

ORIGINAL ARTICLE

Antimicrobial Resistance Profiles and Diversity in *Salmonella* from Humans and Cattle, 2004–2011

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Impacts

- Most *Salmonella* from non-clinical dairy cattle sources that could potentially enter the human food chain were susceptible to 11 anti-microbials, as were isolates derived from human clinical cases.
- Although some anti-microbial resistance (AMR) profiles in the three predominant serovars (*Salmonella* Typhimurium, *Salmonella* Newport and *Salmonella* Montevideo) were common between host populations (human and cattle), more profiles were unique to source populations than were shared. Also, AMR profile richness was greater in the common serovars from humans, although relatively few profiles dominated in both host populations.
- Our finding suggests AMR *Salmonella* recovered from humans likely has multiple origins; hence, managing AMR requires a better knowledge of those origins and developing multiple control strategies.

Keywords:

Salmonella; anti-microbial resistance; humans; cattle

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Summary

Analysis of long-term anti-microbial resistance (AMR) data is useful to understand source and transmission dynamics of AMR. We analysed 5124 human clinical isolates from Washington State Department of Health, 391 cattle clinical isolates from the Washington Animal Disease Diagnostic Laboratory and 1864 non-clinical isolates from foodborne disease research on dairies in the Pacific Northwest. Isolates were assigned profiles based on phenotypic resistance to 11 anti-microbials belonging to eight classes. *Salmonella* Typhimurium (ST), *Salmonella* Newport (SN) and *Salmonella* Montevideo (SM) were the most common serovars in both humans and cattle. Multinomial logistic regression showed ST and SN from cattle had greater probability of resistance to multiple classes of anti-microbials than ST and SN from humans ($P < 0.0001$). While these findings could be consistent with the belief that cattle are a source of resistant ST and SN for people, occurrence of profiles unique to cattle and not observed in temporally related human isolates indicates these profiles are circulating in cattle only. We used various measures to assess AMR diversity, conditional on the weighting of rare versus abundant profiles. AMR profile richness was greater in the common serovars from humans, although both source data sets were dominated by relatively few profiles. The greater profile richness in human *Salmonella* may be due to greater diversity of sources entering the human population compared to cattle or due to continuous evolution in the human environment. Also, AMR diversity was greater in clinical compared to non-clinical cattle *Salmonella*, and this could be due to anti-microbial selection pressure in diseased cattle that received treatment. The use of bootstrapping techniques showed that although there were shared profiles between humans and cattle, the expected and observed number of profiles was different, suggesting *Salmonella* and associated resistance from humans and cattle may not be wholly derived from a common population.

Introduction

Non-typhoidal *Salmonella* (NTS) are related bacterial pathogens transmitted mainly via food (Majowicz et al., 2010), but also via non-foodborne mechanisms (Hoelzer et al., 2011). Worldwide, they are associated with significant morbidity and mortality in humans and animals. *Salmonella* is classified into over 2610 serovars (Guibourdenche et al., 2010), yet only a few (~30) serovars account for over 90% of described clinical disease in a given country (Popoff et al., 2004). The serovars that cause typhoid fever are restricted to humans while NTS infect multiple hosts. Food animals are considered the main reservoirs of NTS for human infections (Angulo et al., 2004; Hoelzer et al., 2010). *Salmonella* mostly causes self-limiting gastroenteritis, although severe systemic infections do occur in infants, the elderly and immune compromised individuals (Gordon, 2008; Crump et al., 2011). Severe infections require treatment, and one of the challenges for treating these infections is anti-microbial resistance (AMR) (CDC, 2013).

