JOURNAL OF CLINICAL MICROBIOLOGY, Aug. 2003, p. 3574–3578 Vol. 41, No. 8
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.8.3574–3578.2003

Antimicrobial Susceptibilities of *Salmonella* Strains Isolated from Humans, Cattle, Pigs, and Chickens in The Netherlands from 1984 to 2001

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Received 18 March 2003/Returned for modification 16 May 2003/Accepted 27 May 2003

We monitored antimicrobial susceptibility data for *Salmonella* strains isolated from humans, cattle, pigs, and chickens in The Netherlands from 1984 to 2001 in order to provide insight into the dynamics of resistance over time. The strains were tested for their susceptibilities to seven antimicrobial agents by the agar diffusion method. Resistance was most common in *Salmonella enterica* subsp. *enterica* serovar Typhimurium. Among the strains from humans, pigs, and chickens, it was found that the level of resistance of serovar Typhimurium strains to tetracycline, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole increased from 1984 to 2001. This increase could be attributed to the emergence of multidrug-resistant serovar Typhimurium DT 104. Among the strains from cattle, it was found that the level of resistance of serovar Typhimurium strains, which was already very high in the 1980s, declined during the study period to the same levels as those for the strains from the other species from 1996 to 2001. Serovar Enteritidis isolates remained susceptible during the entire survey period. Among serovar Paratyphi B variation Java strains isolated from chickens, resistance to furazolidone, flumequine, trimethoprim-sulfamethoxazole, and ampicillin emerged, although furazolidone was not used after 1990. Together, the data indicate that the levels and patterns of resistance differed considerably between *Salmonella* serovars isolated from one host species.

Nontyphoid salmonellosis is a major zoonotic disease. In The Netherlands, with a population of 15.8 million, it has been estimated that approximately 50,000 cases of salmonellosis occurred in 1999 (19). The emergence of resistance to antimicrobial drugs within the salmonellae is a problem for humans and animals worldwide. The extensive use of antimicrobials in human and veterinary medicine has led to an increase in multidrug-resistant strains. *Salmonella* strains may acquire resistance in food animals before transmission to humans through the food chain (15). Therefore, surveillance for antimicrobial resistance in humans and food animals is important in order to detect changes in susceptibility, to implement control measures on the use of antimicrobial drugs, and to prevent the further spread of multidrug-resistant strains. We reviewed susceptibility data for *Salmonella* strains isolated from humans, cattle, pigs, and chickens in The Netherlands for routine surveillance from 1984 to 2001. We analyzed whether the levels of resistance to antimicrobials increased with time and whether changes in susceptibility coincided for the *Salmonella* strains isolated from the different sources.

MATERIALS AND METHODS

Bacterial isolates. (i) Human isolates. A total of 45,198 *Salmonella* isolates tested for antimicrobial resistance were included in this study. The isolates were sent to the Dutch National Institute of Public Health (RIVM) by the Dutch regional public health laboratories. All strains were the first isolates recovered from patients with salmonellosis (clinical isolates). Approximately 1.6% of these isolates originated from blood.

(ii) Animal isolates. The majority of the animal isolates were sent to RIVM by the regional Dutch Animal Health Services. They were from pigs (n = 5,822), cattle, including calves (n = 5,892), and chickens (n = 32,326) with clinical (approximately 85%) and nonclinical (approximately 15%) *Salmonella* infections; and samples were obtained both on the farm and at slaughterhouses.

Serotyping and phage typing. Isolates were submitted to the Diagnostic Laboratory for Infectious Diseases and Perinatal Screening of RIVM for further serotyping based on O- and H-group antigens, according to the latest versions of the Kauffmann-White scheme, by slide and microtiter plate agglutination. *Salmonella enterica* subsp. *enterica* serovar Typhimurium strains were phage typed by using the Dutch phage typing system (6). The Dutch phage typing system for serovar Typhimurium was gauged against the English system in 1997, and it was shown that no one-to-one relationship exists between the English and the Dutch types. Of the phage types mentioned in this paper, Dutch phage type 61 (pt 61) corresponds mainly to English type DT 12; pt 150 corresponds to atypical reacting strains (ARS), DT 161, and DT 12 (and, to a lesser extent, DT 66, DT 99, and DT 32); pt 200 corresponds to DT 208 and ARS; and pt 510 corresponds to DT 208 and ARS (to a lesser extent DT 193 and DT 195). Recently, it was shown that pt 204 corresponds to DT 204b and pt 193 corresponds to DT 193.

