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The antibiotic resistance patterns of *Salmonella* Typhi isolates in Italy, 1980–96

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SUMMARY

In this paper we report the distribution of *Salmonella* Typhi isolates in Italy and their resistance patterns to antibiotics. The data were collected by the Italian SALM–NET surveillance system in a pilot retrospective study of the period 1980–96. Data on drug-resistance were available for 82 isolates out of 176 *S.* Typhi isolated in Italy. Of these 82 isolates, 32 (39%) were resistant or intermediate to 1 or more antibiotics. Eight isolates were resistant and 7 intermediate to streptomycin; 4 isolates were resistant to ampicillin alone or in association with other antibiotics; only 2 strains (1 isolated in Lombardia in 1993 and the other 1 in Lazio in 1994) were resistant to chloramphenicol, and 2 (isolated in Sardegna and Piemonte in 1995 and 1996, respectively) showed intermediate resistance to chloramphenicol. The strains showing resistance to 3 or more antibiotics were very scarce: 1 (with 5 complete resistances) was isolated in Lazio in 1994, and another 1 (with complete resistance to 10 antibiotics and intermediate resistance to 2 antibiotics) was isolated in Molise in 1988. In conclusion, besides the routine activities to control typhoid fever, an accurate and continuous surveillance is necessary in order to quickly identify multidrug-resistant (MDR) *S.* Typhi strains and prevent their spread, even though their level, in our country, is still quite low.

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INTRODUCTION

Typhoid fever continues to pose a serious public health hazard in many developing countries, with an annual incidence, in 1995, of 16·6 million cases, and approx. 600000 deaths most of which occurring in Asia (440000) and Africa (130000) [1]. This threat is especially high in Southeast Asia which has one of the highest incidences of typhoid fever in the world (more than 1000 cases per 100000 inhabitants) [2].

The cases of typhoid fever in Italy reported to the National Institute for Statistics [3, 4] and the Ministry

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of Health [5, 6] have amounted to a remarkable number in the past 30 years. A peak of more than 18000 cases was recorded in 1972, then a progressive decrease to about 2000 cases in 1985 down to almost 1000 cases in 1996.

According to the data yielded by the laboratory-based surveillance system, in 1973, the *S.* Typhi isolates from humans in Italy accounted for 13·2% of the total salmonella isolates from human sources [7]. Between 1973 and 1995, the number decreased from 576 (13·2%) to 52 (0·4%) isolates [8]. During the 3-year period 1994–6, the data collected through the SALM–NET system showed that the strains of *S.* Typhi isolated in our country were 117 (unpublished data).

At the 2nd Asia–Pacific Symposium on typhoid fever and other Salmonellosis held in Bangkok [2], the rapid rise, all around the world, of multidrug-resistant (MDR) salmonella strains was discussed. In particular, multi-drug resistance becomes a serious problem with *S.* Typhi, because of the nature of the disease and the world-wide diffusion of multi-drug resistant *S.* Typhi strains.

Since 1992, Italy has been participating in the *Salmonella* Network (SALM–NET): the Program for the European Community Surveillance of salmonella isolates from human sources [9] in which each laboratory-confirmed and typed salmonella isolate from humans was included in a computerized database together with a core set of microbiological and epidemiological data items.

Therefore, the SALM–NET European Group decided to review the actual extent of the surveillance over antibiotic resistance within salmonella, the range of antibiotics tested, and the number of countries conducting this surveillance. Inside the wider project of surveillance of the antibiotic resistance, a retrospective pilot study was conducted circumscribed on the resistance pattern of all isolates of *S.* Typhi identified in each participating country. In Italy, specifically, the pilot study regarded 176 *S.* Typhi whose data were collected through the SALM–NET System in the period 1980–96.

The number of antibiotics to be tested for the antibiotic resistance surveillance had also been defined in the SALM–NET European Project. This first step should help prepare the mechanisms for the transfer of data and identify the potential benefits of resistance surveillance for salmonellas in order to standardize or harmonize the different methodologies used for testing sensitivity to antibiotics. This is a most pressing aim that member countries expect to attain in the shortest time possible.

METHODS

The strains studied were isolated from human clinical sources, mainly stools, from carriers and ill subjects involved in both sporadic and epidemic episodes. All the strains were serologically typed according to the White–Kauffman scheme using commercially available diagnostic antisera [10, 11].

The European SALM–NET Project for the *S.* Typhi pilot surveillance programme will focus on the following antibiotics: ampicillin (AM), chloramphenicol (C), ciprofloxacine (CIP), gentamicin (G), streptomycin (S), sulphonamides (S3), sulphamethoxazole/trimethoprim or co-trimoxazole (SXT), tetracycline (TE).

