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Antimicrobial resistance in non-typhoidal salmonellas from humans in Northern Ireland, 2001–2003: standardization needed for better epidemiological monitoring

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SUMMARY

This study investigated the identification and antimicrobial susceptibility testing of *Salmonella* isolates in Northern Ireland during 2001–2003. All six participating hospital laboratories used similar methods. Identification and antimicrobial resistance of human enteric ($n=897$) *Salmonella* isolates were analysed by retrospective collation of laboratory records. Resistance of human *Salmonella* isolates to nalidixic acid was 16% but resistance to ciprofloxacin or cefotaxime was rare (<1%). Minor inter-laboratory variations in sensitivity testing practices make it difficult to compare antimicrobial sensitivity results reliably and also to monitor for epidemic clones such as *S.* Typhimurium DT104 with the ACSSuT resistance pattern. The outcome of this study was the adoption of a standardized regional approach to the isolation of salmonella antimicrobial resistance. This should improve epidemiological monitoring of epidemic clones and assure optimum treatment options are available. In cases of treatment failure, MICs to third-generation cephalosporins and ciprofloxacin should be determined.

INTRODUCTION

Salmonellosis is a major bacterial zoonosis and animal sources of *Salmonella* may be asymptomatic depending on the animal species and *Salmonella enterica* serovar. Consumption of contaminated food, person-to-person spread, and contact with infected animals are the most common routes of human infection. Certain serovars cause defined syndromes in animal species and require antimicrobial treatment to avert death. Complicated *Salmonella* infections may require antimicrobial treatment and the acquisition of resistance to these drugs may result in treatment failure [1].

There has been a continuous decline in the number of salmonella cases in the United Kingdom since the late 1990s and UK salmonella trends have been presented [2]. Improved animal management practices have perhaps eradicated *Salmonella* Enteritidis PT4 in chickens and eggs, but eggs imported into England and Wales have caused outbreaks due to other phage types [3]. Reports of *S.* Typhimurium, including multiresistant *S.* Typhimurium DT104 [4], have also declined nationally, and in Northern Ireland (NI) fell from 66 in 1999 to 10 in 2003 [5]. Human salmonella reports fell by over two-thirds, mainly due to a sharp

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decrease in *S*. Enteritidis (462 in 1999, 94 in 2003) [5]. The decline was part of an international trend [6, 7]. Two differences from mainland United Kingdom are of note. *Salmonella* vaccination of broiler-breeder flocks in Northern Ireland began in 1997, later than in England and Wales. Human salmonellosis (including *S*. Enterititis PT4) continued to rise until 2000, mirroring the delay between poultry vaccination and reduced human infection that was found in England and Wales. Unlike England and Wales, no eggs were imported into Northern Ireland from continental Europe, which limited this source of infection.

Laboratories in Northern Ireland had not agreed upon standardized methods as suggested in 'Getting Ahead of the Curve' [8]. The aim of the study was to document the identification and antimicrobial resistance (AMR) testing, and trends in salmonella AMR as recommended by The Department of Health, Social Services and Public Safety (DHSSPS) in their 'Antimicrobial Resistance Action Plan 2002–5' [9].