Antimicrobial susceptibilities. The antimicrobial susceptibilities of the isolates were determined by the agar diffusion method with Iso-Sensitest agar (CM471; Oxoid) and Neo-sensitab disks (Rosco, Taastrup, Denmark). The antimicrobials tested were ampicillin, chloramphenicol, furazolidone, tetracycline, kanamycin (which was replaced by neomycin in 1997), trimethoprim (which was replaced by trimethoprim-sulfamethoxazole in 1997), and flumequine (which ahs been tested since 1992). The categories susceptible or resistant were assigned on the basis of the breakpoints recommended by the Dutch Committee on Guidelines for Susceptibility Testing (3).

RESULTS

Serovar Typhimurium. Resistance was most common in serovar Typhimurium strains. The rates of resistance to tetracycline, chloramphenicol, ampicillin, and trimethoprim-sulfame-

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TABLE 1. Percentages of resistant, fully susceptible, and multidrug-resistant *Salmonella* serovar Typhimurium strains from humans, pigs, cattle, and chickens in The Netherlands from 1984 to 2001

Resistance phenotype	% of isolates											
	Humans			Pigs			Cattle			Chickens		
	1984–1989 (17,163)[a]	1990–1995 (3,208)	1996–2001 (1,668)	1984–1989 (2,196)	1990–1995 (1,042)	1996–2001 (809)	1984–1989 (1,705)	1990–1995 (808)	1996–2001 (235)	1984–1989 (5,147)	1990–1995 (1,613)	1996–2001 (119)
Tetracycline	35.3	45.0	61.2	47.0	58.6	60.3	80.0	75.6	63.0	3.5	5.0	28.6
Chloramphenicol	2.1	8.4	35.1	2.8	10.9	24.6	63.5	56.4	40.0	1.0	1.9	22.7
Kanamycin (neomycin)	1.2	2.4	1.0	1.4	2.4	0.1	46.0	39.5	0.9	0.8	1.4	0.0
Ampicillin	3.0	14.3	41.4	3.3	14.4	30.0	60.6	59.5	48.1	1.8	4.9	36.1
Trimethoprim (trimethoprim-sulfamethoxazole)	1.9	8.2	14.6	1.4	9.8	20.4	60.5	50.1	16.6	1.3	9.4	4.2
Furazolidone	2.0	2.3	2.0	1.0	2.5	2.5	9.9	13.5	3.8	0.9	1.7	1.7
Flumequine			0.9			0.0			1.3			1.7
Susceptible	61.6	50.4	35.9	52.0	38.1	34.2	19.4	21.5	32.4	94.5	83.1	57.5
Multiresistant[b]	3.2	16.9	45.0	3.9	20.2	41.7	65.4	62.1	51.9	1.8	3.6	25.2

[a] The values in parentheses are the total number of isolates tested.
[b] Resistant to more than one antibiotic.

thoxazole increased dramatically (Table 1) among the serovar Typhimurium strains isolated from humans, pigs, and chickens from 1984 to 2001. Among the isolates from cattle, the levels of resistance to these antimicrobials was also high but declined in comparison to the levels in 1984, which were already very high. In addition, the proportion of bovine strains susceptible to all antimicrobials increased from 19.4 to 32.4%. The percentages of resistant strains from cattle, humans, pigs, and chickens were similar from 1996 to 2001.

Among the isolates from cattle, multidrug-resistant serovar Typhimurium strains were already common from 1984 to 1989; serovar Typhimurium pt 200, pt 204, and pt 193 strains, all of which were resistant to ampicillin, chloramphenicol, kanamycin, tetracycline, and trimethoprim, predominated until 1995; and pt 401 and 506 (both classified as DT 104 in the English phage typing system) predominated beginning in 1996. *Salmonella* serovar Typhimurium pt 510, which was resistant only to tetracycline, was isolated frequently throughout the whole period. Most of the DT 104 isolates were resistant to ampicillin, chloramphenicol, and tetracycline (their susceptibilities to streptomycin and sulfonamides were not tested) (Table 2). Resistance to the aminoglycosides kanamycin (tested before 1997) and neomycin (tested after 1997) was found only sporadically among serovar Typhimurium DT 104 isolates. Resistance to trimethoprim-sulfamethoxazole, however, has been emerging in DT 104. From 1996 to 2001 the proportion of trimethoprim-sulfamethoxazole-resistant strains ranged from 2.7% among strains isolated from chickens to 11.9% among strains isolated from cattle. Resistance to flumequine was detected in only 1 and 1.8% of DT 104 strains from humans and cattle, respectively. Among the strains from chickens and humans, serovar Typhimurium pt 150 was one of the most frequently isolated phage types until 1992. Strains of this phage type were generally susceptible to all drugs tested. Among the strains from pigs and humans, serovar Typhimurium pt 61 was a common phage type from 1984 to 1989, and 20 to 40% of these strains were resistant to tetracycline, but they were generally susceptible to the other antimicrobials tested.