In addition, the Italian SALM–NET Project already collects data on: amikacin (AN), ceftazidime (CFZ), ceftriaxone (CRO), cephotaxime (CTX), cephuroxime (CXM), nitrofurantoin (FT), nalidixic acid (NA), piperacillin (PIP), tobramycin (TM).

As the European SALM–NET Project also intended to collect retrospective data for some salmonella strains that were isolated prior to 1994, other antibiotics are included in this study, namely: carbenicillin (CB), cephalothin (CF), colimicin (CL), colistin (CS), cephalexin (CX), fosfomycin (FOS), kanamycin (K), kanendomycin (KA); cephamandol (MA), rifampicin (RA), sulphonamides (S3).

Antibiotic sensitivity was assessed through one of the three standardized methods [12] currently used in different Italian laboratories, namely: the agar diffusion disk method [13] for which the standard measurements were determined as defined by NCCLS [14]; the break points, according to those established by BSAC [15] and NCCLS [14]; the determination of the minimum inhibitory concentration (MIC) for which results were recorded according to NCCLS definitions [14]. The data collected were analysed by using the public domain EPI–INFO Software Programme [16].

RESULTS

From unpublished data, based on the SALM–NET surveillance, *S.* Typhi was never present among the ten serotypes most frequently isolated from human sources since 1981. Conversely, in a review of data collected by the traditional, non-computerized system

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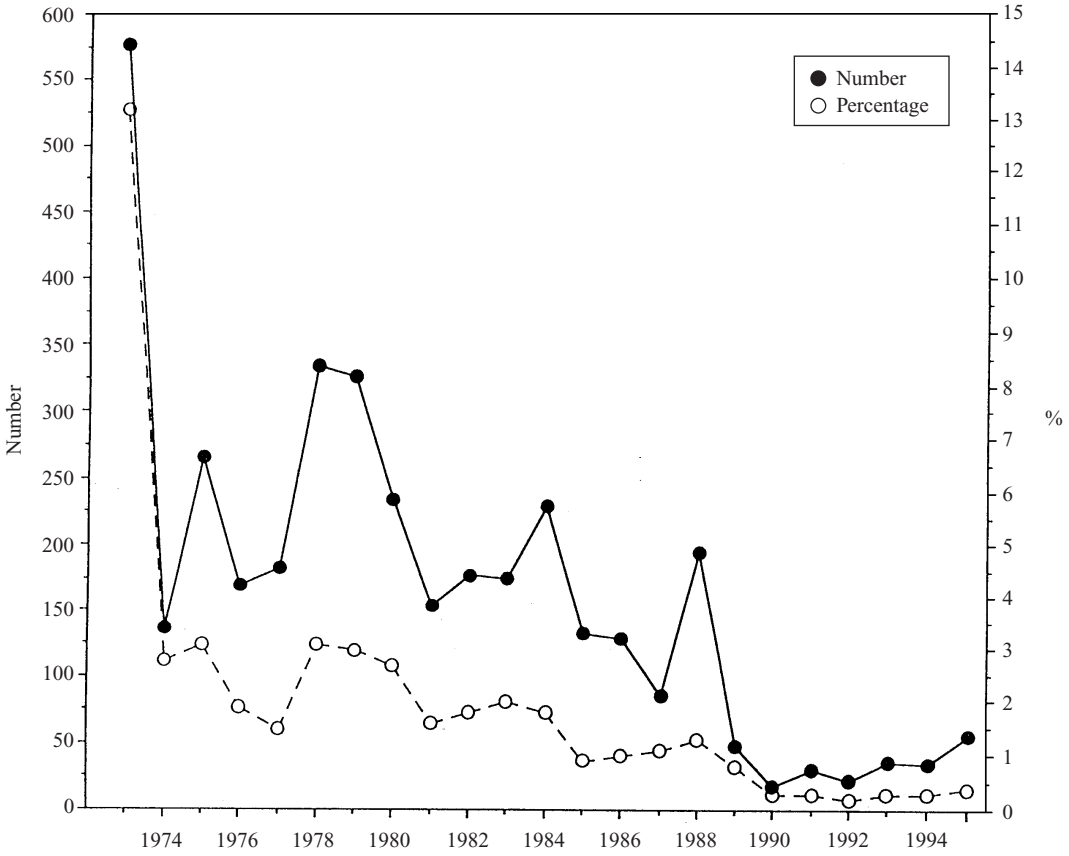

Fig. 1. Trend in isolations of *S.* Typhi in Italy, 1973–95 (source: Fantasia et al., 1998 [13]).

of surveillance of salmonella serotypes in Italy, *S.* Typhi was in the top ten list in the period 1973–80. In 1973 this serotype accounted for 576 isolates, but progressively decreased to 52 isolates in 1995. Its percentage over the total number of salmonella isolates from human sources dropped from 13·2% in 1973 to 0·4% in 1995 (Fig. 1) [8].