METHODS

Non-typhoidal *Salmonella* isolates were obtained from faecal specimens taken from patients with gastroenteritis presenting to General Practitioners in the community and patients admitted to hospitals. The six main hospital laboratories in Northern Ireland were involved and included large teaching hospitals and area and district general hospitals. Two laboratories used National Committee for Clinical Laboratory Standards (NCCLS, now Clinical and Laboratory Standards Institute) methods [10], two used British Society for Antimicrobial Chemotherapy (BSAC) methods [11] and two used modified Stokes methods. Minimum inhibitory concentrations (MIC) by broth dilution or E-test were not carried out routinely on enteric isolates unless there was failure to respond to treatment. The equivalent MIC breakpoints as defined for NCCLS are; ampicillin (8 μg/ml), amoxicillin-clavulanic acid (8/4 μg/ml), gentamicin (4 μg/ml), kanamycin (16 μg/ml), streptomycin (none), tetracycline (4 μg/ml), ciprofloxacin (1 μg/ml), nalidixic acid (8 μg/ml), sulphonamides (100 μg/ml), trimethoprim (4 μg/ml), chloramphenicol (8 μg/ml). Only isolates that were fully resistant were recorded as resistant. Appropriate serovars were sent to the Health Protection Agency Laboratory of Enteric Pathogens for phage typing. All laboratories tested for a minimum of five antimicrobials and all included ampicillin, ciprofloxacin and trimethoprim. Epidemiological surveillance is organized through the Health Protection Agency Communicable Disease Surveillance Centre (Northern Ireland).

Table 1. *Clinical* Salmonella *isolates from hospital laboratories 2001–2003* ($n=897$)

Salmonella serovar	2001 *n* (%)	2002 *n* (%)	2003 *n* (%)
S. Enteritidis	209 (53·3)	102 (39·1)	107 (43·9)
S. Enteritidis PT4	107 (25·6)	33 (7·9)	24 (5·7)
S. Typhimurium	82 (20·9)	84 (32·2)	57 (23·4)
S. Typhimurium DT104	44 (19·7)	42 (18·8)	23 (10·3)
Other *Salmonella* serovars	101 (25·8)	75 (28·7)	80 (32·8)
Annual total	392	261	244

S. Typhimurium DT104 refers to both DT104 and DT104b.

RESULTS

The number of *Salmonella* isolates from humans fell over the 3-year period and there were no substantial outbreaks. Table 1 shows the breakdown of 897 *Salmonella* isolates by *S*. Enteritidis, *S*. Typhimurium and other *Salmonella* isolates by year. This falling trend was also seen in *S*. Enteritidis PT4 and *S*. Typhimurium DT104. Table 2 shows the prevalence of resistance to 13 antimicrobials by *Salmonella* serovar, the percentage that are resistant to multiple antibiotics, and the total prevalence of resistance to individual antimicrobials. The denominator for each antimicrobial shows the number of isolates tested against that antimicrobial and cannot show the permutations of tests used in different hospitals. One isolate was resistant to ciprofloxacin and another resistant to cefotaxime. Multiresistance, defined as resistance to four or more antimicrobials, was present in 12% of *S*. Typhimurium and 40% of *S*. Typhimurium DT104. Less than 2% of *S*. Enteritidis were multiresistant. In other serovars multiresistance was <10%, and 59% were sensitive to all antimicrobials tested. Overall ciprofloxacin and cephalosporin resistance was <1%. The laboratories had sensitivity-tested 752 out of 897 isolates. Retrospective testing against a common panel of discs and molecular testing were not possible because isolates from smaller hospitals had not been archived.

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Table 2. *Antimicrobial drug resistance in non-typhoidal* Salmonella *isolated from humans by serovar 2001–2003*

