughout the year but peaking in the dry season. However, the real magnitude of the problem is difficult to determine. In rural areas where access to diagnostic facilities is limited, there are probably many cases that remain undiagnosed. On Sulawesi Island, blood culture, the standard laboratory diagnostic for typhoid fever, is not available and so diagnosis is based mainly on clinical symptoms. This not an ideal situation as prompt diagnosis can lead to appropriate antibiotic therapy which can reduce the case-fatality rates from 10% to less than 1% [3].

Transmission of typhoid is usually by ingestion of contaminated food or water or direct contact with recently recovered patients [4,5]. Sanitation and municipal water supply systems have successfully contributed to the control of typhoid in countries where the illness was once endemic. However, infrastructure projects to improve sanitation and to provide safe water are expensive and an unattainable goal in many rural areas of Indonesia. Early diagnosis and prompt anti-microbial treatment to reduce the pool of infected persons, and hence reduce transmission, however, is an achievable goal and so health services must play an important role in the control of typhoid fever. This requires functioning medical services, including access to appropriate drugs and reliable diagnostic facilities. In Indonesia, the health care system Puskesmas (Pusat Kesehatan Masyarakat, Primary Health Centre) is well developed in some areas but is deficient in many other typhoid endemic areas (Figure 1) [5].

Studies in Indonesia have shown that enteric fever can also be prevented by improving hygienic

behaviour. The consumption of uncooked vegetables, not washing hands before eating, and not using soap when washing hands, in addition to contaminated water supplies, are important risk factors for typhoid in endemic areas of Indonesia [5]. In addition, in March 2000 an epidemiological survey was performed in 5 villages in the Paitana sub-district of the Jeneponto area, South Sulawesi, Indonesia, to determine the true incidence of typhoid fever and the efficacy of treatment, as well as to identify risk factors. Medical and hygiene standards in addition to nutritional, social, economic and cultural data were collected from all inhabitants and entered in an electronic database. Although not yet published, initial results estimate an annual incidence rate of 623/100,000, with a female to male ratio of 1:1.2. Further analysis of collected data is presently being undertaken to (i) compare results of disease incidence with medical records at the district hospital and primary healthcare centre; (ii) determine the geographical distribution of cases; and (iii) determine major risk and protective factors. Simple hygienic measures will be formulated that may be used to prevent infection. To control typhoid fever, active case detection combined with laboratory testing and structured education in simple hygienic measures will be implemented in different districts, to begin in the 5 villages of the Paitana sub-district. Active case detection together with improved hygiene can be expected to reduce disease, to improve early diagnosis and treatment, and to reduce disease severity [5].

Figure 1. Puskesmas (Pusat Kesehatan Masyarakat, Primary health care) in a rural typhoid fever endemic area of Indonesia.

Self-medication and consultation at a late stage are also likely to contribute to disease severity. The local epidemiology of typhoid in endemic regions is poorly understood. Chronic carriers and convalescent patients are the main source of infection in the community and the attack rate peaks in younger age groups.

The majority (80-90%) of typhoid patients are treated at home (self-medication) with antibiotics and bed-rest; other patients, those with more severe disease and those treated at home who then develop persisting complaints, present at health care centres and hospitals [6]. Most of patients will receive chloramphenicol as the first-line drug of choice in health centres or hospitals, but data in several primary health centres and hospitals in South Sulawesi reveal that the percentage of chloramphenicol resistance increased during the last 7 years (1.04 % in 2001 versus 7.84 % of cases in 2007) (Table 1).

Studies from laboratories in several primary health care centres and hospitals have shown that the treatment failure and relapse rates vary. The failure rate is in the range of two to 10% and the relapse rate varies from zero to 6% and usually occurs two to three weeks after the resolution of fever. Several studies in Indonesia performed more than 3 decades ago indicated a treatment failure rate of 7.0% and a relapse rate of over 10% for chloramphenicol, the most commonly used drug in Indonesia [7].

