

## Regional Review

### Enteric Fever in Mediterranean North Africa

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#### Abstract

Typhoid fever is endemic in the Mediterranean North African countries (Morocco, Algeria, Tunisia, Libya, and Egypt) with an estimated incidence of 10-100 cases per 100,000 persons. Outbreaks caused by *Salmonella enterica* serovar Typhi are common and mainly due to the consumption of untreated or sewage-contaminated water. *Salmonella enterica* Paratyphi B is more commonly involved in nosocomial cases of enteric fever in North Africa than expected and leads to high mortality rates among infants with congenital anomalies. Prevalence among travellers returning from this region is low, with an estimate of less than one per 100,000. Although multidrug resistant strains of *Salmonella* Typhi and Paratyphi are prevalent in this region, the re-emergence of chloramphenicol- and ampicillin-susceptible strains has been observed. In order to better understand the epidemiology of enteric fever in the Mediterranean North African region, population-based studies are needed. These will assist the health authorities in the region in preventing and controlling this important disease.

**Key words:** typhoid, paratyphoid, *Salmonella*, Egypt, Libya, Tunisia, Algeria, Morocco

*J Infect Dev Ctries* 2009; 3(10):753-761.

(Received October 23, 2009 – Accepted October 26, 2009)

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#### Introduction

Enteric fever is an acute systemic infection caused mainly by *Salmonella enterica* serotype Typhi (*S. Typhi*) [1]. *Salmonella enterica* serotype Paratyphi A, B, and sometimes C (*S. Paratyphi* A, B and C) cause similar but less severe disease compared with *S. Typhi* [2]. As recently as the year 2000, typhoid fever has been estimated to cause 21.6 million illnesses and 216,500 deaths among children and young adults worldwide [2-6]. These data represent the tip of the iceberg since the real burden of enteric fever remains almost unknown in different developing countries where the disease is a serious public health problem.

The aim of this review is to provide an overview, on the basis of limited data available in literature, with respect to the epidemiology, spread of antimicrobial resistance, and treatment practices of typhoid fever in the Mediterranean North African region (Morocco, Algeria, Tunisia, Libya, and Egypt [Figure 1]).

#### Epidemiology

Little data is available regarding the incidence of typhoid fever in the Mediterranean North African

countries, mainly due to a lack of or insufficient epidemiological surveillance activities and limited diagnostic facilities. In order to facilitate the interest of under-represented nations and their problems, an online *Salmonella* Network [7], which links with activities conducted by the *Journal of Infection in Developing Countries* (JIDC), has recently been established. This network encourages the sharing of data and results from developing areas such as North Africa and provides an opportunity to create a collection of clinical *Salmonella* strains for further research. Areas of potential interest are as follows: 1) dissection of mechanisms of antibiotic resistance, 2) pathogenicity, 3) epidemic potential and 4) infection control. A number of scientists from North African countries including Morocco, Tunisia, Algeria, and Libya are now part of this educational and scientific activity.

According to a recent surveillance (2000-2002) supported by the World Health Organization (WHO) *S. Typhi* ranked as the third (8%) most prominent *Salmonella* spp. isolated in Africa after *S. Typhimurium* (26%), and *S. Enteritidis* (25%) [8].

**Figure 1.** Map of Mediterranean North Africa.

This study was extended through the WHO Global Salm-Surv program until 2005 [9]. During this period, *S. Typhi* dropped to sixth place overall (5%) following *S. Typhimurium*, *S. Enteritidis*, *S. Isangi*, *S. Livingstone*, and *S. Corvalis*. At present, typhoid is considered an endemic disease in Mediterranean North African countries with estimated medium incidence of 10 to 100 cases per 100,000 persons (Table 1) [2,3,10]. The most important point is that epidemiological reports, not always based on population studies and outbreak descriptions, have been sporadically reported mainly in national rather than international publications.