Table 1 illustrates the distribution of the *S.* Typhi isolates known to have been tested for antibiotic resistance, plus their total number per region, per year. Out of 176 *S.* Typhi isolates, whose data were collected in the period 1980–96 through the SALM–NET System, data on drug resistance were available for only 82 isolates. Thirty-two out of the 82 (39·0%) isolates showed a complete or intermediate resistance to one or more antibiotics by different patterns.

The number and the percentage of resistant or intermediate *S.* Typhi strains are different for each Region, ranging from 9·1% (1 out of the 11 isolates) in Campania to 83·3% (5 out of the 6 isolates) in Sicilia.

Table 2 shows the resistance-patterns. For streptomycin (S), 8 isolates were resistant and 7 intermediate. Four isolates exhibited resistance to ampicillin (AM) alone or in association with other antibiotics. Strains resistant to chloramphenicol (C) are not as yet numerous in Italy: 2 resistant and 4 intermediate strains were isolated. Two multi-drug-resistant strains (i.e. resistant to 3 or more antibiotics) were isolated: 1 resistant to 4 antibiotics and 1 with a remarkably wide pattern, i.e. it was resistant to 10 antibiotics and intermediate to 2, but sensitive to chloramphenicol. Of the resistant strains, 62·5% were isolated in 1995–6.

Table 3 reports the number of isolates resistant or intermediate to single antibiotics. Of the 32 strains exhibiting resistance to 1 or more antibiotics, only 4 were resistant to AM, 2 were resistant and 2 intermediate to C, 8 resistant and 7 intermediate to S. It is noteworthy that no strain was resistant or intermediate to CIP, G or S3.

DISCUSSION

The continuous increase in antibiotic resistance among salmonella poses a serious problem, par-

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Table 1. *Distribution of* S. *Typhi strains tested for antibiotic resistance on the total number of* S. *Typhi isolates, per region, per year* (*Italian SALM–NET data*)

Region/year	1980–8	1989	1990	1991	1992	1993	1994	1995	1996	Total
Basilicata									0/1	0/1
Campania									11/11	11/11
Friuli V.G.									4/4	4/4
Lazio						0/3	1/1	1/3		2/7
Lombardia						4/4	3/12	7/10	1/2	15/28
Molise	15/24	3/3	2/2	0/1						20/30
Piemonte								1/1	4/4	5/5
Puglia								2/3	3/4	5/7
Sardegna								9/14	2/2	11/16
Sicilia							1/9	4/4	1/1	6/14
Umbria								2/2		2/2
Veneto		0/5	0/6	0/3	0/11	0/7	0/6	0/7	0/4	0/49
Italy n.sp.*							1/2			1/2
Total	15/24	3/8	2/8	0/4	0/11	4/14	6/30	26/44	26/33	82/176

* n.sp., not specified.

Table 2. S. *Typhi R-pattern per region, per year* (*Italian SALM–NET data*)

R-Pattern*	No. of isolates	Region and year of isolation
CXM	1	Sardegna 1 (1995)
NA	1	Campania 1 (1996)
PIP	1	Lombardia 1 (1995)
RA	1	Lombardia 1 (1993)
S	6	Molise 1 (1988); Sicilia 4 (1995), 1 (1996)
(S)	7	Molise 3 (1980–88), 2 (1989), 2 (1990)
AM PIP	1	Friuli 1 (1996)
C CF	1	Lombardia 1 (1993)
(C) CXM	1	Sardegna 1 (1995)
(C) TE	1	Piemonte 1 (1996)
(CXM) NA	2	Sardegna 1 (1995), 1 (1996)
(CXM) (PIP)	1	Puglia 1 (1995)
CXM (PIP)	1	Puglia 1 (1996)
CXM TM	1	Italy n.sp. 1 (1994)
CTX TE	1	Friuli 1 (1996)
(CL) (NA) (SXT)	1	Piemonte 1 (1995)
AM PIP (SXT) (TE)	1	Friuli 1 (1996)
(CF) CXM (PIP) TM	1	Puglia 1 (1995)
AM C S SXT TE	1	Lazio 1 (1994)
AM CB CF CX CXM FOS (FT) KA MA RA S (TE)	1	Molise 1 (1988)
Total	32 resistant isolates	

* AM, ampicillin; C, chloramphenicol; CF, cephalothin; CL, colimicin; CX, cephalexin; CTX, cephotaxime; CXM, cephuroxime; FOS, fosfomycin; FT, nitrofurantoin; KA, kanendomycin; MA, cephamandol; NA, nalidixic acid; PIP, piperacillin; RA, rifampicin; S, streptomycin; SXT, sulphamethoxazole/trimethoprim; TE, tetracycline.
( ), intermediate resistance.

