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## ABSTRACT

**Background:** *Salmonella* are significant bloodstream infection (BSI) pathogens worldwide and are routinely monitored for antimicrobial resistance (R) by the SENTRY Program.

**Methods:** 601 BSI strains of *Salmonella*, collected over a 5-year period from the SENTRY Program were susceptibility (S) tested by NCCLS methods and trended against 20 antimicrobials, comparing year (1997-2001) and geographical region (Asia-Pacific [APAC], Europe [EU], Latin [LA] and North America [NA]). ESBL phenotypes were confirmed by Etest ESBL strips.

**Results:** *Salmonella* ranked 13<sup>th</sup> among 67,046 BSI isolates. The variations among regions (rank order/% of all BSI) were: APAC (11/2.3%), EU (13/1.0%), LA (11/1.9%) and NA (16/0.4%). *S. typhi* was the most frequently "identified" species (43% of speciated strains), followed by *S. enteritidis* (20%) and *S. typhimurium* (12%), although overall "unspecified" strains predominated (54%). The rank order of potency for 6 key drugs tested by MIC<sub>90</sub> values was ciprofloxacin (0.12 µg/ml) > ceftriaxone (≤ 0.25) > tobramycin (2) > tetracycline (TC; >8) > amox/clav (A/C; 16) > ampicillin (AMP; >16). Over 99% of strains were S to both ciprofloxacin and ceftriaxone. Most *Salmonella* spp. remained highly S to all 20 agents tested, exception *S. typhimurium* (35% S to TC, 41% to AMP, 62% to A/C). S by region for the six drugs were similar, except for AMP and TC; % AMP/TC-S strains for LA (93/87%) > APAC (90/84%) > NA (78/76%) > EU (66/72%). R to both AMP (34%) and TC (28%) was highest in EU. Unexpectedly, LA had the highest S rates overall with the highest R being TC at 13%. DT104 R phenotypes were noted in 3.4 and 60% of unspecified *Salmonella* spp. and *S. typhimurium*, respectively. 1.2% ESBLs were noted, mainly in NA and APAC (2.3-2.4%). 4 strains overall were R to quinolones, 2 among the ESBLs.

**Conclusions:** 5-year results show no clear trend toward greater BSI *Salmonella* spp. R to commonly used antimicrobial classes. With the exception of *S. typhimurium* DT104, most *Salmonella* spp. remain highly S to the tested antimicrobials.

## INTRODUCTION

Salmonellosis is a major bacterial enteric disease in both animals and humans with over 1.4 million cases reported in the United States each year. Human non-typhoidal infection has been associated with animal contact and consumption. Mortality rates associated with BSI can reach 25% in some populations. Patients who receive appropriate and timely antimicrobial therapy have the lowest mortality rate, stressing the importance of using potent agents early in *Salmonella* BSIs. There has been an increase in resistance to the fluoroquinolones in some non-typhoidal *Salmonella* attributed to 1) the use of antimicrobial agents in agriculture, 2) the selection of spontaneous mutants with reduced susceptibilities to the quinolones during therapy, and 3) the increase in travel by humans to geographical regions where drug-resistant *Salmonella* resistance is endemic, especially in Europe, southeast Asia and the Indian subcontinent.

Multidrug-resistant (MDR) *Salmonella enterica* serotype Typhimurium definitive phage type 104 (DT 104) was first seen in humans in 1984 and over the last decade has become a recognized global health concern. MDR DT 104 strains have obtained integron-mediated resistances through chromosomally-encoded gene cassettes for ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines (R-type ACSSuT). Also strains resistant to "third-generation" cephalosporins and monobactams (ESBLs) have been rarely reported.

The SENTRY Antimicrobial Surveillance Program is a global study that monitors the susceptibilities and resistance patterns of key bacterial and fungal pathogens from nosocomial and community-acquired infections. The SENTRY Program is a key resource in understanding the trend development of resistance for antimicrobial agents used to treat serious invasive *Salmonella* infections.

## MATERIALS AND METHODS

A total of 601 isolates of *Salmonella* spp. were collected over a five-year period (1997-2001) from Asia-Pacific (128 strains), Europe (180 strains), Latin America (166 strains), and North America (127 strains). MIC values were established for more than 20 different antimicrobial agents using reference microdilution panels, with NCCLS methods and interpretations. QC tests and colony counts were regularly performed with *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922 and 35218.

The production of ESBL enzymes by was confirmed using the ESBL Etest (AB BIODISK, Solna, Sweden). Strains exhibiting an inhibition of enzymatic activity in the presence of clavulanic acid (≥ eight-fold MIC decrease) indicated ESBL production.