#### Libya

In Libya, a comprehensive study was conducted on 30,165 patients who were hospitalized with acute diarrhoea during 1975-1980 [11]. A low prevalence of *S. Typhi* and *S. Paratyphi* in stool samples of patients was shown. Among different serotypes of *Salmonella* identified in 7,560 patients, 81 were identified as *S. Typhi*, 3 *S. Paratyphi* A and 4 *S. Paratyphi* B. In recent years, an increased rate of typhoid has been observed. For example, according to information resources of the Libyan Center for Information and Documentation (CID) of the Secretary of Health and Environment, the incidence rate for the years 2004, 2005 and 2006 were seven, 21 and 16/100,000 persons/year respectively [12-14]. The diagnosis of the cases included in the previously mentioned studies was based only on clinical features and further confirmation by laboratory testing was required. The significant increase in the incidence over this period is probably due to the improvement of the data reporting system and improved infrastructure in local health care facilities.

#### Egypt

In order to establish the etiology of enteric infections with a particular emphasis on the identification of *Salmonella* spp and *S. Typhi* in Egypt, several studies have been performed. Most of these studies have been conducted in cooperation with the Egyptian Ministry of Health and Population (MOHP) and the U.S. Naval Medical Research Unit-3 (NAMRU-3), often in partnership with the US Center for Diseases Control and Prevention (CDC).

The first study that attempted to establish the incidence of enteric fever in Egypt was conducted during a vaccination campaign in 1972-1973; a high incidence of cases (209/100,000 persons [15]) was reported. An additional surveillance study (1978-1981) in the same social context, examining school-aged children in Alexandria, reported a lower incidence of 48/100,000 [16,17].

Wasfy and co-workers [18] conducted a study on stool samples collected from 6,278 young patients (mean age of 14.1 years) admitted to the Abbassia Fever Hospital in Cairo from 1986 to 1993 with acute enteric infections. *Salmonella* spp was isolated from 465 patients in this cohort. The majority of the isolated strains (53%) were *S. Typhi*, while only 3% were *S. Paratyphi* A. The peak of cases was observed during February-March, June-July, and October-November.

An outbreak of typhoid fever caused by a chloramphenicol resistant strain of *S. Typhi* occurred in Gharbeya Governorate in 1990, involving 90 children and 43 adults [19]. Although, the source of infection was not confirmed, consumption of contaminated food was hypothesized as the main cause of infection due to the involvement of children and young adults in urban areas.

**Table 1.** Incidence of typhoid fever in North African Countries.

Country	Incidence/100,000	References
Algeria	3-22	34
Egypt	13-59	3, 22
Libya	7-21	12,13,14
Morocco	8-17	21,22,32
Tunisia	1-6	24,28

A study performed in the period from 1999 to 2003 by a sentinel surveillance network involving several hospitals in the country demonstrated that *S. Typhi* and *Brucella* spp were the most common infective agents of acute febrile illness. Particularly *S. Typhi* was detected in blood samples from 5% of the patients under study [20].

At the beginning of the second millennium, the incidence of typhoid fever was estimated to be 15 cases per 100,000 persons on the basis of the Egyptian National Syndrome-Based Surveillance [3].

Between 2001 and 2005, several authors [21,22] reported a decrease of cases to 13 per 100,000 in different districts of Egypt. However, these data included mainly clinical notifications with only a low percentage confirmed by laboratory culture methods.

Recently, a laboratory-based surveillance project was conducted in Upper Egypt involving governorate health officers, clinicians and several health care centres (from the Regional Hospital to the rural health units and primary care physicians). The results from this study showed that the incidence of typhoid fever was 59/100,000 persons/year [3]. This number was higher than that previously reported from studies based on hospital syndromic surveillance. Despite this finding, Egypt remains a country with intermediate incidence of one to 100 per 100,000 cases of enteric fever, below nations such as India and Indonesia which claim more than 100 cases per 100,000 persons [21]. These results also indicate that the majority of typhoid cases (71%) were managed by a primary care facility, an observation that may demonstrate the importance and the efficacy of these structures as a first barrier to combat this disease. Interestingly *S. Typhi* was isolated in blood culture in 5% of cases of all 1,815 patients evaluated with fever, particularly in school-aged children. We believe that this research approach provides a more realistic picture and is closer to the real burden of typhoid fever in Egypt. Furthermore, the methodological approach reported in this study [3] could be an example of an accurate research and

public health activity and can be a model for other developing countries, especially those with the involvement of the large health structures.