Salmonella serovar (*n* = total tested)	% resistant (no. resistant/total no. tested)											% (*n*) resistance to n antibiotics				
	AMP	CIP	TMP	CHL	NAL	S	CTX	GEN	TET	STR	FR	KAN	AUC	0	1	2	3	⩾4
Enteritidis (*n* = 382)	8·1 (31/382)	0·3 (1/382)	2·6 (10/382)	0·7 (2/281)	20·5 (65/317)	6·8 (17/249)	0 (0/133)	0·8 (2/244)	9·0 (15/167)	3·5 (5/143)	2·1 (3/143)	0·7 (1/143)	3·5 (5/143)	72·3 (276)	20·7 (79)	3·4 (13)	1·8 (7)	1·8 (7)
Typhimurium Non-DT104 (*n* = 99)	38·4 (38/99)	0 (0/99)	10·1 (10/99)	21·5 (14/65)	0 (0/82)	50 (31/60)	2·6 (1/39)	0 (0/58)	61·3 (19/31)	62·5 (15/24)	8·3 (2/24)	0 (0/24)	26·1 (6/23)	46·0 (40)	18·4 (16)	9·2 (8)	11·1 (11)	12·1 (12)
Typhimurium DT104 (*n* = 96)	83·1 (78/96)	0 (0/96)	25·3 (24/96)	86·9 (53/61)	6·5 (5/77)	94·5 (52/54)	0 (0/41)	0 (0/64)	93·1 (35/39)	82·8 (24/29)	0 (0/29)	0 (0/29)	96·6 (28/29)	12·5 (12)	18·8 (18)	13·5 (13)	15·6 (15)	39·6 (38)
Other serovars* (*n* = 175)	10·9 (19/175)	0 (0/175)	5·1 (9/175)	4·7 (6/128)	19·5 (27/128)	19·2 (20/102)	0 (0/71)	0 (0/94)	20·6 (13/63)	34·8 (16/46)	6·5 (3/46)	0 (0/46)	10·6 (5/47)	68 (119)	13·7 (24)	9·1 (16)	4·0 (7)	5·1 (9)
Total % (no.) isolates resistant/tested	22·1 (166/752)	0·1 (1/752)	7 (53/752)	14 (75/535)	16·1 (97/604)	25·8 (120/465)	0·4 (1/284)	0·4 (2/460)	27·3 (82/300)	24·8 (60/242)	3·3 (8/242)	0·4 (1/242)	18·2 (44/242)					

* *S.* Virchow (*n* = 19), *S.* Hadar (*n* = 11), *S.* Infantis (*n* = 11), *S.* Braenderup (*n* = 7), *S.* Dublin (*n* = 7), unspecified (*n* = 38), other serovars (*n* = 82).

AMP, Ampicillin; AUG, co-amoxiclav; CHL, chloramphenicol; CIP, ciprofloxacin; GEN, gentamicin; S, sulphamethoxazole; TET, tetracycline; TMP, trimethoprim; NAL, nalidixic acid; STR, streptomycin; FR, furazolidone; KAN, kanamycin; CTX, cefotaxime.

S. Typhimurium DT104 refers to both DT104 and DT104b.

DISCUSSION

The use of different disc strengths between laboratories makes comparison of antimicrobial resistance patterns difficult, for example, for ciprofloxacin, ampicillin, chloramphenicol and trimethoprim (Table 2). All isolates were tested against a minimum of five discs, but only three antimicrobials were tested by all laboratories (ampicillin, ciprofloxacin and trimethoprim) because some hospitals test only for therapeutically relevant antimicrobials, while others test for a wider range to increase the amount of epidemiological data. This leads to difficulties in identifying the *S.* Typhimurium DT104 epidemic clone with resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines (ACSSuT).

Prevalent *Salmonella* serovars

There was an 11% fall in the number of human cases of salmonellosis in the United Kingdom (30% fall in NI) between 2000 and 2001 [12]. *S.* Enteritidis including PT4, and *S.* Typhimurium, including DT104, in which multiresistance is prevalent, fell over the 3-year period [2]. However the number of *Salmonella* isolates of other serovars or non-specified serovars remained at a steady level (101–180 cases per year).

Between 2001 and 2003 antimicrobial resistance data were available from 752 out of 897 *Salmonella* clinical isolates from hospital laboratories throughout Northern Ireland. Forty percent (327/821) of the human isolates were associated with travel abroad. The most common *Salmonella* isolates from the hospital laboratories were *S.* Enteritidis (418/897, 46·6%) and *S.* Typhimurium (223/897, 24·9%). Broadly similar trends were noted in the Republic of Ireland [13].

