Salmonella spp. Bloodstream Infections Worldwide: 5-Year Report from the SENTRY Antimicrobial Surveillance Program

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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 13th 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 "unspeciated" strains predominated (54%). The rank order of potency for 6 key drugs tested by MIC_{00} values was ciprofloxacin (0.12) μ g/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 unspeciated 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 riboprinting (RiboPrinter[™]) and PFGE.

• Salmonella spp. ranked 13th (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 unspeciated 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).

		% of all occurrence by region:						
Rank	Organism	North America	Europe	Latin America	Asia-Pacific	All regions		
	0	05.0	40.5	01.0	04.4	04.5		
1	S. aureus	25.2	18.5	21.0	21.1	21.5		
2	E. coli	17.7	21.9	18.1	21.4	19.8		
3	CoNS ^a	11.9	15.9	13.2	10.9	13.0		
4	Klebsiella spp.	7.7	7.3	10.9	8.5	8.6		
5	Enterococci	10.1	6.8	2.9	4.6	6.1		
6	P. aeruginosa	4.5	5.6	6.4	4.9	5.4		
7	Enterobacter spp.	3.8	4.2	5.7	4.3	4.5		
8	Other streptococci ^b	5.1	4.3	3.4	4.7	4.4		
9	S. pneumoniae	4.6	2.9	4.0	4.6	4.0		
10	Acinetobacter spp.	1.2	2.8	4.2	2.8	2.8		
11	Serratia spp.	1.5	1.6	1.7	1.4	1.6		
12	P. mirabilis	1.5	2.0	0.9	1.5	1.5		
13	Salmonella spp.	0.4	1.0	1.9	2.3	1.4		
		04450	40.470	0.001	40	07.040		

18.476

8.904

5.510

67,046

Total no. of cases

a. CoNS = coagulase-negative staphylococci.

b. Includes viridans group and ß-haemolytic streptococci (not *S. pneumoniae*).

34.156

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).

	Salmonella sp	p. (n=326)ª	S. enterica serotype	e Typhi (n=117)	S. Enteritidis	s (n=55)	S. Typhimuriu	ım (n=34)	All Salmonella	a (n=601)
Antimicrobial agent	MIC _{50/90} μg/ml	% susc ^b	MIC _{50/90} μg/ml	% susc ^b	MIC _{50/90} μg/ml	% susc ^b	MIC _{50/90} μg/ml	% susc ^b	MIC _{50/90} µg/ml	% susc ^b
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	96.6	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	98.1	2/2	100.0	2/4	98.7
Ceftazidime	0.25/0.5	99.1(2.1) ^c	≤0.12/0.25	100.0(0.0) ^c	0.25/0.5	100.0(0.0) ^c	0.25/0.5	100.0(0.0) ^c	0.25/0.5	99.5(1.2) ^c
Ceftriaxone	≤0.25/≤0.25	99.1(1.8) ^c	≤0.25/≤0.25	100.0(0.0) ^c	≤0.25/≤0.25	100.0(0.0) ^c	≤0.25/≤0.25	100.0(0.0) ^c	≤0.25/≤0.25	99.5(1.0) ^c
Cefepime	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/0.5	100.0	≤0.12/≤0.12	99.7
Aztreonam	≤0.12/≤0.12	98.8(1.8)°	≤0.12/≤0.12	100.0(0.0) ^c	≤0.12/≤0.12	100.0(0.0) ^c	≤0.12/≤0.12	100.0(0.0) ^c	≤0.12/≤0.12	99.0(1.0) ^c
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 ^d
Gatifloxacin	≤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	99.5
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	95.7	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 unspeciated Salmonella spp.

- b. Susceptible by NCCLS [2002] criteria for Enterobacteriaceae.
- c. ESBL phenotype rate (MIC, $\geq 2 \mu g/ml$) [NCCLS, 2002].
- d. Twenty-six (4.3%) strains with an MIC at $\ge 0.25 \ \mu$ g/ml.

Antimicrobial agent Ampicillin Piperacillin Amoxicillin/clavulanate Piperacillin/tazobactam Ticarcillin/clavulanate Cefuroxime Cefoxitin Ceftazidime Ceftriaxone Cefepime Aztreonam Imipenem Ciprofloxacin Gatifloxacin Levofloxacin Amikacin Gentamicin Tobramycin Tetracycline Trimethoprim/sulfamethoxazole . Susceptibility as defined by the NCCLS [2002]. Percentage of ESBL phenotypes [NCCLS, 2002].b