#### Tunisia

In 1977 and 1982, the National Center of *Salmonella* at the Institute Pasteur, Tunis, identified 1,715 *Salmonella* isolates from throughout Tunisia; *S. Typhi* and *S. Paratyphi* were the most predominant (99.6%) isolates [10].

As predicted, contaminated drinking water was the main source of the disease's transmission, and infant septicemia was a major cause of death in one third of the cases [23]. In 1989, an incidence of about 6 cases per 100,000 per year was reported [24].

During the summer of 1999, an outbreak of typhoid fever occurred in and around the coastal city of Sousse. Samples from patients admitted to Farhat Hached Sousse Hospital and M'saken Hospital were examined. Ribotyping used to identify genetic similarities among the isolates demonstrated that 22 of the 24 isolates were indistinguishable [25], an indication that this outbreak may have originated from a single source.

Recently, Ben Aissa *et al.* [26] reported the first investigation on the trends of *S. enterica* serotypes isolated from different sources all over Tunisia during a decade (1994-2004). Isolates were collected during a national surveillance programme conducted by the National Centre of Enteropathogenic Bacteria, Institute Pasteur, Tunis (a member of WHO Global *Salmonella* Surveillance Program). *S. Typhi* was among the eight most frequently isolated *Salmonella* serotypes identified, detected in 1% of stool samples and 39% of blood samples examined [26]. Peak isolation rates were detected in 1999 and 2004, which corresponds to two outbreaks that occurred in Sousse. The first was detected in a hospital and the second was detected in the community.

Another group of investigators [27] studied two successive outbreaks of typhoid fever that were reported in 2004 and 2005 in southeast Tunisia. A total of 86 isolates of *S. Typhi* were recovered. All isolates were susceptible to ampicillin, chloramphenicol, trimethoprim-sulphamethoxazole and ciprofloxacin. Pulsed field gel electrophoresis using the restriction enzyme *XbaI* indicated that a single clone appeared to be responsible for the 2004 outbreak. Interestingly, investigation of the 2005 outbreak revealed isolates possessing five different *XbaI* profiles, although the 2004 outbreak pattern predominated. This finding indicated that several

strains were involved in the second epidemic episode. The 2006 Bulletin of the Ministry of Health showed an incidence of typhoid fever of about 1 case per 100,000 per year in Tunisia [28]. However, there are only scattered reports directly examining the incidence of typhoid fever in Tunisia. More comprehensive surveillance data are necessary to evaluate the actual burden of disease and relevant risk factors in the country.

#### *Morocco*

*S. Typhi* and *S. Paratyphi* are endemic in Morocco [29,30]. Recent studies from national and international agencies such as the National Institute of Hygiene (Rabat) and the WHO Global *Salmonella* Surveillance Program have provided useful epidemiological data regarding the prevalence of *S. Typhi* in Morocco [31]. In 1999, *S. Typhi* was the most common isolate of *Salmonella*; however, by the year 2000 it had dropped to the third most common isolate. No cases of typhoid were reported in 2001, and a year later, it was only the fourth most commonly isolated *Salmonella* serotype. In 2003, only *S. Paratyphi B* was isolated. According to the data published by Ministry of Health, typhoid fever was observed in 8-17 cases per 100,000 per year from 1993-1999, [32] and recent data gives an estimate of 8 cases per 100,000 [21,22].

#### *Algeria*

The prevalence of *Salmonella* infections in Algeria was first reported by Guechi and Hamza [33], covering the years from 1986 to 1990. *S. Typhi* was the dominant serotype, claiming 98% of the 3,340 clinical isolates of *Salmonella* spp recovered. However, from 1985 to 2005, the National Institute of Public Health reported only 3-22 cases of typhoid fever per 100,000, [34] which is similar to what has been reported from Middle-Eastern countries [35]. In Algeria, the highest incidence rates for enteric fever are reported during the hot summer months and among school-aged children (*i.e.* from 5 to less than 20 years of age) [32]. In addition, available data from this geographic area suggested that typhoid fever occurs more commonly among males than females [36].