A considerable number of reports describe mechanisms of AMR (Aarestrup, 2006), factors that favour the emergence, maintenance and spread of resistant bacteria (Rabsch et al., 2001), and AMR genetic determinants (O'Brien et al., 1982). Many of the published reports are based on prevalence study designs, which limit inference to a single point in time. Analyses of longitudinal AMR data provide insights into temporal relationships between sources and help to infer transmission processes of resistant strains. For instance, clonal dissemination played a more critical role than anti-microbial selection pressure in AMR changes observed in *Salmonella* Typhimurium (ST) from cattle in north-western United States. (Davis et al., 1999). Another study that used epidemiological and ecological approaches to analyse phenotypic AMR data in ST DT104 from Scotland reported greater AMR diversity in human isolates compared to temporally related sympatric animal isolates. Furthermore, some AMR profiles from animals were distinct from those in humans. Thus, the study concluded local animals may not be the major source of AMR diversity for human DT104 infections in those populations (Mather et al., 2012). A subsequent study by the same authors using molecular data also concluded there was limited exchange of ST DT104 and resistance genes between sympatric humans and animals (Mather et al., 2013). However, the topic is complex, and the debate on where AMR is generated, and how best to control it is ongoing (Wassenaar, 2005; Silbergeld et al., 2008).

There is some evidence that AMR patterns differ within serovars isolated from different hosts, as well as between different serovars from the same host. ST, *Salmonella* Newport (SN) and *Salmonella* Dublin (SD) are the most common serovars with resistance encompassing two clinically

important phenotypes: ACSSuT (A, ampicillin; C, chloramphenicol; S, streptomycin; Su, sulfisoxazole; T, tetracycline) and ACSSuTAuCx (Au, amoxicillin-clavulanic acid and Cx, ceftriaxone) (CDC, 2013). These serovars also have a wide range of resistance phenotypes including pan susceptible. Associations between certain AMR-encoding plasmids and particular serovars and hosts have been documented (Folster et al., 2010). These studies lead us to conclude that while host and environmental factors may influence resistance patterns, it appears the ability to become resistant to particular drugs is serovar dependent.

Here we examine and compare AMR profiles and diversity in *Salmonella* isolates from humans and temporally and spatially related dairy cattle. We find that although similar AMR profiles occur in the three common serovars from humans and cattle, more profiles are unique to host population, and more diversity (richness) is observed in the human isolates.

Materials and Methods

Salmonella databank and selection of isolates

The Food and Waterborne Disease Research group at the College of Veterinary Medicine, Washington State University has collected *Salmonella* isolates from humans and animals since 1982. On 4 June 2012, the databank had 23 088 isolates with 13 606 having anti-microbial susceptibility profiles using disc diffusion methods (Bauer et al., 1966) against a panel of eleven drugs (Table 1).

For this study, we analysed 5124 human and 2255 cattle isolates. The human isolates were obtained from the Washington Department of Health and represent all isolates submitted to the Department through its passive surveillance system. The majority of cattle isolates ($n = 1864$) were research-based from a proportional sampling scheme of dairy farms that reflected the dairy cattle population within the state of Washington. These samples were an active surveillance of apparently healthy dairy cattle. We also evaluated 391 isolates obtained from clinical specimen submissions to the Washington Animal Disease Diagnostic Laboratory. This laboratory serves the Pacific Northwest region; hence, specimens came from Washington ($n = 233$), Oregon ($n = 106$) and Idaho ($n = 20$). All isolates evaluated were acquired between 2004 and 2011 (Table 2) because the isolate collection was fairly consistent across sources. We also analysed data subsets of the five most common serovars in humans, cattle and the most common serovars in both humans and cattle.

Generation of AMR phenotypes

The AMR data for each isolate consisted of measured inhibition zone size (mm) for each of the tested anti-microbials.

Table 1. Anti-microbials and interpretation of zone of inhibition (mm) to evaluate anti-microbial resistance in non-typhoidal *Salmonella* (NTS) from human and cattle sources in north-western United States, 2004–2011

