

## Antimicrobial resistance patterns and genotypes of *Salmonella enterica* serovar Hadar strains associated with human infections in Switzerland, 2005–2010

N. CERNELA, M. NÜESCH-INDERBINEN, H. HÄCHLER AND R. STEPHAN\*

*Institute for Food Safety and Hygiene, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland*

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### SUMMARY

*Salmonella* Hadar ranks in the top ten serovars reported from humans in Switzerland. In this study, all 64 *S.* Hadar strains isolated from different patients from 2005 to 2010 in Switzerland were characterized by (i) assessing phenotypic antimicrobial resistance profiles using the disk diffusion method and (ii) by genotyping using pulsed-field gel electrophoresis (PFGE) in order to evaluate the relationship of the strains. The annual incidences varied between 0·32/100 000 in 2005 (highest incidence) and 0·065/100 000 in 2007 (lowest incidence). In total 71·8% of the isolates were resistant to nalidixic acid. Although 40·6% of the strains were resistant to the  $\beta$ -lactam antibiotic ampicillin, they remained susceptible to the third-generation cephalosporin cefotaxime. Genotyping revealed a primary cluster consisting of 42 strains, sharing a similarity of >92%, with a subcluster of 18 strains with indistinguishable patterns. Resistance profiles allowed further differentiation within this subcluster providing a link of two strains to an outbreak in Spain.

**Key words:** genotypes, human infections, resistance profiles, *Salmonella* Hadar.

### INTRODUCTION

Non-typhoidal *Salmonella* are commonly acquired from contaminated food and are an important cause of gastroenteritis and bacteraemia, posing a worldwide threat to public health [1, 2]. It is estimated that *Salmonella* causes 93·8 million human infections and 155 000 deaths annually worldwide [3]. Although more than 2500 serovars have been identified, *S.* Enteritidis and *S.* Typhimurium are responsible for the majority of reported cases of salmonellosis. For Europe, the distribution of other *Salmonella* serovars is reported to vary widely geographically and over time [4].

*S.* Hadar ranks in the top ten serovars isolated from humans in Switzerland over recent years and has been reported to be associated with poultry [5]. This serovar has been responsible for several foodborne outbreaks, e.g. in Italy in 1994 [6] and 2000 [7], and in Spain in 2005 [8].

As with other non-typhoidal *Salmonella*, infections due to *S.* Hadar often manifest themselves as self-limiting gastroenteritis, but severe invasive infections can also occur which require antimicrobial treatment. Drugs for *Salmonella* infection include fluoroquinolones, trimethoprim-sulfamethoxazole, ampicillin, or third-generation cephalosporins [9]. The emergence and spread of resistant bacteria and subsequent failure of treatment of infections is a significant and increasing global public health problem [10]. Resistance to antimicrobials used to treat invasive *Salmonella* is also increasing, including extended spectrum cephalosporins and quinolones [11]. *S.* Hadar is reported

\* Author for correspondence: Professor R. Stephan, Institute for Food Safety and Hygiene, Vetsuisse Faculty University of Zurich, Winterthurerstr. 272, CH-8057 Zurich, Switzerland.  
(Email: stephanr@fsafety.uzh.ch)

less frequently compared to other serovars; nonetheless, these isolates have been described as a reservoir of antimicrobial resistance [12].

In this study, all 64 *S. Hadar* strains isolated from different patients from 2005 to 2010 in Switzerland were further characterized by (i) assessing phenotypic antimicrobial resistance profiles using the disk diffusion method and (ii) by genotyping using pulsed-field gel electrophoresis (PFGE) after macrorestriction with *XbaI* in order to evaluate the relationship of the strains.

## METHODS

### Strains

Human salmonellosis is a notifiable disease in Switzerland and isolates have to be submitted to the National Centre for Enteropathogenic Bacteria (NENT). NENT, in cooperation with the Swiss Federal Office of Public Health, collects clinical data and conducts final serological identification by slide agglutination with commercial antisera according to the Kauffmann–White scheme [13]. From 2005 to 2010, 10048 cases of *Salmonella* infection were reported to the Swiss Federal Office of Public Health [14]. During this period, 64 human isolates of *S. Hadar* were collected and selected for this study. Multiple isolates from the same patient were excluded, isolates from individual family members were regarded as distinct isolates. All samples were collected and submitted by diagnostic laboratories, hospitals or family doctors throughout Switzerland.