In January 1996, a typhoid fever outbreak with more than 900 suspected cases was reported in Ain Taya, located 20 km East of Algiers. The outbreak resulted from contamination of the village water reservoirs by sewage water [37]. Another outbreak caused by the use of untreated water was reported in

2004 in Batna province with 328 typhoid fever cases; 38 patients required hospital care [38].

### **Complications of typhoid fever**

Benkortibi *et al.* [39] studied 1,310 children with typhoid fever admitted to El Kettar Hospital in Algeria during a 16-year period from January 1975 to December 1990. In 9% of these children, one or more gastrointestinal, neurological or cardio-vascular complications were identified. Similarly, a high percentage (13%) of complications was reported in Moroccan children admitted to a Casablanca hospital from January 1980 to December 1991 [40]. Most frequent complications were neurological (46%), gastrointestinal (35%), and hematological (16%). Interestingly it was observed that female gender, poor hygiene conditions, and digestive parasitosis were the most important determining factors of complicated typhoid fever in the children studied [40]. Similar complications including lower gastrointestinal bleeding, relapse, uraemia and icterus were observed during an outbreak of typhoid fever among children in Egypt [19]. A rare complication of typhoid fever, splenic abscess, was reported in Algerian patients with acute lower thoracic pain by using abdominal ultrasound [41].

Studies from several developing countries have shown a positive association between the chronic typhoid carrier state and carcinoma of the gallbladder [42-44]. Recently, Nath *et al.* in India [45], using nested PCR for the flagellin gene specific sequences of *S. Typhi*, detected the organism in 67.3% of patients with gallbladder carcinoma and in 8.2% of a healthy population not matched for age and sex ( $P < 0.001$ ). However, no data is available regarding the association of typhoid carriage and gallbladder carcinoma in the Mediterranean North Africa region.

### **Nosocomial (hospital-acquired) typhoid and paratyphoid fever**

Although *S. Typhi* and *S. Paratyphi* are not common causes of nosocomial infections, several hospital-acquired infections due to both organisms have been described in North Mediterranean Africa with high mortality rates in newborns. During the period from August 1994 to June 1995, stool, blood, and CSF samples were collected from 468 infants (1 to 35 days old) who developed watery diarrhoea 4 to 18 days after admission to a neonatal unit at the Children's Hospital of Benghazi in Libya [46].

*Salmonellae* were detected in 8% (36) of the collected samples, with 26 isolates being *S. Paratyphi B* and 10 *S. Typhi*. Of the laboratory-confirmed *Salmonella*-positive infants, eight died and six had congenital anomalies. A strong association between bottle feeding and infection was observed. The majority of the infections were acquired during the hot months of the year (June-September). In another study also conducted in Benghazi in the period from July 2000 to June 2001, forty-one *Salmonella* strains isolated from stool samples of children aged between 3 days and 12 years were serotyped. Of these, seven were *S. Paratyphi B* and two *S. Typhi*. The investigators reported that all the *S. Paratyphi B* isolates were nosocomially acquired [47].

### **Typhoid and paratyphoid fever in travellers to North Africa**

Enteric fever is rare in industrialized countries; however it does present among travellers returning from areas of endemicity [48]. Therefore, it is important to see the risk for travellers acquiring enteric fever during their visits in this region. Previous studies have reported a low prevalence of typhoid and paratyphoid among travellers to North Africa; however, for travellers planning to remain in the region for six months or longer, vaccination against typhoid is recommended by the WHO and the CDC (<http://www.who.int/ith/en/> and <http://wwwn.cdc.gov/travel/>).

An Australian study [49] reviewed 232 patients (15% travelled to Africa) admitted to a tertiary-care hospital for management of febrile illness acquired overseas. Typhoid fever was found in eight (3.5%) patients and was more common in travellers returning from a trip to Asia. A larger clinical-based sentinel surveillance study analyzing 17,353 sick travellers indicated that typhoid fever was one of the primary contributors to systemic febrile illness among travellers returning especially from south central Asia but not from other regions (including North Africa) [50]. Similar findings were reported for Swedish and French travellers [51,52]. Incidence of typhoid fever in Israeli and American travellers to Egypt and Morocco is estimated at 0.3 and 0.7 per 100,000 visits [21,22], while the rate of infection in all travellers to the Indian subcontinent was 17.3 per 100,000 visits. Although much evidence suggests the low risk of typhoid fever for travellers to North African countries, it is important for tourists to avoid

eating and drinking contaminated food and water, the typical transmission factors.