Other serovars. Serovar Enteritidis strains remained predominantly susceptible to the antimicrobials tested (Table 3). Among the strains from humans and chickens, the proportion of strains resistant to more than one antimicrobial drug ranged from 0.9 to 2.2%. However, among serovar Enteritidis isolated from humans and chickens, the rate of resistance to furazolidone increased from 0.9 and 0.7%, respectively, in the period from 1984 to 1989 to 7.3 and 7.9%, respectively, in the period

TABLE 2. Percentages of resistant, fully susceptible, and multidrug-resistant *Salmonella* serovar Typhimurium DT 104 strains from humans, pigs, cattle, and chickens in The Netherlands from 1990 to 2001

Resistance phenotype	% of isolates							
	Humans		Pigs		Cattle		Chickens	
	1990–1995 (184)[a]	1996–2001 (576)	1990–1995 (80)	1996–2001 (209)	1990–1995 (58)	1996–2001 (109)	1990–1995 (22)	1996–2001 (37)
Tetracycline	96.2	93.4	92.5	96.7	96.6	86.2	72.7	67.6
Chloramphenicol	76.6	80.2	78.8	77.5	86.2	74.3	72.7	67.6
Kanamycin (neomycin)	2.7	0.3	1.3	0	1.7	0.9	0	0
Ampicillin	87.5	87.7	86.3	89	93.1	89.9		99.9
Trimethoprim (trimethoprim-sulfamethoxazole)	2.7	8.7	6.3	7.2	0	11.9	4.5	2.7
Furazolidone	0.5	1.4	1.3	1.4	0	1.8	0	0
Flumequine		1.0		0		1.8		0
Susceptible	1.6	4.3	6.3	2.9	1.7	9.2	27.3	16.2
Multiresistant[b]	89.7	87	88.8	88.5	93.1	85.3	72.7	67.6

[a] The values in parentheses are the total number of isolates tested.
[b] Resistant to more than one antibiotic.

TABLE 3. Percentages of resistant, fully susceptible, and multidrug-resistant *Salmonella* serovar Enteritidis strains isolated from humans and chickens in The Netherlands from 1984 to 2001

Resistance phenotype	% of isolates					
	Humans			Chickens		
	1984–1989 (1,961)[a]	1990–1995 (3,192)	1996–2001 (2,058)	1984–1989 (1,071)	1990–1995 (1,466)	1996–2001 (430)
Tetracycline	1.7	1.4	2.5	2.1	1.6	1.6
Chloramphenicol	0.4	0.4	0.4	0.3	0.2	0.2
Kanamycin (neomycin)	0.7	0.1	0	0.4	0.3	0
Ampicillin	4.2	2.2	3.6	3.6	2.7	2.8
Trimethoprim (trimethoprim-sulfamethoxazole)	0.7	1.0	0.3	1.2	0.7	0.2
Furazolidone	0.9	4.5	7.3	0.7	1.2	7.9
Flumequine			2.0			0.9
Susceptible	93.5	91.6	86.7	94.3	94.5	87.5
Multiresistant[b]	1.1	0.9	2.2	2.0	1.1	1.4

[a] The values in parentheses are the total number of isolates tested.
[b] Resistant to more than one antibiotic.

from 1996 to 2001. Among the serovar Paratyphi B variation Java strains isolated from chickens, the rate of resistance to furazolidone increased from 16.1% in the period from 1984 to 1989 to 98.2% in the period from 1996 to 2001 and the rate of resistance to ampicillin increased from 3.2 to 46.4%. The rate of resistance to flumequine among strains of this serovar in the period from 1996 to 2001 was 18.8%, and the rate of resistance to trimethoprim-sulfamethoxazole was 69.0%. Serovar Dublin isolates from cattle were often resistant to tetracycline (66.7%) and chloramphenicol (84.0%) in the period from 1984 to 1989, but the rates of resistance to these antimicrobials decreased over time. For the period from 1996 to 2001, only 2.9 and 24.7% of serovar Dublin isolates were resistant to tetracycline and chloramphenicol, respectively (Table 4). Serovar Dublin isolates remained susceptible to ampicillin, furazolidone, flumequine, and trimethoprim.