S. *Typhimurium DT104*

DT104 is the most common *S.* Typhimurium phage type in cattle, sheep and pigs, and although numbers are low and falling in the United Kingdom [14], they are not falling internationally [15]. In this study almost half (49%, 109/223) of the *S.* Typhimurium isolates were DT104, of which 40% (38/96) were multiresistant. In some countries DT104 has been viewed as more virulent than other phage types, with a greater likelihood of treatment failure. There is concern about co-integration and co-selection of

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virulence and resistance genes on plasmids, chromosomes and bacteriophages leading to strains that are both more virulent and more difficult to treat [16]. A study of over 7000 non-typhoidal *Salmonella* isolates in the United States found that bloodstream infections were more common with isolates resistant to one or more antimicrobials than in those that were susceptible to all antimicrobials tested (adjusted OR 3·1, 95% CI, 1·4–6·6.) [17]. The same authors found that 22% of 13286 persons in 10 *Salmonella*-resistant outbreaks were hospitalized, compared with 8% of 2194 persons in 22 outbreaks caused by pan-susceptible *Salmonella* strains ($P<0·01$). Inherently greater virulence is not the only possibility, and the authors discussed prior antimicrobial use, failed empirical therapy, and an unknown factor as other possible explanations of these results [18]. In contrast, DT104 isolates from blood and faeces in the United Kingdom have not been proven to be more invasive than other common serovars [4], with bloodstream invasion in only 1·6% of 408 cases [19].

This study revealed difficulties in identifying the *S.* Typhimurium DT104 epidemic clone (ACSSuT) since only ampicillin, ciprofloxacin and trimethoprim were tested by all laboratories, and only 29 isolates were tested for the ACSSuT phenotype. Threlfall *et al.* found that ACSSuT resistance pattern was associated with resistance to trimethoprim and nalidixic acid in 10% of isolates [4]. Furthermore, resistance to nalidixic acid was associated with decreased susceptibility to ciprofloxacin. Acquisition of this resistance is a two-step process. One mutation in the *gyrA* gene mediates full resistance to narrow-spectrum quinolones, such as nalidixic acid and decreased susceptibility to fluoroquinolones. A second mutation in either *gyrA* or *gyrB* genes confers full resistance to fluoroquinolones. Evidence exists that the use of the NCCLS breakpoint at 4 μg/ml for ciprofloxacin may have the effect of obscuring the true occurrence of resistance among *Salmonella* strains and that low-level resistance is associated with increased mortality [20]. These authors have recommended using a fluoroquinolone breakpoint of 0·125 μg/ml since a higher figure may result in wrong clinical decisions and may obscure surveillance data. The widespread adoption of this recommendation could alter the epidemiological picture of resistance. In our survey, 29 out of 96 *S.* Typhimurium DT104 from human isolates were tested for the ACSSuT-resistant phenotype. The ACSSuT phenotype was confirmed in 79·3% (23/29). None of these isolates were resistant to ciprofloxacin, although 8·7% (2/23) were resistant to nalidixic acid and 21·7% (5/23) were resistant to trimethoprim. This could relate to the use of trimethoprim-containing agents and enrofloxacin in cattle and poultry [21]. It is noteworthy that the US Food and Drug Administration has withdrawn approval for the use of enrofloxacin in poultry for reasons including its failure to eradicate carriage of *Campylobacter* and its selection of resistance [22].

S. *Enteritidis PT4*

S. Enteritidis PT4 accounted for 164 out of 418 (39·2%) of all *S.* Enteritidis isolates and the majority (72%) were sensitive to all the antibiotics that were tested. Only 2% of all *S.* Enteritidis were resistant to four or more antimicrobials. This result was similar to the European study [23] where 71% of *S.* Enteritidis were fully sensitive and 2% were multiresistant. Resistance of all salmonella to naladixic acid was similar in the European study (14%) and Northern Ireland (16·1%). *S.* Enteritidis isolates accounted for 20·5% of the total number of resistant isolates in this study and *Salmonella* of other serotypes accounted for 19·5%. Nalidixic acid resistance among *S.* Enteritidis isolates was slightly higher than that in the European study which had a higher breakpoint for nalidixic acid of 16 μg/ml compared with our survey of 8 μg/ml (NCCLS). The breakpoint for ciprofloxacin in the Northern Ireland survey was higher at 1 μg/ml compared to the European study of 0·1 μg/ml. Clinical resistance to ciprofloxacin was judged to be present at 1 μg/ml in the European survey. The significance of these differences is not clear. It is probable that they reflect variations in breakpoints and methods rather than true epidemiological differences between countries. However, in the context of the recommendation by Aarestrup *et al.* [20] it cannot be assured that the differences are clinically insignificant in all cases.