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Table 3. *Number of* S. *Typhi isolates resistant or* (*intermediate*) *to a single antibiotic on the total isolates tested* (*Italian SALM–NET data*)

Antibiotic*	Isolates†
AM	4/76
AN	0/57
C	2+(2)/73
CB	1/2
CF	2+(1)/61
CFZ	0/43
CIP	0/49
CL	(1)/45
CRO	0/34
CS	0/2
CX	1/2
CTX	(1)/58
CXM	6+(3)/37
FOS	1/17
FT	(1)/60
G	0/76
K	0/30
KA	1/2
MA	1/3
NA	3+(1)/64
PIP	3+(3)/32
RA	2/3
S	8+(7)/55
S3	0/19
SXT	1+(2)/75
TE	3+(2)/74
TM	2/59

* AM, ampicillin; AN, amikacin; C, chloramphenicol; CB, carbenicillin; CF, cephalothin; CFZ, ceftazidime; CIP, ciprofloxacin; CL, colimicin; CRO, cephtriaxone; CS, colistin; CX, cephalexin; CTX, cephotaxime; CXM, cephuroxime; FOS, fosfomycin; FT, nitrofurantoin; G, gentamicin; K, kanamycin; KA, kanendomycine; MA, cephamandol; NA, nalidixic acid; PIP, piperacillin; RA, rifampicin; S, streptomycin; S3, sulphonamide; SXT, sulphamethoxazole/trimethoprim; TE, tetracycline; TM, tobramycin.

† Number of isolates resistant or (intermediate)/Number of total isolates.

ticularly with regard to the treatment of typhoid fever and systemic infections caused by other salmonella serotypes.

S. Typhi strains resistant to several antibiotics have been sporadically isolated in the period 1950–86, in South East Asia (Vietnam, Korea, India) but also in UK, USA, Peru, Madagascar, Hungary, Portugal and France [17]. From this date, multidrug-resistant *S.* Typhi have been increasing all over the world [18], starting from strains of *S.* Typhi isolated in Mexico City, resistant first to chloramphenicol [19] followed by strains which were resistant not only to chloramphenicol but also to many other antibiotics, such as tetracycline, streptomycin, sulphonamide and sometimes even to ampicillin [20].

The pattern of multi-drug-resistance changed subsequently to other antibiotics: *S.* Typhi strains with resistance to chloramphenicol, ampicillin and co-trimoxazole appeared in Asia, particularly in India during 1989–92 [21–26]. In Italy, the first similar strain was isolated from an Indian man who came in 1991 [27].

The appearance of *S.* Typhi strains resistant to chloramphenicol since 1972 [28] and subsequently to ampicillin and to trimethoprim [29–31] has been particularly threatening.

We must note that a resistant strain causing an outbreak affects a larger number of people than a sensitive one, because of its selective advantage. The Mexican epidemics demonstrate that an outbreak caused by an unrecognized resistant strain can be devastating; the high mortality rate was due to the clinical use of an antibiotic to which the strain was resistant.

In Italy strains of *S.* Typhi resistant to chloramphenicol are as yet scarce and so are strains showing multi-drug-resistance. However, in view of the above considerations, we should be ready to no longer consider chloramphenicol as the drug of choice in the treatment of typhoid fever. The same holds true for ampicillin and trimethoprim, that were used in the treatment of the chloramphenicol-resistant strains of *S.* Typhi. Indeed, strains resistant to these two antibiotics have been reported in many developed countries since 1989 [18]. At the moment, even if strains with resistance to ciprofloxacin have been identified, such an antibiotic is a good drug for the treatment of MDR typhoid fever [32]. Although ciprofluoxacin-resistant isolates have been reported sporadically in UK [33], this antibiotic may be recommended as an initial therapy in areas where MDR strains of *S.* Typhi are prevalent [34, 35].

Considering that multi-drug-resistant bacteria are appearing all over the world, and that a long time is required to discover new antimicrobial molecules – not to mention the time needed for demonstrating their efficacy and the lack of unexpected adverse side effects – great attention must be paid to preventing the selection and spread of strains resistant to the new antimicrobial drugs.

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