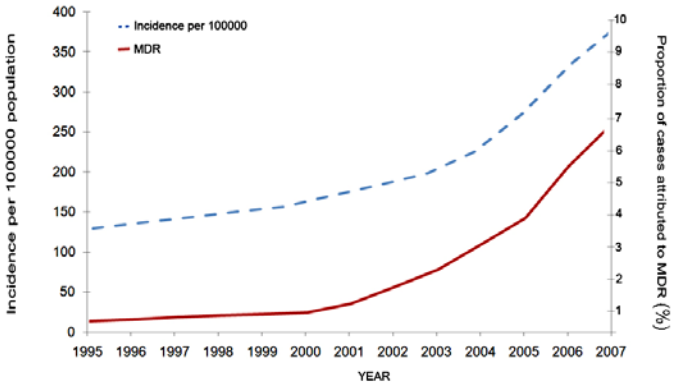
The mortality rate due to typhoid infection in Indonesia and New Guinea is reported to be higher than in other countries in Southeast Asia. We do not know whether this difference is due to genetic variation in local *Salmonella* Typhi strains, differences in host susceptibility, quality of medical care or other factors [8].

Due to the highly clonal nature of *S.* Typhi, genetic typing methods have always provided limited information on the population structure and epidemiology of this organism [9,10]. If we are to understand the maintenance and transmission of typhoid fever, we need to know the genetic relationship between strains. There is genetic variation amongst *S.* Typhi isolates found in Indonesia and although genotyping schemes may describe the epidemiology of typhoid strains, simpler, more rapid and reproducible techniques are needed for laboratories such as ours. Multi-locus variable number of tandem repeat (VNTR)

analysis provides a powerful tool for *S.* Typhi strain characterisation; this method may well be used to determine strain variation and dynamics in a population and to study relatedness with specific clinical features of typhoid. Currently we are studying H:d, H:j and H:z66 flagella variation in *S.* Typhi strains isolated from several islands of Indonesia to describe the diversity of flagella variants of these *S.* Typhi strains [11].

Although typhoid remains a serious public health problem, no national systematic approach has been developed to control the disease. The government has not established specific programs to tackle the disease, as is the case for other communicable diseases, and even the vaccines available for typhoid are not currently being used because vaccination is still difficult to administer in remote endemic areas of Indonesia. This is of particular concern given the increase in reported cases (Figure 2). Trends in incidence of typhoid fever in Indonesia and the proportion of cases of typhoid fever attributed to multidrug resistance (MDR, defined as resistance to the three first-line drugs chloramphenicol, ampicillin and co-trimoxazole) has gradually increased each year. This is probably due to improved and simple methods for diagnosis, such as the dipstick, lateral flow, and typhoid dry-dot [12-16].

Figure 2. Trends in incidence of typhoid fever in Indonesia and the proportion of cases of typhoid fever attributed to MDR.



Conclusions

Unlike other regions of South East Asia where MDR was common [17,18] reported levels of antibiotic resistance in *S.* Typhi from South Sulawesi, Indonesia, was very low (< 1%) before 2001, and chloramphenicol remained the treatment of choice. Since 2001, however, resistance has been rising (Table 1) alongside an increase in the number of reported cases (Figure 2). This may be because of improved diagnostics or it may be a genuine outbreak of drug resistant typhoid fever. Tetracycline resistance, a marker for plasmid carriage, is currently seen in 8.13% of cases and MDR in 6.83%. Disturbingly, ciprofloxacin resistance (3.90%) is also increasing. We have no data on the strain types carrying this resistance or on the relationship of Indonesian strain types with types from other South East Asian countries. Genotyping of the strains and their plasmids circulating in South Sulawesi, Indonesia, would shed light on the emergence of resistance in this important human pathogen.

Table 1. Proportion of MDR in typhoid fever according to cases and antibiotic treatment during 7 years in South Sulawesi, Indonesia.

	Year (% of cases)						
Antibiotic*	2001	2002	2003	2004	2005	2006	2007
Tetracycline	1.34	2.94	3.13	4.12	4.86	6.43	8.13
Ampicillin	1.87	2.52	3.38	4.12	4.95	6.53	7.96
Chloramphenicol	1.04	2.43	2.84	3.87	4.25	6.21	7.84
Ciprofloxacin	0.11	0.15	0.18	0.29	1.68	2.19	3.90
MDR	1.21	1.82	2.5	3.12	3.91	5.82	6.83

*Antibiotic commonly used for typhoid fever treatment in hospitals and primary health care.

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Conflict of interest: No conflict of interest is declared.