CLSI class	Antimicrobial agent	Disk content μg	Breakpoints used (mm)		CLSI breakpoints (mm) Resistant
			Susceptible	Resistant	
Aminoglycosides	Gentamicin	10	>15	<14	<12
	Kanamycin	30	>14	<13	<13
	Streptomycin	10	>12 ^a	<11 ^a	None
β -lactam/ β -lactamase inhibitor	Amoxicillin-clavulanic acid	20/10	>14 ^b	<13 ^b	<13
Cephem	Ceftazidime	30	>19	<18	<14
Folate pathway inhibitors	Sulfisoxazole	0.25	>13 ^b	<12 ^b	<12
	Trimethoprim–sulfamethoxazole	1.25/23.75	>11 ^b	<10 ^b	<10
Penicillin	Ampicillin	10	>14 ^b	<13 ^b	<13
Phenicol	Chloramphenicol	30	>15	<14	<12
Quinolone	Nalidixic acid	30	>14 ^b	<13 ^b	<13
Tetracycline	Tetracycline	30	>16	<15	<14

^aValue based on NARMS (National Antibiotic Resistance Monitoring System) breakpoints.

^bValues based on Clinical and Laboratory Standards Institute break points.

Table 2. Yearly distribution of NTS isolates from humans and cattle sources in north-western United States used for this study

Source	Year								Total
	2004	2005	2006	2007	2008	2009	2010	2011	
Human clinical isolates	167	545	668	897	839	897	594	517	5124
Cattle clinical isolates	34	66	57	78	51	42	42	21	391
Cattle nonclinical isolates	14	72	466	402	12	841	25	32	1864
Total	215	683	1191	1377	902	1780	661	570	7379

Across the entire data set ($n = 13\,606$ isolates), the frequency distributions of inhibition zone sizes were plotted (Fig. 1). For those anti-microbials with inhibition zones following a bimodal distribution with a clear trough between the modes, a break point at the trough between modes was used to categorize an isolate as susceptible or resistant. For antimicrobials without a clear trough between the modes, that is the distributions were skewed, Clinical and Laboratory Standards Institute (CLSI) break points for resistance were used. As there was no CLSI break point for streptomycin, the National Antimicrobial Resistance Monitoring Systems (NARMS) break point was used. The values above the resistance break point were defined susceptible (Watts, 2008). Our break points for resistance were similar to CLSI guidelines except for ceftazidime where we interpreted intermediate resistance (14–18 mm) as resistant (Table 1). We then generated a unique AMR profile for each isolate by concatenating the categorical AMR results for the 11 anti-microbials.

Calculation of AMR phenotypic diversity

Biological diversity has two components: species richness (total number of species) and species evenness (variabil-

ity in abundance). Here, we adopted an approach described previously (Mather et al., 2012) to compare phenotypic AMR profile diversity of *Salmonella* from cattle and human using multiple measures of diversity. Briefly, indices of diversity that weight the importance of species richness and evenness differently were calculated for the cattle and human data separately and compared. We calculated four frequently used measures of diversity: Shannon's index (H'), species richness (R), Simpson's diversity index (SD) and Berger–Parker (BP), which cover the range of weightings for richness and evenness (Renyi, 1961). These are related to Hill's numbers (N_∞), (Hill, 1973) as following: $N_0 = R$, $N_1 = \exp(H')$, $N_2 = 1/SD$ and $N_\infty = 1/BP$, where N_0 is the total count of species present irrespective of abundance, N_1 and N_2 reflect common species and N_∞ the predominant species. As diversity measures are greatly influenced by sample size and the number of isolates for humans and cattle differed in our data set, we compared AMR diversity within and between humans and cattle by subsampling the larger data set 10 000 times without replacement to the size of the smaller data set. We then calculated the mean and 95% confidence intervals (CI) of the subsamples.

Important resistance phenotypes and resistance to multiple antibiotic classes

We assessed the frequency of four clinically important phenotypes: ACSSuT, ACSSuTAuCx, ACSx (Sx, trimethoprim–sulfamethoxazole) and CxNal (Nal, nalidixic acid) (CDC, 2013). However, isolates in our database were tested for ceftazidime but not ceftriaxone, so we substituted ceftazidime for ceftriaxone (CDC, 2013).