### **Antimicrobial resistance and treatment**

Since 1984, several investigators reported *S. Typhi* resistance to one or more antibiotics [53,54]. In Algeria the first *S. Typhi* strain with multidrug resistance (MDR) to ampicillin, chloramphenicol, streptomycin, and kanamycin was reported in 1973 linked to the presence of a plasmid [55]. In order to explore the emergence of MDR *Salmonella* strains in the country, 752 *S. Typhi* and *S. Paratyphi* strains isolated during the period between October 1973 and August 1974 were tested for their resistance to different antibiotics. All the examined strains were susceptible to antibiotics used in the study except one *S. Typhi* isolate. This plasmid-bearing strain was MDR, including to drugs that are commonly used to treat typhoid fever [56]. However, in a study with a larger number of *S. Typhi* (5,940 strains), *S. Paratyphi A* (123 strains) and *S. Paratyphi B* (115 strains) isolated between 1979 and 1984, no resistance was found while seven strains isolated in the middle of 1973 to December 1978 were resistant to some antibiotic indicating that the spread of MDR strains was still limited [57].

A paper published in 1982 reported studies in which all *S. Typhi* (392 strains) isolated from blood were susceptible to ampicillin and tetracycline [58]. These studies showed that, although sporadic strains were resistant to some antibiotics, MDR strains were not spread at that time in Algeria.

In 1981, Sippel *et al.* [59] reported the isolation of a chloramphenicol-resistant *S. Typhi* strain isolated from the stool of a patient with typhoid fever in Upper Egypt. Nearly a decade later, Mikhail *et al.* [60] isolated for the first time MDR (chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole) *S. Typhi* from the blood of an Egyptian patient suffering of typhoid fever.

During the last 15 years a steady increase of MDR *S. Typhi* in some North African countries has been observed. In 1993, El-Mahdy *et al.* [61], in Mansoura, Egypt, examined blood cultures obtained from 42 Egyptian children (aged 4 to 12 years) clinically suspected of typhoid fever, with no response to antibiotics treatment for two weeks. Only nine (21%) children were positive for *Salmonella* (five *S. Typhi*, two *S. Paratyphi A* and two *S. Paratyphi B*) and two strains were MDR (one *S. Typhi* and one *S. Paratyphi A*). However, in a phage-Vi surveillance-based study conducted in the same

year at Alexandria Fever Hospital (Alexandria, Egypt), 43% of the isolated *S. Typhi* strains were MDR. Moreover, the identified phage types were E2 or D1-N [62] which are different from the phage type E1 that dominates in the Indian subcontinent [63,64]. It is not known whether *S. Typhi* E2 and D1-N are also the dominant types in the other North African countries.

Wasfy *et al.* [18] described the resistance of 537 *S. Typhi* isolates identified in Egypt. MDR was detected in more than 71% of the isolates, particularly to the most commonly used antibiotics for the treatment of typhoid fever (*i.e.* ampicillin, chloramphenicol and TMZ-SMZ). In addition, the authors demonstrated that the resistance was associated with the presence of a transferable 120 MDa plasmid. However, the *S. Typhi* isolates were sensitive to amikacin, aztreonam, ceftriaxone, gentamicin and nalidixic acid, suggesting the possible use of aztreonam and ceftriaxone as alternative therapeutic drugs of choice for the treatment of infections due to MDR *S. Typhi* strains.

In a population-based surveillance study conducted in 2002 in Fayoum, Egypt, the majority (65%) of *S. Typhi* isolates were resistant to all first-line antibiotics used in the treatment of the disease, and 25% of the isolates were classified as MDR [3]. Also in Egypt, Abdel Wahab and co-workers reported MDR *S. Paratyphi* A [65].

