THE DISEASE

Awareness of the importance of Salmonella typhi as a disease producing agent in febrile patients in Indonesia has grown during the past twenty years. Numerous collaborative efforts from Ministry of Health, other health institutes, and NAMRU have played important roles in the recognition of this important cause of significant morbidity and mortality. Anderson et al. in 1976\(^1\) studied the causes of occult febrile disease during a one year period in Jakarta. A surprising 43% of the 741 patients studied had either blood cultures positive for Salmonella spp., or positive Salmonella serology. This was convincing evidence to clinicians in Jakarta that typhoid fever was an important and treatable cause of fever of unknown origin (FUO).

THE EPIDEMIOLOGY

In 1981, the reported number of cases of typhoid fever in Indonesia was 19,596, increasing to 26,606 in 1986\(^2\), most of the increase was due to improved detection and recognition of the pathogen. A more realistic estimate of incidence for this underreported and underdiagnosed disease would be from 540,000 to 1,210,000 cases per year. This was based on results of a household survey done by Budiarso R. et al. in 1980 and 1986\(^3\), and on result of a community surveillance done by Ruwido\(^4\) and Simanjuntak et al.\(^5,6\) from 1983-1988. These studies were done in Plaju, South Sumatera, representing an urban area and Paseh, West Java, representing a semi-rural area. The results showed that the incidence rate of typhoid fever in the semi rural area was 358/100,000 population/year, and between 760-810/100,000 population/year in the urban area. These studies also indicated that the high risk group in the population was school age children between ages of 3-19 years. From other observations, it is also noted that the case fatality in urbanized and growing areas of Indonesia, may be higher than it is reported in other areas of the world\(^7,8\).

LABORATORY DIAGNOSIS

Non-culture method

To overcome the delay of 3-7 days in laboratory diagnosis using conventional culture techniques, Sanborn and Lesmana, et al.\(^9,12\),

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showed that salmonellosis could be detected by a more rapid coagulation method. Later, Rockhill et al. demonstrated that *Salmonella* C1, D and Vi antigens could be accurately detected in blood cultures after only 18 hours of incubation, by using *S. aureus* coagglutination methods which were rapid, cheap, and easy to perform. Follow-up studies by Rockhill et al. using the coagglutination method on urine specimens, provided a presumptive diagnosis within 30 minutes after receiving the specimen, although false positives were a problem. Studies with enrichment cultures from feces have been developed which detect the presence of typhoid antigens within four hours after inoculation.

The Widal test has been used extensively in Indonesia as an aid to diagnose typhoid fever instead of costlier and time-consuming *S. typhi* culture techniques. Two studies have been done to evaluate the Widal test for diagnosis of typhoid fever. In 1981 Rockhill et al. reported that in Indonesia a clinically significant Widal titer was not well defined, and that the test was not very sensitive, nor specific. It has certain restrictions and that diagnosis of typhoid fever still rested primarily on isolation of *S. typhi* from the patient.

Using serum from hospitalized febrile patients Hoffman et al. showed that the Widal slide agglutination test was highly specific with a high positive predictive value and low negative predictive value. However, the sensitivity and specificity of this test for each particular laboratory and its patients population must be known in order to be able to calculate its predictive value. The results of these studies suggest the usefulness of the Widal test for diagnosis of typhoid fever in Indonesia is dependent on the procedure used in an individual hospital and its associated laboratory.

With the ever widening acceptance of genetic engineering technics, DNA probes offer a newer approach to the detection and identification of *S. typhi* in the blood of typhoid patients. Studies by Rubin et al. have shown that a Vi-antigen-specific probe can be used to detect *S. typhi* using about 2.5 ml of blood. These results were the first demonstration of the use of a DNA probe to detect bacteria in blood.

**Culture method**

Our institutions have conducted various investigations of non-humoral body fluid and materials with the aim of improving isolation from typhoid patients. In 1984, Hoffman et al. determined the sensitivity of the duodenal string capsule culture for isolating *S. typhi* and *S. paratyphi* A from patients with enteric fever. They compared these results to those from bone marrow aspirate (BMA) culture, single blood culture, rectal swab culture, and various combinations of these. Duodenal string culture was shown to have no advantage over the combination of rectal swab and blood culture, and was less sensitive than the BMA culture done alone. The addition of the duodenal string culture to blood and rectal swab cultures could improve the likelihood of isolation in cases when a BMA culture cannot be obtained.

The BMA culture was shown to be significantly more sensitive than an 8 ml blood culture (of a 1:10 ratio blood to broth), an 8 ml
streptokinase clot culture, a 3 ml blood culture (the routine culture for most Indonesian hospitals and clinics) and rectal swab culture\(^2\). When BMA culture cannot be performed Tjaniadi et al.\(^{23}\) and Simanjuntak et al.\(^{24}\) confirmed that standard whole blood cultures are of greater sensitivity than blood-clot cultures.

**TREATMENT**

In a landmark study, Hoffman and Punjabi in 1984\(^25\) documented that the use of high dose dexamethasone in antibiotic-treated severely ill typhoid patients resulted in dramatic improvement in outcome. Although the drug is costly, its use for treatment of the severe typhoid cases has become standard in hospitals where admission for typhoid fever is common. Interestingly, this documentation stands alone and unchallenged in showing utility of steroid treatment in an acute infectious disease of bacterial origin.

**PREVENTION**

Typhoid vaccines have been used for a number of years in areas of Indonesia. However, the present vaccine is associated with unpleasant side effects and relatively short periods of protection. Recently, a large field trial was sponsored by the WHO to evaluate the efficacy of a different formulation of the Ty21a oral typhoid vaccine. The trial was performed as a collaboration between NIH, NAMRU and Pertamina, and involved over 20,000 participants.

Based on the high protection rates previously demonstrated in Egypt and Chile, the Indonesian trial was designed to confirm these results in a different population, and to evaluate the liquid vs. enteric coated capsule forms of the vaccine. In contrast to the high protection rates seen in the previous studies, the Indonesian trial demonstrated that at best, the vaccine (3 doses of the liquid formulation) provided a 53% protective efficacy lasting for a period of at least 30 months, somewhat more in adults over 19 years\(^6\). It must be noted that this relatively low protective efficacy was accomplished in a population having extremely high rates of disease transmission, compared with the studies done in Chile and Egypt which have one tenth and one quarter, respectively, the transmission rates of Indonesia.

In an ongoing collaboration with WHO the same group at NAMRU and NIH has been investigating the immunogenicity and side-effects of the newer injectable Vi-capsular polysaccharide vaccine. Side-effects have been minimal, and the immunogenicity conferred was greater than 95%\(^27\) in children as young as 2 years of large.

**REFERENCES**