### Antimicrobial susceptibility testing

The strains were tested for antimicrobial resistance by the disk diffusion method according to the Clinical and Laboratory Standards Institute [15]. The panel of antibiotic disks (Becton, Dickinson and Company, USA) consisted of ampicillin (AM10), amoxicillin/clavulanic acid (AMC30), cephalothin (CF30), cefotaxime (CTX30), ciprofloxacin (CIP5), gentamycin (GM10), tetracycline (Te30), streptomycin (S10), chloramphenicol (C30), kanamycin (K30), nalidixic acid (NA30), sulfamethoxazole (SMZ), and trimethoprim (TMP5). The strains were classified as resistant, intermediate or susceptible to each antimicrobial agent according to CLSI criteria [15]. For calculations of percentages, intermediate susceptibility was considered as resistant. Strains displaying resistance to three or more antimicrobial compounds of different classes were defined as multidrug resistant.

### Genotyping

PFGE was performed by following the CDC PulseNet protocol (<http://www.cdc.gov/pulsenet/protocols.htm>) with minor modifications. In brief, strains were grown on blood agar at 37 °C overnight. Colonies from blood agar were re-suspended in cell suspension buffer (OD<sub>600</sub> = 1). The bacterial cell suspension was mixed with 400 µl of 1.4% pulsed-field certified agarose (Bio-Rad, Germany) and cells were lysed by proteinase K treatment (0.1 mg/ml at 55 °C) overnight. After lysis the plugs were washed twice for 30 min in ultrapure water and four times for 1 h in 0.5 × Tris-EDTA (TE) buffer. After washing with TE buffer, DNA agarose plugs were incubated overnight in the presence of *XbaI* (Roche, Germany) according to the manufacturer's instructions. Restricted DNA in plug slices was separated in a 1% SeaKem Gold (BioConcept, Switzerland) agarose gel at 6 V/cm in 0.5 × Tris-borate-EDTA buffer cooled to 12 °C in a CHEF-DR III system (Bio-Rad). The pulse times were ramped from 2 s to 64 s for 20 h at an angle of 120°. Gels were stained with ethidium bromide and visualized under UV light transillumination with Gel Doc (Bio-Rad) and analysed with BioNumerics software (Applied Maths, Belgium). Pairwise similarities between the *XbaI* pulsed-field patterns were calculated using the DICE similarity coefficient. Clustering was based on the unweighted pair-group method with averages (UPGMA), setting tolerance and optimization each at 1.5%. *S. Braenderup* strain H9812 (ATCC BAA 664) was used as a reference strain.

## RESULTS

### Clinical and epidemiological data

Sixty-one (95%) *S. Hadar* strains were isolated from stool samples. Of the remaining strains, one originated from a blood sample, one from urine and one isolate was of unknown origin.

During the whole study period *S. Hadar* was ranked in the top ten serovars reported from humans in Switzerland. Of the total annual *Salmonella* isolates, this serovar accounted for 1.3% in 2005, 0.6% in 2006, 0.3% in 2007, 0.4% in 2008, 0.8% in 2009 and 0.5% in 2010. The annual incidence of *S. Hadar* was highest in 2005 with a value of 0.32/100 000. In 2006 the annual incidence was 0.13/100 000, followed by the lowest incidence of 0.065/100 000 in 2007, 0.1/100 000 in 2008, 0.14/100 000 in 2009 and finally, 0.076/100 000 in 2010.

Age was known for 62 of the 64 patients (Fig. 1). In the  $\leq 5$  years age group, eight strains were identified accounting for 12.5% of the study collection. In the 6–14 years age group, four (6.3%) strains were found. The majority of 47 (73.4%) cases was found in the 15–65 years age group; 7.8% of the strains originated from people aged  $>65$  years (five strains).

Of all patients, only three had a documented history of foreign travel. One patient aged  $>65$  years had visited Kenya. Two patients were infants in the  $<5$  years age group; one had been to Macedonia and the other to Egypt. Two patients were members of the same family and both were in the 15–65 years age group.

