

A LARGE, SINGLE SOURCE OUTBREAK OF MULTI-DRUG RESISTANT TYPHOID FEVER IN BHARATPUR, CHITWAN, NEPAL

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In June 2002, at the request of HMG, Ministry of Health, Department of Health Services, a team of medical researchers from the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, CIWEC Travel Medicine Clinic, and the Nepalese National Public Health Laboratory assisted the investigation of a large number of patients with high fever in the Bharatpur district of Nepal.

In conjunction with the Bharatpur District Hospital and the College of Medical Sciences, we were able to obtain specimens to identify and characterize the organism causing the outbreak of fever, assess the size and number of people affected by the outbreak, and most importantly, make recommendations to HMG as to what medicines to use to treat affected patients.

Blood was drawn from 98 febrile patients attending the District Hospital on 26-27 June for blood cultures and malaria smear. Of 98 blood cultures, 33 were confirmed as *Salmonella typhi*, one as *S. paratyphi* and one stool culture was positive for *S. typhi*. All of the smears (97 in total) were negative for malaria parasites. Isolates from earlier in the outbreak and prior to the outbreak were obtained from the College of Medical Sciences (CMS) in Bharatpur, the National Public Health Laboratory (NPHL) in Kathmandu, and water samples were obtained from Bharatpur municipal and ground water sources. Many of these isolates were also positive for *Salmonella typhi* including one water sample.

At AFRIMS, complete antimicrobial susceptibility testing was performed using NCLLS standard disk diffusion methods. The majority of the isolates were resistant to Nalidixic Acid, Ampicillin, Tetracycline, Bactrim, Chloramphenicol, Streptomycin, and Sulfazoxidole. The isolates appeared to all be sensitive to Ciprofloxacin and Ceftriaxone *In vitro* even though there were reports of clinical failure. Using the "E Test" strip method for Minimal Inhibitory Concentration (MIC) to Ofloxacin, Ciprofloxacin, and Ceftriaxone revealed an overall decrease in susceptibility as compared to what is reported in the literature.

By performing Pulsed Field Gel Electrophoresis (PFGE), we were able to determine that all 34 isolates obtained from the District Hospital, all 7 isolates obtained from Bharatpur by the NPHL, all 21 isolates obtained from the CMS, and the water sample taken from the municipal water supply by NPHL showed an analytical similarity of 97-100%.

In conclusion, the MDR typhoid epidemic in Bharatpur affected over 6000 patients in a 4-5 week period and was from a single source (municipal water supply) causing a large increase above the normal endemic level of typhoid/enteric fever. The data shows multiple isolate resistance patterns prior to the outbreak and from around the country, but isolates collected from the time and place of the outbreak have a consistent resistance and PFGE pattern. There appears to be a decrease in the sensitivity by MIC compared to what is reported in the literature for Ciprofloxacin, Ofloxacin, and Ceftriaxone. Our conclusions are that this outbreak represents further movement along the continuum towards complete fluoroquinolone and Ceftriaxone resistance in *Salmonella typhi*.

Lack of finding a single malaria positive slide in these febrile patients during peak malaria season confirms that this was not an outbreak of malaria in Bharatpur.

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