DISCUSSION

A major finding from our study was the different trends in resistance between *Salmonella* isolates from humans, pigs, and chickens on the one hand and isolates from cattle on the other. In the 1980s the incidence of resistance was considerably higher among bovine serovar Typhimurium isolates than among isolates of this serovar from the other species. This was due to the predominance in cattle of multidrug-resistant serovar Typhimurium pt 200, pt 204, and pt 193 resistant to ampicillin, chloramphenicol, kanamycin, tetracycline, and trimethoprim in the 1980s and early 1990s; the serovar Typhimurium phage types isolated from humans, pigs, and chickens during this period were generally susceptible to most antimicrobials. The increasing rates of resistance to ampicillin, tetracycline, and chloramphenicol since 1996 among isolates from humans, pigs, and chickens can be attributed to the emergence of multiresistant serovar Typhimurium pt 506 and pt 401 strains (DT 104 in the English phage typing system), which are resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline and to ampicillin, streptomycin, sulfamethoxazole, and tetracycline, respectively. *Salmonella* serovar Typhimurium DT 104 was the most important emerging phage type in humans, pigs, chickens, and cattle in The Netherlands: in 2001, this phage type was responsible for 15, 16, 10, and 3% of all *Salmonella* infections in humans, pigs, cattle, and chickens, respectively, and 43, 25, 31, and 57% of all serovar Typhimurium infections, respectively (16, 17). The rate of resistance to flumequine was low (<2%) among serovar Typhimurium (including DT 104) strains. In other countries, the rates of resistance to fluoroquinolones among DT 104 strains are increasing (2, 14). Time will tell if serovar Typhimurium DT 104 will maintain its current prevalence in The Netherlands and whether it will acquire additional determinants of resistance, particularly to the fluoroquinolones. The replacement of multidrug-resistant serovar Typhimurium pt 200, pt 204, and pt 193 strains resistant to ampicillin, chloramphenicol, kanamycin, tetracycline, and trimethoprim by DT 104 strains resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline in cattle explains why the rate of resistance to kanamycin (neomycin) declined from 46% in the period from 1984 to 1989 to 0.9% in the period from 1996 to 2001. The proportion of bovine *Salmonella* strains susceptible to all drugs tested increased from 19.4 to 32.4% during the study period, and thus, the rates of resistance to most antimicrobial drugs decreased. In conclusion, the levels of resistance of serovar Typhimurium strains from humans, cattle, pigs, and chickens were greatly influenced by the emergence and subse-

TABLE 4. Percentages of resistant, fully susceptible, and multidrug-resistant *Salmonella* serovar Dublin strains from cattle in The Netherlands from 1984 to 2001

Resistance phenotype	% of isolates		
	1984–1989 (1,278)[a]	1990–1995 (1,144)	1996–2001 (278)
Tetracycline	66.7	9.2	2.9
Chloramphenicol	84.0	46.8	24.7
Kanamycin (neomycin)	10.7	9.1	1.4
Ampicillin	3.4	1.3	0.7
Trimethoprim (trimethoprim-sulfamethoxazole)	5.3	3.0	0.0
Furazolidone	3.9	3.0	4.3
Flumequine			0.7
Susceptible	14.0	49.8	74.8
Multiresistant[b]	67.7	14.4	3.6

[a] The values in parentheses are the total number of isolates tested.
[b] Resistant to more than one antibiotic.

quent decline in the prevalence of a few multidrug-resistant serovar Typhimurium phage types. Our finding that antibiotic resistance primarily concerned serovar Typhimurium is in agreement with previous observations (1, 4, 10).

Another notable finding was the emergence of multidrug-resistant *Salmonella* serovar Paratyphi B variation Java strains in chickens. From 1996, 73.2% of these isolates were resistant to more than one antimicrobial drug, with resistance to ampicillin, trimethoprim-sulfamethoxazole, furazolidone, and flumequine predominating (20). This serovar emerged in The Netherlands in 1996, and its prevalence has since increased, being the predominant serotype found in chickens and chicken products in 2001 (30 and 43% of all *Salmonella* isolates, respectively), replacing *Salmonella* serovar Enteritidis (16, 18). The increasing frequency of isolation of *Salmonella* serovar Paratyphi B variation Java from chickens has also been reported from Germany (5) but not from other European countries. The high level of resistance of strains of this serovar to trimethoprim, ampicillin, and fluoroquinolones was also reported by Miko et al. (11).