### Antimicrobial susceptibility

A total of 28 (43.8%) strains were resistant and 30 (46.9%) strains revealed multidrug resistance (Fig. 1). Only six (9.4%) strains showed full susceptibility to all antimicrobials.

Resistance rates were high for the quinolone nalidixic acid (71.8%). Only two strains were resistant to ciprofloxacin. The frequency for resistance to tetracycline was 70.3%. For the class of aminoglycosides, resistance to streptomycin was detected in 75% of the strains. All strains were fully susceptible to gentamycin and three (4.7%) strains were resistant to kanamycin.

A high percentage (40.6%) of the strains were resistant to the  $\beta$ -lactam antibiotic ampicillin and 29.7% revealed resistance to the first-generation cephalosporin cephalothin. Four isolates were resistant (intermediate) to the combination of amoxicillin with the  $\beta$ -lactamase inhibitor clavulanic acid and all strains were fully susceptible to the third-generation cephalosporin cefotaxime. Combined resistance to ampicillin and nalidixic acid was exhibited by 24 strains (37.5%). We found 21 sulfamethoxazole- and three trimethoprim-resistant strains, which amounted to 32.8% and 4.7%, respectively. Three strains were resistant to both antimicrobials. All isolates except two (3.1%) were susceptible to chloramphenicol.

From 2005 to 2010 no major shift in resistance patterns was observed. However, resistance rates were maintained at high levels. In different years 80–100% of the isolated strains were resistant to at least one antimicrobial.

### Genetic relationship of Swiss *S. Hadar* isolates

PFGE analysis with the *Xba*I restriction enzyme revealed 34 banding patterns in the 64 isolates

(Fig. 2). In general, PFGE analysis of the different strains showed a close clonal relationship. One primary cluster was observed, consisting of 42 strains sharing a similarity of  $>92\%$ . Within this cluster 18 strains shared a similarity of 100%. Eight of these indistinguishable strains were isolated in 2005, which amounted to 33.3% of the 24 isolates collected in 2005. In the following years, this pulsotype appeared less frequently (in 2006 two strains were detected, in 2007 there was one strain, in 2008 we found three, in 2009 there were four, and in 2010 one strain was found). Except for strains N05-1373 and N05-1374, which originated from two individuals from the same family, no connection between the patients could be established. Samples had been obtained and submitted to NENT from all over Switzerland. Age groups and gender were distributed evenly and all strains originated from stool samples.

Two of these 18 strains (N05-1374, N06-1737) showed the resistance pattern AM-CF-S-NA-TE; four strains (N05-216, N05-1556, N05-1957, N09-1491) showed the resistance pattern AM-CF-S-NA-TE-SMZ and the rest of these 18 strains were heterogeneous in regard to their resistances.

## DISCUSSION

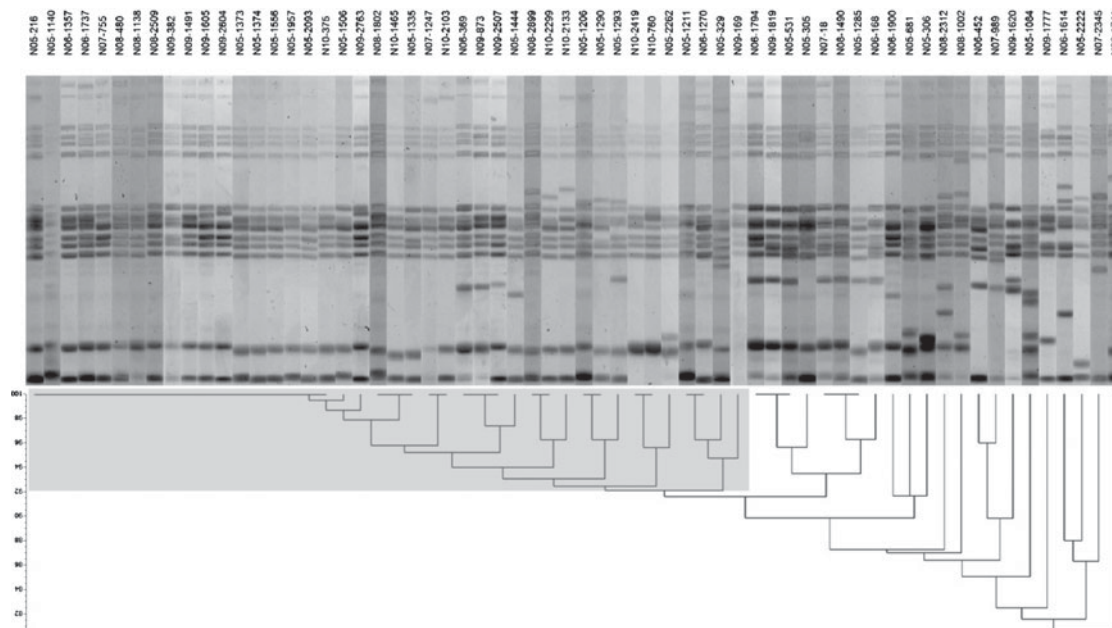
On average, the annual incidence of salmonellosis in Switzerland for 2005–2010 was 21.78/100 000 [14]. From this period, isolates from 64 cases of human infections with *S. Hadar* were selected and screened for antibiotic resistance and for genetic relationship. Strains were from medical institutions from all over Switzerland.