Multinomial logistic regression was used to determine whether *Salmonella* from cattle were more likely to be resistant to multiple classes of drugs compared to those from humans. The anti-microbials used in this study belong to eight CLSI classes: aminoglycosides, β -lactam/ β -lactamase inhibitors, cepheims, folate pathway inhibitors, penicillins, phenicols, quinolones and tetracyclines (Table 1). AMR was categorized as pan susceptible, resistant to 1 class, 2 classes, 3 classes, up to resistance to all (8) classes of antimicrobials. The multinomial model outcomes were the eight resistant class category versus the pan-susceptible reference group with source as the dependent variable (cattle source isolates compared to human isolates). Separate models were created for each of the commonly shared serovars. The analysis was performed using SAS version 9.3

software (PROC CATMOD; SAS Institute, Inc., Cary, NC, USA).

Assessment of common pool of resistance phenotypes

Here, again we have used an approach described previously (Mather et al., 2012) employing a bootstrapping method to assess whether or not *Salmonella* AMR profiles from human and cattle sources could have been drawn from a single pool of resistance profiles. We assessed AMR profiles in data sets of ST, SN and *Salmonella* Montevideo (SM) containing 943, 350 and 202 human isolates and 315, 243 and 459 bovine isolates, respectively. Briefly, the null hypothesis that AMR profiles were derived from a single population shared by humans and cattle was tested by randomizing source (human or cattle) for each isolate 10 000 times without replacement. This was performed independently for each serovar. The number of AMR profiles in each source category (cattle only, human only and common to both cattle and human isolates) by serovar was recorded for each bootstrap iteration. The observed and bootstrapped data were considered to be significantly different, considering each source/serovar combination separately, if the number of observed AMR profiles fell within the first or last 2.5th percentile of the bootstrapped distribution.

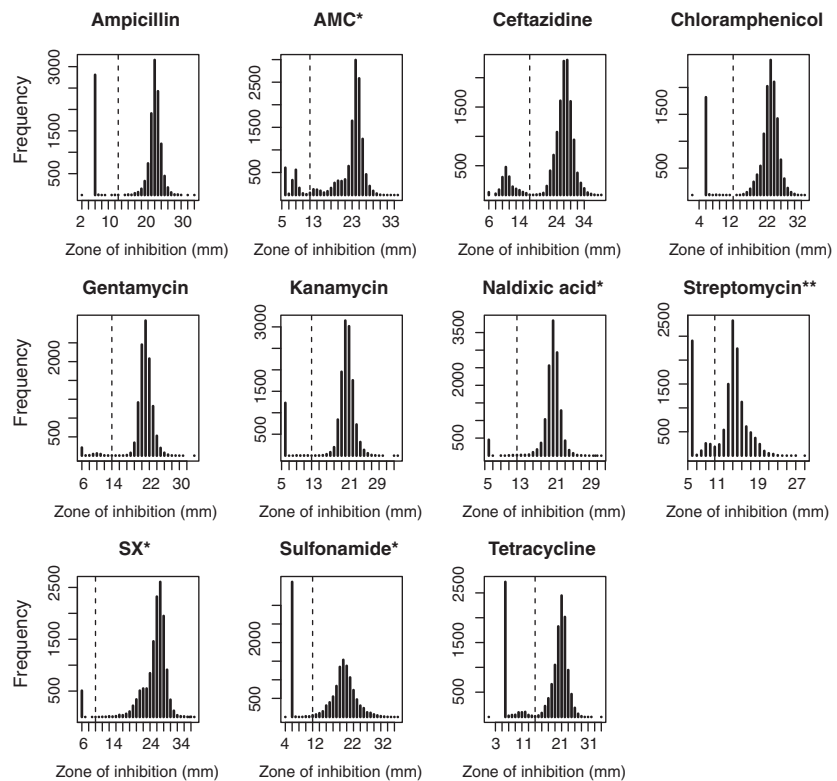


Fig. 1. Frequency distributions of disk diffusion inhibition zone sizes based on 13 606 *Salmonella* isolates from humans and animals in the *Salmonella* databank at Washington State University against 11 antimicrobials. A cut-off (dashed vertical line) at the trough of a bimodal distribution, Clinical and Laboratory Standards Institute guidelines (antibiotics marked *), or NARMS guidelines (antibiotics marked **) was used to categorize isolates as susceptible or resistant. Our break points were similar to CLSI guidelines except for ceftazidime where we interpreted intermediate resistance (14–18 mm) as resistant. AMC, amoxicillin-clavulanic acid; SX, trimethoprim/sulfamethoxazole.