Another striking feature apparent from our study were the marked differences in the rates of antimicrobial resistance between *Salmonella* serovars isolated from the same animal species, e.g., serovar Typhimurium and serovar Dublin isolates from cattle. This difference in rates of resistance between bovine serovar Dublin and Typhimurium strains was also found by Jones et al. (7) in England and Wales. However, marked differences in rates of resistance were also found between serovar Enteritidis and Paratyphi B variation Java strains isolated from chickens and serovar Typhimurium and Enteritidis strains isolated from humans in the present study. It is uncertain to what extent the veterinary use of antimicrobials has contributed to the emergence of multidrug-resistant *Salmonella* spp. In The Netherlands, tetracyclines, trimethoprim, sulfonamides, and penicillins are the drugs most often used in animal production (C. H. P. Pellicaan, personal communication); and resistance to these antimicrobials is common. The veterinary use of antimicrobial agents may select resistant organisms and facilitate their spread. Resistance may be mediated by chromosomally located resistance determinants or through the acquisition of resistance genes by horizontal transfer through plasmids and transposons. Many of the resistance genes present on plasmids and transposons of gram-negative bacteria are integrated in integrons. Class 1 integrons are widespread among *Salmonella* species, especially in serovars Typhimurium and Enteritidis (9, 10; A. C. Fluit, A. T. A. Box, E. van Duijkeren, D. J. Mevius, M. A. Leverstein-van Hall, and J. Verhoef, Proc. 13th Congr. Clin. Microbiol. Infect. Dis., abstr. O67, 2003). Leverstein-van Hall et al. (8) found a significant relation between multidrug resistance in members of the family *Enterobacteriaceae* and the presence of integrons; integron-carrying strains of the family *Enterobacteriaceae* resistant to sulfamethoxazole (trimethoprim-sulfamethoxazole), ampicillin, and/or piperacillin were more likely to acquire additional resistance genes than strains with the same resistance pattern but without an integron (8). This suggests that integron-carrying elements facilitate the insertion of additional resistance genes. However, this does not explain the considerable differences in resistance patterns that we found between different serovars isolated from the same source. These serovars are likely to be exposed to the same antimicrobial pressure, and resistance genes could easily be transferred between these serovars. Perhaps additional characteristics are present in the multidrug-resistant strains and selection pressures other than those exerted by antimicrobial use select for the successful types. Mirold et al. (12) found that the *sopE*, a gene encoding a protein involved in bacterial invasion of intestinal epithelial cells, was mainly present in certain epidemic, multidrug-resistant cattle-associated serovar Typhimurium phage types. Their data suggest that the horizontal transfer of *sopE* by lysogenic infection with a bacteriophage takes place between different *Salmonella* serovar Typhimurium strains. Another argument against the use of antimicrobials as the only explanation for the increasing rates of resistance is that the rates of resistance to certain drugs has increased without selective pressure: furazolidone resistance emerged in serovar Enteriditis and serovar Paratyphi B variation Java strains isolated from humans and chickens beginning in 1996, while furazolidone has not been used in veterinary medicine since 1990. Resistance to furazolidone is almost exclusively chromosomally mediated and involves either the absence of intracellular reductase enzymes or the development of a permeability barrier. The latter is sometimes associated with the presence of R factors specifying resistance to unrelated antibiotics (13). The use of other antibiotics may therefore have contributed to the emergence of furozolidone resistance. Molecular characterization of *Salmonella* serovar Paratyphi B variation Java strains from Germany has shown that a new multidrug-resistant clonal line emerged in 1995 and has spread successfully (11). Most of these strains do not carry integrons. Van Pelt et al. (20) suggested that the clonality of the *Salmonella* serovar Paratyphi variation Java strains is the determining factor for the high level of resistance to furazolidone.

In conclusion, our results indicate that the relative contribution of certain *Salmonella* serotypes and phage types greatly influences the overall rates of resistance to antimicrobial drugs within a host species. The rates of resistance among serovar Typhimurium strains isolated from cattle declined, whereas the rates of resistance among strains isolated from humans, pigs, and chickens increased over time. This increase can be attributed to the emergence of multidrug-resistant type DT 104. Large differences in the percentages of resistant strains of different serovars isolated from the same species were found. Resistance to antimicrobials which are not used in animal production was also found. Thus, antibiotic resistance data for *Salmonella* in a host species should mainly be interpreted in view of the emergence and decline of certain serotypes and phage types.

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