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

Region	Antimicrobial agent	1997	1998	1999	2000	2001
sia-Pacific	Ampicillin	NT ^b	96.4	80.0	92.9	NT
	Amoxicillin/clavulanate	NT	92.9	83.0	97.6	NT
	Ceftazidime (% ESBL) ^c	NT	98.2(1.8)	100.0(6.7)	100.0(0.0)	NT
	Ciprofloxacin (% ≥0.25) ^d	NT	100.0(0.0)	93.3(16.7)	100.0(0.0)	NT
	Tobramycin	NT	96.4	100.0	95.2	NT
	Tetracycline	NT	89.3	73.3	83.3	NT
	(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	83.3	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(5.6)	96.0(4.0)	100.0(0.0)
	Tobramycin	98.3	96.0	94.4	92.0	100.0
	Tetracycline	75.0	72.0	61.1	68.0	74.1
	(no. tested)	(60)	(50)	(18)	(25)	(27)
atin America.	Ampicillin	90.2	96.2	100.0	87.1	89.5
	Amoxicillin/clavulanate	92.2	96.2	100.0	93.5	89.5
	Ceftazidime (% ESBL)	100.0(0.0)	100.0(3.8)	100.0(0.0)	100.0(0.0)	100.0(0.0)
	Ciprofloxacin (% ≥0.25)	100.0(0.0)	100.0(3.8)	100.0(0.0)	100.0(0.0)	100.0(0.0)
	Tobramycin	90.2	96.2	97.4	100.0	94.7
	Tetracycline	82.4	92.3	92.3	87.1	78.9
	(no. tested)	(51)	(26)	(39)	(31)	(19)
lorth 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(6.7)
	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	74.4	73.9	77.3	79.2	80.0
	(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(1.6)	98.4(1.6)
	Ciprofloxacin (% ≥0.25)	100.0(0.0)	100.0(0.6)	98.2(5.5)	98.4(3.3)	100.0(0.0)
	Tobramycin	95.5	94.8	98.2	95.9	98.4
	Tetracycline	77.3	81.9	78.9	80.3	77.0
	(no. tested)	(154)	(155)	(109)	(122)	(61)

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).

		(1.2.2)		Region (no. tested):					
Asia-Pacific (128)		(128)	Europe (180)		Latin America (166)		North Americ	ca (127)	
	MIC _{50/90} μg/ml	% susc ^a	MIC _{50/90} µg/ml	% susc ^a	MIC _{50/90} µg/ml	% susc ^a	MIC _{50/90} μg/ml	% susc ^a	
	0.5/>16	89.8	2/>16	66.1	1/4	92.8	2/>16	78.0	
	2/32	89.8	2/>128	67.2	2/4	93.4	4/>128	78.0	
	2/8	93.8	2/16	85.0	1/2	94.6	2/16	85.8	
	2/4	98.4	2/8	97.8	2/4	98.8	2/4	98.4	
	2/16	90.6	2/128	79.4	2/4	93.4	2/128	81.1	
	4/8	96.1	4/8	95.0	4/8	97.0	4/8	92.1	
	2/4	99.2	2/4	99.4	2/4	98.8	2/8	96.9	
	≤0.25/≤0.25	99.2(2.3) ^b	0.25/0.5	100.0(0.0) ^b	0.25/2	100.0(0.6) ^b	0.25/0.5	98.4(2.4) ^b	
	≤0.25/≤0.25	99.2(2.3) ^b	≤0.25/≤0.25	100.0(0.0) ^b	≤0.25/≤0.25	100.0(0.0) ^b	≤0.25/≤0.25	98.4(2.4) ^b	
	≤0.12/≤0.12	100.0	≤0.12/≤0.12	100.0	≤0.12/≤0.12	98.8	≤0.12/0.25	100.0	
	≤0.12/0.25	99.2(2.3) ^b	≤0.12/≤0.12	100.0(0.0) ^b	≤0.12/≤0.12	100.0(0.0) ^b	≤0.12/0.25	97.6(2.4) ^b	
	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	
	≤0.015/0.25	98.4	≤0.015/0.12	99.4	≤0.015/0.12	100.0	≤0.015/0.06	99.2	
	≤0.03/0.06	98.4	≤0.03/0.12	99.4	≤0.03/0.06	100.0	≤0.03/0.12	100.0	
	≤0.5/≤0.5	98.4	≤0.5/≤0.5	99.4	≤0.5/≤0.5	100.0	≤0.5/≤0.5	100.0	
	1/2	100.0	2/4	100.0	2/4	99.4	2/4	100.0	
	≤1/≤1	96.9	≤1/≤1	97.8	≤1/≤1	95.8	≤1/≤1	96.9	
	0.5/2	96.9	1/2	96.7	1/2	95.2	1/2	96.1	
	≤4/>8	83.6	≤4/>8	71.7	≤4/>8	86.7	≤4/>8	76.4	
	≤0.5/≤0.5	93.0	≤0.5/≤0.5	91.7	≤0.5/≤0.5	92.8	≤0.5/≤0.5	93.7	

- $(16 \ \mu g/ml; 89.7\%) > ampicillin (>16 \ \mu g/ml; 81.0\%) > tetracycline (>8 \ \mu g/ml; 79.4\%).$
- type ACSSuT (Table 2).
- lowest in Europe (71.7%).
- resistance (MIC, >1 μ g/ml) was very rare, but noted in all regions except Latin America.
- (Table 4).
- Pacific (Philippines 3; Taiwan 2), 3 from Europe (Spain 2; Greece 1), 3 strains from the USA.
- using the NCCLS criteria of $\leq 1 \mu g/ml$ for susceptible.