Results

Distribution of *Salmonella* serovars

We analysed a total of 7379 isolates composed of 5124 human and 2255 cattle isolates. The distribution of the 20 most frequently isolated serovars in each host population is presented in Table 3. SE was the most common serovar isolated from humans followed by ST, SN, SH and SM; while in cattle, the order was SM, ST, SN, SD and *Salmonella* Soerenga (SS). Three predominant serovars (ST, SN and SM) were common in both human and cattle populations and used for comparative analyses. Although there is overlap of serovars between the two sources, SD (a cattle-adapted serovar) was commonly observed in cattle and rarely in people, and SE (a poultry-associated strain) was common in people and rare in the cattle source isolates.

Composition of AMR profiles including clinically important phenotypes

The AMR phenotypic structure of ST, SN and SM in humans and cattle is shown in Tables S1, S2 and S3. A high proportion (94%) of ST isolates from cattle was resistant to at least one anti-microbial compared to 54.4% in human isolates. Also, 70% of SN isolates from cattle were resistant to at least one drug compared to 44.9% in human isolates. Conversely, SM isolates from cattle were predominantly pan susceptible (PS) (97.8%) compared to 75.2% in human isolates.

The percentage for clinically important AMR phenotypes in the common serovars is presented in Table 4. The frequency of ACSSuT, the characteristic pentaresistance profile associated with ST DT104 (Threlfall et al., 1994), was greatest in ST irrespective of host population. The MDR pattern of 'at least ACSSuT', which includes the pentaresistance core and patterns with additional resistance, was similarly common in ST and SN. This reflects the addition of ceftazidime resistance to the core that was mainly observed in SN from both humans and cattle. Focusing on the percentage of 'at least ceftazidime' resistance, it was greatest in SD, SN and ST from cattle compared to SN and ST from people. However, 'at least nalidixic acid' resistance was mainly associated with SE from humans. The aforementioned phenotypes did not occur in SS and were also not seen or occurred at very low frequencies in SM. SE, with the exception of nalidixic acid, likewise was uncommonly associated with the other MDR phenotypes.

Is AMR diversity consistent between sources for the same serovar?

The effective number of AMR profiles ranging from profile richness, N_0 to the relative abundance of the most predom-

Table 3. The 20 most frequently isolated NTS serovars from human and cattle sources in Northwest United States, 2004–2011

Human sources			Cattle sources		
Rank	Serovar	No. of isolates %	Serovar	No. of isolates %	
1	Enteritidis	1020 19.9	Montevideo	459 20.4	
2	Typhimurium	943 18.4	Typhimurium	315 14.0	
3	Newport	350 6.8	Newport	243 10.8	
4	Heidelberg	328 6.4	Dublin	168 7.5	
5	Montevideo	202 3.9	Soerenga	146 6.5	
6	14,[5],12i-	134 2.6	Mbandaka	132 5.9	
7	Saintpaul	109 2.1	Anatum	96 4.3	
8	Infantis	105 2.1	Meleagridis	83 3.7	
9	Paratyphi B	102 2.0	Senftenberg	66 2.9	
10	Typhi	87 1.7	Havana	47 2.1	
11	Oranienburg	84 1.6	Uganda	43 1.9	
12	Thompson	83 1.6	Tennessee	39 1.7	
13	Muenchen	82 1.6	Barranquilla	33 1.5	
14	Agona	81 1.6	Poona	25 1.1	
15	Stanley	81 1.6	Muenster	24 1.1	
16	Braenderup	77 1.5	Ohio	22 1.0	
17	Senftenberg	70 1.4	Cerro	21 0.9	
18	Javiana	66 1.3	Brandenburg	20 0.9	
19	Hadar	55 1.1	Infantis	20 0.9	
20	4,12i-	48 0.9	Oranienburg	14 0.6	
	Subtotal	4107 80.2		2016 89.4	
	Other serovars	1017 19.8		239 10.6	
	Total	5124 100		2255 100	