*Salmonella* spp. showing a DT 104 resistance pattern were further characterized with automated ribotyping (RiboPrinter™) and PFGE.

- Salmonella* spp. ranked 13<sup>th</sup> (1.4%) among all 67,046 BSI isolates collected during 1997-2001 (Table 1). The most frequently identified species was *S. enterica* serotype Typhi (117 isolates, 43%), although unspecified strains predominated overall (54.2%; data not shown).

**Table 1.** Occurrence rates of pathogens isolated from bloodstream infections observed in the SENTRY Antimicrobial Surveillance Program, 1997-2001 (67,046 episodes).

Rank	Organism	% of all occurrence by region:				
		North America	Europe	Latin America	Asia-Pacific	All regions
1	<i>S. aureus</i>	25.2	18.5	21.0	21.1	21.5
2	<i>E. coli</i>	17.7	21.9	18.1	21.4	19.8
3	CoNS <sup>a</sup>	11.9	15.9	13.2	10.9	13.0
4	<i>Klebsiella</i> spp.	7.7	7.3	10.9	8.5	8.6
5	Enterococci	10.1	6.8	2.9	4.6	6.1
6	<i>P. aeruginosa</i>	4.5	5.6	6.4	4.9	5.4
7	<i>Enterobacter</i> spp.	3.8	4.2	5.7	4.3	4.5
8	Other streptococci <sup>b</sup>	5.1	4.3	3.4	4.7	4.4
9	<i>S. pneumoniae</i>	4.6	2.9	4.0	4.6	4.0
10	<i>Acinetobacter</i> spp.	1.2	2.8	4.2	2.8	2.8
11	<i>Serratia</i> spp.	1.5	1.6	1.7	1.4	1.6
12	<i>P. mirabilis</i>	1.5	2.0	0.9	1.5	1.5
13	<i>Salmonella</i> spp.	0.4	1.0	1.9	2.3	1.4
<b>Total no. of cases</b>		<b>34,156</b>	<b>18,476</b>	<b>8,904</b>	<b>5,510</b>	<b>67,046</b>

- a. CoNS = coagulase-negative staphylococci.
- b. Includes viridans group and β-haemolytic streptococci (not *S. pneumoniae*).

**Table 2.** Antimicrobial activity of 20 agents tested against 601 isolates from documented *Salmonella* bacteremias in the SENTRY Antimicrobial Surveillance Program (1997-2001; ≥25 isolates/species only).