In an analysis of the global distribution of the 15 most frequently identified serovars of *Salmonella* isolated from humans, *S. Hadar* was found in a proportion of 1.5% in Europe [16]. In Switzerland, *S. Hadar* ranked in the top ten serovars reported from humans during to whole study period.

Although salmonellosis is a notifiable disease, it is normally self-limiting in otherwise healthy individuals and hence many infections go undetected by the authorities, accounting for an unknown number of unreported cases. It has been suggested that reported laboratory-confirmed *Salmonella* incidences should be adjusted for under-ascertainment using multipliers ranging from 3.2 to 14.3 for European countries and as high as 38 for the USA [3]. Consequently, it must be assumed that the true population burden of disease

Year	Strain No.	Resistance profiles														Gender	Age	Source
		AM	AMC	CF	CTX	GM	K	S	TE	CIP	NA	SMZ	TMP	C				
2005	N05-216	6	18	13	28	20	21	10	6	27	6	16	28	28	m	1	feces	
2005	N05-305	6	21	12	25	19	20	10	6	25	6	9	27	22	f	32	feces	
2005	N05-306	25	25	25	25	32	32	6	6	25	25	25	25	40	m	32	blood	
2005	N05-329	27	30	27	30	20	22	12	6	27	6	16	30	28	m	30	feces	
2005	N05-531	26	30	28	34	19	21	15	25	30	24	16	32	28	f	70	feces	
2005	N05-681	25	25	25	25	24	34	6	16	25	25	25	25	50	f	56	feces	
2005	N05-1084	6	22	19	32	22	21	8	8	32	6	12	14	24	f	34	feces	
2005	N05-1140	26	28	25	32	21	21	10	8	28	6	14	28	26	m	30	feces	
2005	N05-1206	6	17	11	32	21	22	10	6	26	6	14	28	20	f	42	feces	
2005	N05-1211	25	27	24	32	18	20	16	22	28	6	14	28	16	m	55	feces	
2005	N05-1285	6	18	13	28	20	19	9	6	27	6	18	30	9	m	10	feces	
2005	N05-1290	28	30	22	24	22	22	6	8	30	10	18	32	30	f	35	feces	
2005	N05-1293	6	38	22	30	30	30	24	24	40	6	14	38	24	f	42	feces	
2005	N05-1335	6	17	10	32	20	20	8	6	26	6	18	28	24	nd	nd	feces	
2005	N05-1373	23	26	24	30	19	19	10	9	18	6	14	28	27	f	35	feces	
2005	N05-1374	6	18	13	30	20	21	10	6	25	6	20	30	24	m	42	feces	
2005	N05-1444	30	30	30	40	20	21	18	24	46	30	18	32	30	f	59	feces	
2005	N05-1506	25	28	27	34	19	20	16	20	34	6	18	30	25	m	52	feces	
2005	N05-1556	23	30	23	32	17	18	10	6	26	6	14	28	24	f	5	feces	
2005	N05-1957	6	17	11	32	19	20	10	6	26	6	12	27	25	m	1	feces	
2005	N05-2093	6	20	14	36	18	20	6	6	30	6	16	32	27	f	51	feces	
2005	N05-2222	6	22	16	36	20	22	10	7	30	6	20	32	29	m	21	feces	
2005	N05-2262	26	28	25	32	19	20	10	6	26	6	16	30	29	f	69	feces	
2005	N05-2299	6	16	6	25	42	34	14	6	25	14	20	25	30	f	65	urine	
2006	N06-168	24	26	25	30	18	19	14	20	34	25	11	38	25	f	73	feces	