Table 5. Distri -resis		•	RY Antimic	robial Su
				Cij
Nalidixic acid MIC (no. tested)	≤0.016	0.03	0.06	0.12
≤8 μg/ml (236)	162	70	4	0
≥16 µg/ml (50)	0	1	1	21
All strains (286)	162	71	5	21
a. Susceptibility at ≤1	μg/ml [NCCLS,	2002].		

- global resistance development among Salmonella spp. BSI cases.

- potential therapy failures.
- *Typhimurium DT 104* phenotypes mainly in Europe.



• The rank order of susceptibility for 6 selected agents was: ceftriaxone (MIC₉₀, $\leq 0.25 \,\mu$ g/ml; 99.5% susceptible) > ciprofloxacin (0.12 μ g/ml; 99.3%) > trimethoprim/sulfamethoxazole ($\leq 0.5 \mu$ g/ml; 92.7%) > amoxicillin/clavulanate

• Most Salmonella spp. isolates remained highly susceptible to all agents tested, with the exception of S. Typhimurium which were markedly more resistant, especially to ampicillin (41.2%) and tetracycline (35.3%) indicating the R-

• Enzyme-mediated resistance to the penicillins was greatest in Europe where ampicillin susceptibility was only 66.1% compared to 89.8-92.8% in the Asia-Pacific and Latin America. Similarly, susceptibility to tetracycline was

• ESBL phenotype strains were detected in the Asia-Pacific (2.3%) and North American (2.4%) regions. Ciprofloxacin

• Decreased susceptibility to ciprofloxacin among Salmonella spp. strains (MIC, $\geq 0.25 \,\mu$ g/ml) indicates evolving QRDR mutations that were observed in 3.8 % of Salmonella spp. strains from Latin America in 1998. The sporadic occurrences of these first step mutants were noted in all regions usually followed by their disappearance

• Among the S. Typhimurium cases, 25 occurred in Europe, 8 in Latin America and only one in Canada. A total of 11 Salmonella spp. strains (3.4%) had a R-type ACSSuT distributed geographically as follows: 5 from the Asia-

• Among the 236 strains (Table 5) with nalidixic acid MIC at $\leq 8 \mu g/ml$ (susceptible), all strains had ciprofloxacin results at $\leq 0.06 \,\mu$ g/ml (MIC₉₀; 0.03 μ g/ml). In contrast, strains with nalidixic acid MICs at $\geq 16 \,\mu$ g/ml had ciprofloxacin MICs ranging from 0.03 to >2 μ g/ml. Using nalidixic acid to detect Salmonella spp. isolates at-risk for therapy failures had a sensitivity of 100.0% (low specificity). The ciprofloxacin susceptibility rate was 99.0%

> 286 Salmonella BSI strains indexed into nalidixic acid-susceptible and rveillance Program, 1997-2001). iprofloxacin MIC (µg/ml) % susceptible^a 0.25 0.5 1 2 >2
> 0
> 0
> 0
> 0
> 100.0
>
>
> 17
> 4
> 3
> 1
> 2
> 94.0
>
>
> 17
> 4
> 3
> 1
> 2
> 99.0

CONCLUSIONS

• Showing a worldwide ranking of 13th among all BSI pathogens (1.4%), Salmonella spp. continue to account for a stable number of BSI episodes, but are clearly more prevalent in some developing nations.

• The five-year data show little change in susceptibility patterns among drugs and no clear trend toward greater

• MDR DT 104 strains contributed to additional resistances problems. In this study, the R-type ACSSuT was seen in 72% of the European isolates of *S. Typhimurium*, compared to 25% in Latin America and none in Canada.

• There have been reports of therapeutic failures with ciprofloxacin against strains with MICs between 0.12 and 1 μg/ml. These elevated MICs were caused by point mutations in the QRDR of the gyr A gene (data not shown).

• To detect gyr A mutations by phenotypic tests, nalidixic acid has been proposed as a screening test where resistant strains (MIC, \geq 16 µg/ml) indicate Salmonella spp. isolates with elevated ciprofloxacin MICs (\geq 0.12 µg/ml),

Invasive Salmonella infections remain a threat among at-risk patient populations in some areas of the world, and it is important to continue to monitor resistance. This initial report from the SENTRY Program indicates no remarkable increases in antimicrobial resistances in Salmonella BSI cases, except for the MDR S.