Antimicrobial agent	<i>Salmonella</i> spp. (n=326) <sup>a</sup>		<i>S. enterica</i> serotype Typhi (n=117)		<i>S. Enteritidis</i> (n=55)		<i>S. Typhimurium</i> (n=34)		All <i>Salmonella</i> (n=601)	
	MIC <sub>90</sub> µg/ml	% susc <sup>c</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>c</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>c</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>c</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>c</sup>
Ampicillin	1/16	82.5	0.5/2	94.0	2/16	72.2	>16/16	41.2	1/16	81.0
Piperacillin	4/128	82.8	2/2	94.0	2/128	74.1	64/128	41.2	2/128	81.5
Amoxicillin/clavulanate	1/16	89.9	1/2	96.8	2/16	88.9	8/16	61.8	1/16	89.7
Piperacillin/tazobactam	2/4	98.8	2/2	98.3	2/8	100.0	2/16	91.2	2/4	98.3
Ticarcillin/clavulanate	2/32	86.5	2/2	95.7	2/128	87.0	16/128	52.9	2/64	86.0
Cefuroxime	4/8	94.5	4/4	99.1	4/8	96.3	2/8	97.1	4/8	95.2
Cefoxitin	2/4	97.9	2/4	100.0	2/4	100.0	2/2	100.0	2/4	98.7
Ceftazidime	0.25/0.5	99.1(2.1) <sup>b</sup>	≤0.12/0.25	100.0(0.0) <sup>c</sup>	0.25/0.5	100.0(0.0) <sup>c</sup>	0.25/0.5	100.0(0.0) <sup>c</sup>	0.25/0.5	99.5(1.2) <sup>b</sup>
Ceftriaxone	≤0.25/≤0.25	99.1(1.8) <sup>b</sup>	≤0.25/≤0.25	100.0(0.0) <sup>c</sup>	≤0.25/≤0.25	100.0(0.0) <sup>c</sup>	≤0.25/≤0.25	100.0(0.0) <sup>c</sup>	≤0.25/≤0.25	99.5(1.0) <sup>b</sup>
Cefepime	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/≤0.12	99.7
Aztreonam	≤0.12/≤0.12	98.8(1.8) <sup>b</sup>	≤0.12/≤0.12	100.0(0.0) <sup>c</sup>	≤0.12/≤0.12	100.0(0.0) <sup>c</sup>	≤0.12/≤0.12	100.0(0.0) <sup>c</sup>	≤0.12/≤0.12	99.0(1.0) <sup>b</sup>
Imipenem	0.25/0.5	100.0	0.12/0.25	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0
Ciprofloxacin	≤0.015/0.12	99.1	≤0.015/≤0.015	100.0	≤0.015/0.03	100.0	≤0.015/0.03	100.0	≤0.015/0.12	99.3 <sup>b</sup>
Galixofloxacin	≤0.03/0.12	99.4	≤0.03/≤0.03	100.0	≤0.03/0.12	100.0	≤0.03/0.06	100.0	≤0.03/0.12	99.5
Levofloxacin	≤0.5/≤0.5	99.4	≤0.5/≤0.5	100.0	≤0.5/≤0.5	100.0	≤0.5/≤0.5	100.0	≤0.5/≤0.5	99.9
Amikacin	2/4	100.0	1/2	100.0	1/2	100.0	2/4	100.0	2/4	99.8
Gentamicin	≤1/≤1	96.3	≤1/≤1	100.0	≤1/≤1	100.0	≤1/≤1	100.0	≤1/≤1	96.8
Tobramycin	1/2	96.7	0.25/0.5	100.0	1/1	100.0	1/2	97.1	1/2	96.2
Tetracycline	≤4/≥8	77.6	≤4/≥4	94.0	≤4/≥4	90.7	≥8/≥8	35.3	≤4/≥8	79.4
Trimethoprim/sulfamethoxazole	≤0.5/≤0.5	93.3	≤0.5/≤0.5	94.9	≤0.5/≤0.5	100.0	≤0.5/2	82.4	≤0.5/≤0.5	92.7

- a. Includes unspecified *Salmonella* spp.
- b. Susceptible by NCCLS [2002] criteria for Enterobacteriaceae.
- c. ESBL phenotype rate (MIC, ≥2 µg/ml) [NCCLS, 2002].
- d. Twenty-six (4.3%) strains with a MIC at ≤0.25 µg/ml.

## RESULTS

**Table 3.** Antimicrobial activity of 20 agents tested against 601 isolates from documented *Salmonella* spp. bacteremias in four different regions of the SENTRY Program (1997-2001).

Antimicrobial agent	Region (no. tested):							
	Asia-Pacific (128)		Europe (180)		Latin America (166)		North America (127)	
	MIC <sub>90</sub> µg/ml	% susc <sup>a</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>a</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>a</sup>	MIC <sub>90</sub> µg/ml	% susc <sup>a</sup>
Ampicillin	0.5/16	89.8	2/16	66.1	1/4	92.8	2/16	78.0
Piperacillin	2/32	89.8	2/128	67.2	2/4	92.4	4/128	78.0
Amoxicillin/clavulanate	2/8	93.8	2/16	85.0	1/2	94.6	2/16	85.8
Piperacillin/tazobactam	2/4	98.4	2/8	97.8	2/4	98.8	2/4	98.4
Ticarcillin/clavulanate	2/16	90.6	2/128	79.4	2/4	93.4	2/128	81.1
Cefuroxime	4/8	96.1	4/8	95.0	4/8	97.0	4/8	92.1
Cefoxitin	2/4	99.2	2/4	99.4	2/4	98.8	2/8	96.9
Ceftazidime	≤0.25/≤0.25	99.2(2.3) <sup>b</sup>	0.25/0.5	100.0(0.0) <sup>c</sup>	0.25/2	100.0(0.0) <sup>c</sup>	0.25/0.5	98.4(2.4) <sup>b</sup>
Ceftriaxone	≤0.25/≤0.25	99.2(2.3) <sup>b</sup>	≤0.25/≤0.25	100.0(0.0) <sup>c</sup>	≤0.25/≤0.25	100.0(0.0) <sup>c</sup>	≤0.25/≤0.25	98.4(2.4) <sup>b</sup>
Cefepime	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/≤0.12	98.8	≤0.12/0.25	100.0
Aztreonam	≤0.12/0.25	99.2(2.3) <sup>b</sup>	≤0.12/≤0.12	100.0(0.0) <sup>c</sup>	≤0.12/≤0.12	100.0(0.0) <sup>c</sup>	≤0.12/0.25	97.6(2.4) <sup>b</sup>
Imipenem	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0
Ciprofloxacin	≤0.015/0.25	98.4	≤0.015/0.12	99.4	≤0.015/0.12	100.0	≤0.015/0.06	99.2
Galixofloxacin	≤0.03/0.06	98.4	≤0.03/0.12	99.4	≤0.03/0.06	100.0	≤0.03/0.12	100.0
Levofloxacin	≤0.5/≤0.5	98.4	≤0.5/≤0.5	99.4	≤0.5/≤0.5	100.0	≤0.5/≤0.5	100.0
Amikacin	1/2	100.0	2/4	100.0	2/4	99.4	2/4	100.0
Gentamicin	≤1/≤1	96.9	≤1/≤1	97.8	≤1/≤1	95.8	≤1/≤1	96.9
Tobramycin	0.5/2	96.9	1/2	96.7	1/2	95.2	1/2	96.1
Tetracycline	≤4/≥8	83.6	≤4/≥8	71.7	≤4/≥8	86.7	≤4/≥8	76.4
Trimethoprim/sulfamethoxazole	≤0.5/≤0.5	93.0	≤0.5/≤0.5	91.7	≤0.5/≤0.5	92.8	≤0.5/≤0.5	93.7