MDR *S. Typhi* (strain 302) isolated from blood culture in the Department of Infectious Diseases of Rabta Hospital, Tunis, was found resistant to amoxicillin, streptomycin, tetracycline, chloramphenicol, and trimethoprim-sulphamethoxazole (TMZ-SMZ) [66]. The conjugative experiments indicated that resistance was related to a transferable plasmid of about 40 kb. In addition, the *S. Typhi* isolate was found positive for TEM-1 beta-lactamase.

The majority of *S. Typhi* and *S. Paratyphi* B isolated from infants with hospital-acquired typhoid and paratyphoid fevers in Benghazi, Libya, were resistant to chloramphenicol, ampicillin, TMZ-SMZ, cephalosporin and gentamicin [46].

A contribution on the efficacy of pefloxacin in the treatment of typhoid fever was reported in Algeria in 1990 in patients with *S. Typhi*, indicating that a seven-day treatment of 400 mg of this quinolone twice a day provides a good alternative to the treatment of this disease [67]. In Egypt, Girgis *et al.* [68] reported that one gram of azithromycin orally administered once on the first day, followed by 500

mg given orally once daily for the next six days or 500 mg of ciprofloxacin orally twice daily for seven days were both clinically and bacteriologically effective against typhoid fever caused by both susceptible and MDR *S. Typhi* strains. Azithromycin and ciprofloxacin are expensive drugs and usually not available in rural and semi-urban areas of some North African countries [69, KS Ghengesh, unpublished observation]. Furthermore, resistance to ciprofloxacin among *S. Typhi* and *S. Paratyphi* B has recently been reported from Libya [46]. However, recent studies from Egypt observed the re-emergence of chloramphenicol and ampicillin susceptibility and therefore suggest the reintegration of these drugs for the treatment of typhoid fever in Egypt [70]. Their cheaper cost and availability in the developing countries, in addition to their well-established clinical efficiency, are among the benefits of reusing chloramphenicol and ampicillin [71]. In the future, studies are needed to determine whether the reintegration of these drugs can be applied to other countries of North Africa for treatment of typhoid fever. Collection of data that document antibiotic resistance patterns in the Mediterranean North African region is essential, and treatment of infection should be according to the current patterns of resistance.

### **Typhoid fever vaccines**

Worldwide, two vaccines are currently licensed and widely used. The first is based on purified Vi antigen and is administered as one dose either intramuscularly or subcutaneously. The Vi vaccine provides protection for at least three years but is not recommended for use in infants and so is not used to vaccinate children less than two years of age. The second is based on the attenuated *S. typhi* strain Ty21a that lacks both a functional galactose-epimerase (*galE*) gene and the Vi antigen [72]. The Ty21a vaccine is administered orally in a three-dose regimen and provides protection for five to seven years. The vaccine was extensively tested in Alexandria, Egypt, where the liquid formulation showed 96% protection for three years [73]. Both vaccines have been endorsed by the WHO's Strategic Advisory Group of Experts (SAGE) on immunization for their safety, efficacy and affordability, and for use in immunization of school-aged and/or preschool-aged children [74].

There is no published data on whether or not these vaccines were used in the Mediterranean North Africa countries. Because typhoid fever incidence in

most of the Mediterranean North Africa countries falls in the medium range and outbreaks are infrequent, the need to incorporate typhoid vaccine in the vaccination program in such countries may not be needed. However, in some villages and localities within these countries that have poor sanitation systems and are without safe drinking water, typhoid vaccination may have a role in controlling the disease. In addition, typhoid fever vaccines can be used in the control of outbreaks as recommended by the WHO [72].

In conclusion, typhoid and paratyphoid fever are endemic in the Mediterranean North African countries and MDR is common among *S. Typhi* and *S. Paratyphi* isolated in this region. To clarify the typhoid and paratyphoid fever situation in the North African Region, population-based studies are still needed. The information that will be gathered from these studies will support and assist the decision makers and health authorities in the region in the prevention and control of such important diseases. Finally, there is an urgent need to enhance the *Salmonella* surveillance not only in a single country but at the level of all Mediterranean North African Countries with a creation of a common collaboration strategy to defeat salmonellosis and in particular enteric fever in the region.

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**Conflict of Interest:** No conflict of interest is declared