Many of the other non-*S.* Enteritidis and non-*S.* Typhimurium serotypes were serogrouped but not serotyped. The next most common serotypes were *S.* Virchow, *S.* Hadar, *S.* Infantis, *S.* Braenderup and *S.* Dublin in descending order. These findings were similar to reports from laboratories throughout Europe [23]. Overall 40·6% of Northern Ireland *Salmonella* isolates were resistant to at least one antibiotic and 8·8% were multiresistant (i.e. resistant to four or more antibiotics). In a European multi-centre surveillance study of 27000 human *Salmonella*

isolates, 54·1% of isolates were *S*. Enteritidis and 25% were *S*. Typhimurium. Forty percent of European isolates were resistant to at least one antimicrobial, and 18% were multiresistant [24].

S. *Virchow and* S. *Hadar*

S. Virchow and *S*. Hadar are common salmonella serovars associated with multiresistance. Multiresistance had fallen in England and Wales in 1999, but 49% of *S*. Virchow showed multiresistance, and over half of *S*. Virchow and *S*. Hadar isolates exhibited decreased susceptibility to ciprofloxacin [14]. In our study, 5% of *S*. Virchow and 18% of *S*. Hadar isolates were multiresistant, all were susceptible to ciprofloxacin, and travel histories were not available.

Antimicrobial therapy

Ciprofloxacin and cefotaxime are the two antibiotics that are commonly used for treatment of complicated extra-intestinal *Salmonella* infections. The overall resistance to ciprofloxacin was 0·1% and that of cefotaxime 0·5% (cf. European study, 0·5% and 0·6% respectively [24]). Ciprofloxacin resistance (1 μg) was found only in one *S*. Enteritidis PT1 isolate. The patient had no history of foreign travel. This isolate was also reported as sensitive to ampicillin, gentamicin, cefotaxime and trimethoprim but resistant to nalidixic acid. Many *S*. Enteritidis infections with decreased sensitivity to ciprofloxacin have been phage type 1 and associated with travel to Southern Europe and Asia, or consumption of poultry products from these areas [14, 25].

Cefotaxime resistance was found in one *S*. Typhimurium isolate phage type DT193A using a 30 μg disc. There was no history of foreign travel in this patient and the isolate was also resistant to ampicillin. Threlfall *et al*. also reported resistance to cefotaxime (MIC 32–64 μg/ml) in three isolates of *S*. Typhimurium DT193 in 1998–1999 in England and Wales [26]. Although resistance to cefotaxime is low in Europe, a multiresistant strain of *S*. Newport with resistance to third-generation cephalosporins had been reported in outbreaks in bovines and humans in the United States with treatment failures [24, 27]. Extended spectrum β-lactamases (ESBLs) that confer resistance to third-generation cephalosporins are increasingly being reported in the Enterobacteriaceae and concern has been expressed regarding their presence in *Salmonella* [16, 28].

CONCLUSION

As a result of this study laboratories in Northern Ireland have agreed to standardize the range of antimicrobials *Salmonella* isolates are tested against, or to refer isolates to the regional laboratory to improve epidemiological monitoring. In cases of treatment failure, MICs to third-generation cephalosporins and ciprofloxacin should be determined.

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DECLARATION OF INTEREST

None.

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