Multi-drug resistant typhoid: a global problem

Most cases of typhoid or enteric fever are caused by *Salmonella enterica* subsp. *enterica* serovar Typhi (*S. Typhi*), although *S. Paratyphi* A and B and occasionally other serotypes such as *S. Virchov*, *S. Dublin* and *S. Newport* are implicated. *S. Typhi* is solely a human pathogen and there is no animal reservoir. Although typhoid is a rare imported infection in developed countries the antimicrobial agents most readily available for therapy are ampicillin, chloramphenicol and co-trimoxazole. Unfortunately, strains of *S. Typhi* resistant to all three agents have emerged [5].

Chloramphenicol-resistant *S. Typhi* emerged first in the UK within 2 years of the successful use of chloramphenicol in typhoid [6]. Subsequently, isolates carrying transferable chloramphenicol resistance were described from Greece [7] and Israel [8]. Two *S. Typhi* isolates from Aden and Cairo carrying transferable resistance to chloramphenicol, ampicillin and tetracycline were found in 1967 [9]. However, it was not until 1973 that epidemics of typhoid with resistant strains were reported from Mexico [10] and India [11]. Other epidemics occurred subsequently in Vietnam [12], Korea [13] and Peru [14]. Most of these resistant strains carried transferable resistance to chloramphenicol, tetracycline, aminoglycosides and sulphonamides. In 1981, not long after the introduction of co-trimoxazole, transferable resistance to chloramphenicol and trimethoprim was found in sporadic *S. Typhi* isolates [15].

The first multiresistant strains emerged in South-east Asia in 1987 [16] and have since spread throughout the region. Their prevalence in China has increased since 1985 and by 1989, 80% of *S. Typhi* isolates in Shanghai were multiresistant. In these strains resistance to chloramphenicol, ampicillin, tetracycline, trimethoprim, sulphonamides, gentamicin and cephalozolin was encoded on a self-transferable 98 MDa plasmid [17]. Multi-drug resistant strains were first reported in Pakistan in 1987 [18] and have increased in prevalence to almost 90% of *S. Typhi* isolates [19, 20].

All of 25 multiresistant isolates obtained from Rawalpindi in 1990–91 carried a single self-transferable c. 98 MDa plasmid encoding resistance to chloramphenicol, ampicillin, streptomycin, tetracycline, sulphonamethoxazole and trimethoprim, but not to gentamicin [19] and were thus different from the Chinese isolates. By 1994, in Quetta in northern Pakistan, 77% of *S. Typhi* isolated from blood were multiresistant and they represented >50% of positive blood cultures [20].

Multi-drug resistant *S. Typhi* were first described in India in 1990 [21] and several different phage types carrying IncH1 plasmids of 110–120 MDa have been described [22]. Multiresistant strains have also been isolated in Malaysia [23], Bangladesh [24] and Vietnam [25], and the epidemic zone in Asia now appears to stretch from Pakistan in the west to China in the east. In addition, there is a ‟pseudo-epidemic’ zone in the Middle East. Between 30% and 40% of the population of Persian Gulf states are expatriate workers, mainly from the Indian sub-continent and the Far East. These workers travel repeatedly from their home countries to work and 70–80% of multiresistant *S. Typhi* strains in Bahrain [26], Kuwait [27], Qatar [28] and Oman [29] are imported. In this region 5–30% of *S. Typhi* isolates are multi-drug resistant.

Surprisingly, multi-drug resistance does not seem to have had a major impact in Africa, or South and Central America. In Africa, cases have been described in Egypt [30] and a cluster of six cases of multiresistant *S. Typhi* infection was reported from northern Natal [31]. Elsewhere in Africa and America, *S. Typhi* remains sensitive to one or more of the first line agents, although large outbreaks of infection due to
strains resistant to chloramphenicol and some of the other antimicrobial agents continue to occur [10, 14]. In the UK, multiresistant strains now represent >18% of S. Typhi isolates [32], mostly acquired in the Indian sub-continent or the Middle East. Three such strains have been isolated in Spain but their origin is unclear [33].

The emergence of multi-drug resistance has great implications for therapy [32]. For example, children infected with such strains are more ill at presentation, have a longer duration of illness and a significantly higher mortality rate [34]. However, there are no pathognomonic features to distinguish such infections from infection with fully sensitive S. Typhi at presentation. The therapeutic options for treatment include fluoroquinolones such as ciprofloxacin or ofloxacin [20, 25, 32, 35], and expanded-spectrum cephalosporins such as ceftriaxone [35]. Azithromycin appears to be of little value as there was a lack of clinical response by the fourth or fifth day, in three or four patients treated [36]. In comparative and open studies, fluoroquinolones appear superior to cephalosporins [35], producing defervescence within 3–4 days [20, 25]. This speed of clinical response makes them a current treatment of choice even for less resistant S. Typhi. A 3-day regimen of oral ofloxacin was safe and highly effective in treating uncomplicated multi-drug resistant typhoid [25], but the effect of such short courses on carriage of S. Typhi needs further exploration. In children, the risks of mortality and morbidity from infection with multiresistant strains greatly outweigh the risk of potential side-effects of fluoroquinolone therapy [37]. For now, empirical therapy of suspected typhoid should be a fluoroquinolone or expanded-spectrum cephalosporin. Unfortunately, ciprofloxacin-resistant strains have already begun to emerge [38, 39], and this will further limit the therapeutic options.

S. H. MIRZA, N. J. BEECHING and C. A. HART
Tropical Medical Microbiology Centre, Dept. Medical Microbiology and Genitourinary Medicine, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK.

References
31. Bhutta ZA, Naqvi SH, Razzaq RA, Farooqui B.J. Multidrug-