- a. Susceptibility as defined by the NCCLS [2002].
- b. Percentage of ESBL phenotypes [NCCLS, 2002].

**Table 4.** Trends in the antimicrobial activity of six key drugs tested against *Salmonella* spp. isolates over a five year interval in four regions.

Region	Antimicrobial agent	% susceptible by year <sup>a</sup>				
		1997	1998	1999	2000	2001
Asia-Pacific	Ampicillin	NT <sup>b</sup>	96.4	80.0	92.9	NT
	Amoxicillin/clavulanate	NT	92.9	83.0	97.6	NT
	Ceftazidime (% ESBL) <sup>c</sup>	NT	98.2(1.8)	100.0(0.0)	100.0(0.0)	NT
	Ciprofloxacin (% ≥0.25) <sup>d</sup>	NT	100.0(0.0)	93.3(16.7)	100.0(0.0)	NT
	Tobramycin	NT	96.4	100.0	95.2	NT
	Tetracycline (no. tested)	(0)	(56)	(30)	(42)	NT
Europe	Ampicillin	75.0	62.0	50.0	60.0	70.4
	Amoxicillin/clavulanate	90.0	86.0	80.0	72.0	85.2
	Ceftazidime (% ESBL)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)
	Ciprofloxacin (% ≥0.25)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)
	Tobramycin	98.3	96.0	94.4	92.0	100.0
	Tetracycline (no. tested)	(60)	(50)	(18)	(25)	(27)
Latin America	Ampicillin	90.2	96.2	100.0	87.1	88.5
	Amoxicillin/clavulanate	92.2	96.2	100.0	93.5	89.5
	Ceftazidime (% ESBL)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)
	Ciprofloxacin (% ≥0.25)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)	100.0(0.0)
	Tobramycin	98.3	96.0	94.4	92.0	100.0
	Tetracycline (no. tested)	(51)	(26)	(39)	(31)	(19)
North America	Ampicillin	81.4	78.3	72.7	75.0	80.0
	Amoxicillin/clavulanate	88.4	95.7	81.8	79.2	80.0
	Ceftazidime (% ESBL)	100.0(0.0)	100.0(0.0)	100.0(0.0)	95.8(8.3)	93.3(7.7)
	Ciprofloxacin (% ≥0.25)	100.0(0.0)	100.0(0.0)	100.0(0.0)	95.8(12.5)	100.0(0.0)
	Tobramycin	97.7	87.0	100.0	95.8	100.0
	Tetracycline (no. tested)	(43)	(23)	(22)	(24)	(15)
All regions	Ampicillin	81.8	81.3	80.7	81.1	78.7
	Amoxicillin/clavulanate	90.3	92.9	89.0	87.7	85.2
	Ceftazidime (% ESBL)	100.0(0.0)	99.4(1.3)	100.0(1.8)	99.2(1.8)	98.4(1.8)
	Ciprofloxacin (% ≥0.25)	100.0(0.0)	100.0(0.0)	98.2(5.5)	98.4(3.3)	100.0(0.0)
	Tobramycin	96.5	94.9	98.2	95.4	98.4
	Tetracycline (no. tested)	(154)	(155)	(109)	(122)	