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. Virchow, 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 [1, 2], in developing countries where safe water supply, environmental sanitation and food hygiene are not optimal, typhoid is still a major problem. In 1985 there was an estimated global incidence of typhoid of 12.5 million cases each year resulting in over 300,000 deaths [3]. The importance of good sanitation and hygiene is well illustrated by experience in Singapore where there has been a steady decline in typhoid from an incidence of 10 per 100,000 population in the 1950s to 1 per 100,000 in the 1980s [4]. Because of the difficulties in preventing typhoid by public health measures or immunisation, in developing countries great reliance is placed on antimicrobial chemotherapy. The mortality of untreated typhoid can be as high as 30%, whereas with appropriate antimicrobial chemotherapy it is <1%. In developing 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 cephalosporin 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 Rawalpind 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 multi-resistant 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.

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