inant AMR profiles, N_∞ in ST, SN and SM are presented in Table 5. As previously described, we compared diversity between humans and cattle by repeatedly subsampling the larger data sets to the data set with smaller sample size. AMR profile richness was higher in ST and SN derived from humans than cattle, but as relative abundance was considered, the effective number of AMR profiles from human and cattle became similar or slightly higher in cattle isolates (Table 5, Fig. S1). SM isolates from humans had greater AMR diversity than those from cattle across all the calculated diversity measures (Table 5, Fig. S1).

Is AMR diversity consistent between serovars from the same source?

We similarly compared AMR diversity in the five most common serovars isolated from humans by subsampling the SE, ST, SN and SH data sets to the SM data set ($n = 202$). ST was the most diverse serovar across all measures followed by SH and SN (Table S4). The effective number of AMR profiles calculated for SM and SE was similar for all diversity measures and consistently fewer than those for ST and SH (Table S4). To compare AMR diversity in cattle, the SM, ST, SN and SD data sets were subsampled to the size of the SS data set ($n = 146$). Although SD had

Table 4. Percentage of important resistant phenotypes in *Salmonella* and common serovars from humans and cattle in the NW USA, 2004–2011

No. of isolates	S. Typhimurium		S. Newport		S. Montevideo		S. Enteritidis		S. Heidelberg		S. Dublin	
	Humans 943	Cattle 315	Humans 350	Cattle 243	Humans 202	Cattle 459	Humans 1020	Humans 328	Cattle 168			
ACSSuT	11.2 (9.4–13.4)	9.5 (6.7–13.3)	1.1 (0.4–2.9)	0.4 (0.02–2.3)	0	0	0.3 (0.1–0.9)	0	1.8 (0.6–5.1)			
At least ACSSuT	22.8 (20.2–25.6)	23.5 (19.1–28.5)	24.9 (20.6–29.6)	36.2 (30.4–42.4)	0	0.2 (0.1–1.2)	0.3 (0.1–0.9)	2.4 (1.2–4.7)	48.2 (40.8–55.7)			
ACSSuTAmcCaz	1.7 (1.0–2.7)	3.2 (1.7–5.7)	21.4 (1.7–26.0)	31.7 (26.1–37.8)	0	0	0	0	4.2 (2.0–8.3)			
At least ACSSuTAmcCaz	4.8 (3.5–6.3)	9.2 (6.5–12.9)	22.6 (18.5–27.2)	35.8 (30.0–42.0)	0	0.2 (0.01–1.2)	0.1 (0–0.5)	1.5 (0.6–3.5)	39.9 (32.8–47.4)			
At least ACSx	5.2 (3.9–6.8)	4.4 (2.7–7.3)	1.4 (0.6–3.3)	1.2 (0.4–3.6)	0	0	0.1 (0–0.5)	0	0			
At least ceftazidime	8.6 (7.0–10.5)	36.2 (31.1–41.6)	26.0 (21.7–30.8)	66.3 (60.1–71.9)	0	0.2 (0.01–1.2)	0.4 (0.1–1.0)	16.1 (12.6–20.5)	75.6 (68.6–81.5)			
At least nalidixic acid	3.6 (2.6–5.0)	1.0 (0.3–2.8)	0.6 (0.1–2.1)	2.1 (0.9–4.7)	1.5 (0.5–4.3)	0	12.2 (10.3–14.3)	0	3.0 (1.3–6.8)			
At least CazNal	0.7 (0.4–1.5)	0.3 (0.02–1.8)	0	0	0	0	0	0	3.0 (1.3–6.8)			

A, ampicillin; Amc, amoxicillin-clavulanic acid; Caz, ceftazidime; C, chloramphenicol; Nal, nalidixic acid; S, streptomycin; Su, sulfisoxazole; T, tetracycline; and Sx, trimethoprim/sulfamethoxazole.

the highest effective number of AMR profiles followed by ST, the difference was not significant (Table S5). ST had greater diversity than SN across all measures except N_{∞} , the measure for the predominant profile. The calculated effective number of AMR profiles for cattle SM and SS isolates was fewer than that for SD and ST profiles; essentially, SM and SS had a single profile, pan susceptible.