2006	N06-369	30	30	28	34	21	23	16	27	32	6	20	34	32	m	59	feces	
2006	N06-452	28	32	28	36	22	23	10	6	32	6	18	34	27	f	26	feces	
2006	N06-1270	28	30	30	30	20	21	8	8	40	28	16	30	30	m	2	feces	
2006	N06-1357	6	18	6	34	24	25	6	6	15	6	16	32	33	m	21	feces	
2006	N06-1614	6	23	18	46	27	26	6	14	50	36	20	44	38	m	53	feces	
2006	N06-1737	6	20	13	40	20	21	8	8	30	6	17	34	28	f	39	feces	
2006	N06-1741	28	34	27	38	24	24	10	8	40	28	6	6	30	f	26	feces	
2006	N06-1794	30	32	26	36	21	22	17	24	42	28	20	35	28	m	6	feces	
2006	N06-1900	6	24	19	38	25	24	6	6	36	6	12	6	30	m	25	feces	
2007	N07-18	28	33	28	38	24	23	17	24	42	29	22	34	30	m	59	feces	
2007	N07-755	6	21	15	40	24	24	11	10	37	6	23	36	32	f	<1	feces	
2007	N07-989	18	40	27	46	24	25	12	29	38	6	17	44	38	m	27	feces	
2007	N07-1247	28	32	26	38	23	24	19	25	36	6	22	37	26	f	39	feces	
2007	N07-2345	29	31	27	38	24	25	18	6	30	6	18	30	31	f	34	feces	
2008	N08-480	31	32	26	38	22	23	10	9	42	30	24	38	27	f	57	feces	
2008	N08-1002	6	19	28	36	23	23	12	8	34	6	26	38	28	f	26	feces	
2008	N08-1138	28	34	28	36	24	24	11	8	34	6	17	33	31	m	49	feces	
2008	N08-1490	30	33	30	38	23	23	19	25	40	29	18	36	31	f	56	feces	
2008	N08-1802	30	30	30	38	24	23	12	8	42	30	18	36	29	f	2	feces	
2008	N08-2312	34	34	28	37	21	23	17	8	25	6	18	32	28	m	63	feces	
2008	N08-2509	6	18	10	38	22	22	11	8	38	26	20	36	29	f	33	feces	
2008	N08-2899	25	30	24	34	22	23	13	8	32	6	20	36	28	f	59	nd	
2009	N09-169	29	32	28	36	20	22	16	25	38	30	20	37	29	f	3	feces	
2009	N09-382	12	18	9	37	22	22	15	22	35	6	22	36	30	m	69	feces	
2009	N09-873	28	30	28	36	20	21	10	6	36	6	20	34	26	f	41	feces	
2009	N09-1491	6	21	14	38	22	21	10	6	30	6	16	32	29	m	4	feces	
2009	N09-1605	28	28	28	35	16	16	6	6	36	6	20	34	27	m	47	feces	
2009	N09-1620	28	33	23	38	21	21	16	25	34	28	18	34	29	f	43	feces	
2009	N09-1777	29	28	25	34	21	22	10	8	36	26	22	34	29	m	50	feces	
2009	N09-1819	27	28	25	34	20	20	14	22	34	25	20	32	30	m	9	feces	
2009	N09-2507	6	23	14	37	22	23	10	8	24	6	20	37	31	m	61	feces	
2009	N09-2604	6	18	16	38	23	24	11	25	34	6	20	36	32	m	40	feces	
2009	N09-2763	6	19	12	35	20	21	10	21	33	6	16	33	26	m	40	feces	
2010	N10-0375	26	24	25	34	21	21	10	6	32	6	18	30	29	m	24	feces	
2010	N10-0760	30	28	27	34	21	23	10	6	30	6	18	32	28	m	29	feces	
2010	N10-1465	27	28	28	34	21	21	15	6	28	6	16	32	25	f	nd	feces	
2010	N10-2103	8	24	22	34	18	6	10	6	30	6	20	34	25	f	41	feces	
2010	N10-2133	6	22	20	34	20	6	10	6	28	6	20	32	25	f	24	feces	
2010	N10-2419	28	28	28	34	20	21	11	6	32	6	18	30	26	f	78	feces	