AMR profile diversity in *Salmonella*, ST and SN from clinical and non-clinical cattle

To compare AMR diversity between clinical and non-clinical *Salmonella* from cattle sources, the non-clinical isolates ($n = 1864$) were subsampled to the clinical cattle size ($n = 391$). There was greater AMR diversity in *Salmonella* isolated from clinical than non-clinical cattle with all the diversity measures used (Fig. 2). Serovar-specific comparison was only performed for ST and SN due to sample size limitation. Similarly, AMR diversity was higher in clinical ($n = 107$) than non-clinical ($n = 208$) ST and in clinical ($n = 78$) than non-clinical ($n = 165$) SN with all measures used (Fig. 2).

Multinomial logistic regression to assess multidrug resistance (MDR) in cattle versus human isolates

The probability of resistance to 2–7 classes of anti-microbials versus pan susceptible was greater in ST from cattle compared to ST from humans ($P < 0.0001$, Table 6). The main resistance profiles and the number of anti-microbial classes to which they are resistant are also presented. Resistance to 2, 3, 4 or 5 classes of drugs was uncommon in SN irrespective of source. SN from cattle was more likely to be resistant to 6 or 7 classes of anti-microbials than SN from humans ($P < 0.0001$, Table 6). Logistic regression was not performed for SM because resistance to multiple classes of anti-microbials was uncommon irrespective of source.

Are human and cattle AMR phenotypes drawn from a common population?

Three abundant serovars (ST, SN and SM) common to humans and cattle were compared to assess whether observed AMR profiles were derived from common or separate populations. The ST data set comprised 943 human and 315 cattle isolates and had a total of 88 AMR profiles. Fifty-seven of these profiles were exclusive to humans, eight exclusive to cattle and 23 shared. The bootstrapping results showed the number of observed ST profiles exclusive to humans was higher than expected, while the number of profiles common to humans and cattle was lower than expected (Fig. 3). The number of observed cattle-specific profiles was as expected. There were a total of 25 AMR

Table 5. Diversity of antimicrobial resistance profiles in common NTS serovars in humans and cattle

Diversity	Salmonella Typhimurium			Salmonella Newport			Salmonella Montevideo		
	Humans	Human ^a	Cattle	Humans	Humans ^a	Cattle	Humans	Cattle	Cattle ^a
N	943	315	315	350	243	243	202	459	202
N_0	80	47 (40.1–53.9)	31.0	20	16 (12.7–19.3)	12.0	12.0	8.0	4.5 (2.0–7.0)
N_1	12.2	11.1 (9.2–13.1)	9.1	4.1	4.0 (3.6–4.4)	4.7	2.9	1.6	1.1 (1.0–1.2)
N_2	4.4	4.2 (3.5–4.8)	5.0	2.	72.7 (2.5–2.9)	3.8	1.7	1.0	1.0 (1.01–1.1)
N_∞	2.7	2.7 (2.3–3.0)	3.5	2.1	2.1 (1.9–2.3)	3.5	1.4	1.0	1.0 (1.0–1.05)

N , the total no. of isolates; N_0 , N_1 , N_2 & N_∞ , effective number of profiles ranging from the total number of profiles to the relative abundance of the most predominant profiles.

N , the total no. of isolates; N_0 , N_1 , N_2 & N_∞ , effective number of profiles ranging from the total number of profiles to the relative abundance of the most predominant profiles.

^aTo compare diversity between human and cattle isolates, the larger data set was subsampled $\times 10\,000$ to the size of the smaller data set and the mean and 95% CI are reported.