**Fig. 1.** Resistance profiles and anamnestic data of the 64 *S. Hadar* strains. Strains resistant, intermediate or susceptible to a specific antibiotic are highlighted in grey, light grey, or white, respectively. AM, ampicillin; AMC, amoxicillin-clavulanic acid; CF, cephalothin; CTX, cefotaxime; GM, gentamicin; K, kanamycin; S, streptomycin; TE, tetracycline; CIP, ciprofloxacin; NA, nalidixic acid; SMZ, sulfamethoxazole; TMP, trimethoprim; C, chloramphenicol; m, male; f, female; nd, no data.



**Fig. 2.** Pulsed-field gel electrophoresis (PFGE) patterns of the 64 *S. Hadar* strains. The primary PFGE cluster (92% similarity) is indicated by light grey.

caused by *S. Hadar* is greater than that suggested by our findings.

We found that the majority of strains were resistant to nalidixic acid, tetracycline and  $\beta$ -lactam antibiotics, excluding third-generation cephalosporins. The emergence and spread of multidrug resistance in pathogenic as well as commensal bacteria in general and in *Salmonella* spp. in particular is an increasing global concern [10, 17, 18]. Dissemination of resistance genes through bacterial populations needs to be monitored globally as well as locally [19]. Moreover, there is evidence that less frequent serovars, such as *S. Hadar*, are reservoirs of antibiotic resistance genes [12]. The considerable percentage (46.9%) of multidrug-resistant strains in our strain collection is in accord with the results of a European multi-centre study, which describes 37% multidrug-resistant *Salmonella* isolates [20].

Resistance to nalidixic acid in salmonellae is of great concern, as it has been reported to be an indicator for reduced susceptibility to the drug of choice, ciprofloxacin, resulting in possible treatment failure [21–23]. Consequently, the 71.8% nalidixic acid-resistant *S. Hadar* of this study must be considered as having reduced susceptibility to ciprofloxacin, and thus potentially treatment-resistant. Interestingly, the strain that was isolated from blood, and presumably associated with invasive infection, was susceptible to both nalidixic acid and ciprofloxacin.

Reports on the emergence of extended-spectrum  $\beta$ -lactamase (ESBL)-resistant salmonellae give rise to concern [24]. Genes encoding for ESBLs, predominantly *bla*<sub>TEM</sub>, *bla*<sub>SHV</sub> and *bla*<sub>CTX</sub> variants have been detected in various *Salmonella* serovars isolated from humans as well as from poultry and poultry products [25]. However, all the *S. Hadar* isolates in this study were susceptible to cefotaxime. So far, resistance to ESBL antibiotics is not yet an issue in *S. Hadar* isolates in Switzerland. Nevertheless, continued surveillance for the presence of ESBL in *Salmonella* spp. is needed in order to minimize the risks to future treatment [26].

PFGE analysis showed a close clonal relationship for this serovar, similar to what is also known for *S. Enteritidis*. In the primary cluster, consisting of 42 strains sharing a similarity of >92%, a subcluster of 18 strains with indistinguishable patterns was observed. By combining the PFGE and the resistance patterns of these strains, two strains (N05-1374, N06-1737) isolated in 2005 and early 2006 are indistinguishable from a *S. Hadar* strain responsible for a chicken meat-borne outbreak in Spain [8], suggesting a possible exposure of these patients in Spain.

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## DECLARATION OF INTEREST

None.

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