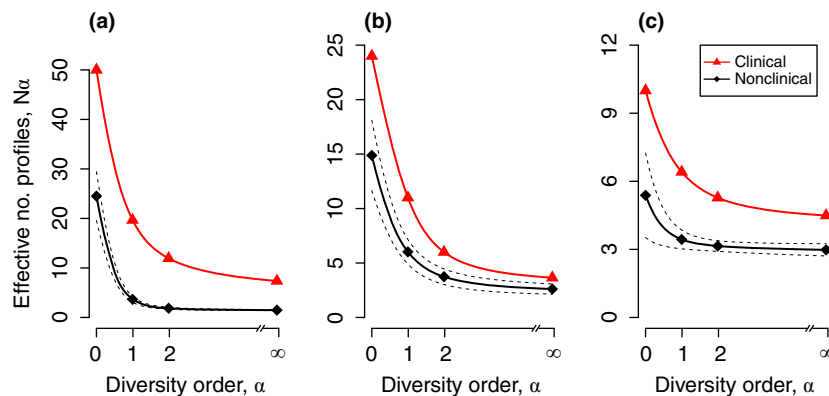


Fig. 2. Effective number of AMR profiles in (a) *Salmonella* spp., (b) *Salmonella* Typhimurium (c) and *Salmonella* Newport from clinical (red line with triangles) and non-clinical cattle (black line with diamonds) and 95% CI (dashed lines) in Northwestern United States, 2004–2011. The effective number of profiles for diversity order $\alpha = 0, 1, 2$ and ∞ are related to the diversity measures as follows: N_0 is AMR profile richness, N_1 , N_2 and N_∞ is the inverse of Shannon's index; Simpson's diversity index (SD) and Berger–Parker (BP), respectively.

profiles in the SN data set (350 human and 243 cattle): 14 exclusive to human source isolates, 4 exclusive to cattle source isolates and 11 shared (Fig. S2). As observed for ST, the bootstrap results for SN and SM found more observed human exclusive AMR profiles than expected and fewer observed shared than expected. The numbers of observed and expected profiles exclusive to cattle were similar.

Discussion

All human isolates in this study were derived from clinical cases, whereas most cattle isolates (82.7%) were non-clinical and of dairy cattle origin with the remainder from clinical cases. The non-clinical cattle isolates from 2005 to 2007 were collected by a previous study that recruited herds from the three main dairy cattle areas in Washington State and was active surveillance (Adhikari et al., 2009). A follow-up to that study in 2008 used the same sampling

scheme and collected a similar number of isolates. Although the human and clinical bovine data sets have the inherent bias of a passive surveillance system, such as under detection and reporting, our data are consistent with data collected in our national surveillance systems that also rely on passive systems. Our data provide an unbiased indication of humans and cattle that were sick enough to seek medical attention in Washington State. Beef and dairy products for human consumption are obtained from apparently healthy cattle, and as cattle are considered to be one of the main reservoirs of *Salmonella* and associated AMR for humans, our data set is suitable for comparing AMR profiles and diversity in *Salmonella* from humans and temporally and spatially related cattle. There is also an additional route of exposure as clinically diseased cattle can infect humans via direct or indirect contact in the course of occupational exposure. While the non-clinical cattle isolates came from Washington State, the clinical isolates also

Table 6. Multinomial logistic regression indicating the probability of resistance to one or more classes of antimicrobial over pan-susceptible (reference class) in cattle isolates compared to human isolates

Serovar	No. of classes	Cattle isolates	Human isolates	Total	%	Predominant resistance profile	Odds ratio	Std error	P value
ST	8 classes	0	7	7	0.6	Infinite ^a	Infinite ^a		
	7 classes	29	39	68	5.4	ACSSuTAmcCaz, ACKSSu SxAmcCaz	16.8	1.4	<0.0001
						ACKSSuTAmcCaz			
	6 classes	90	63	153	12.2	AKSSuTAmcCaz, ACSSuTAmc	32.3	1.3	<0.0001
	5 classes	38	136	174	13.8	ACSSuT	6.1	1.3	<0.0001
	4 classes	118	59	177	14.1	AKSSuT	45.3	1.3	<0.0001
	3 classes	8	43	51	4.1	SSuT, AAmcCaz	4.2	1.6	0.0014
	2 classes	6	53	59	4.7	SSu, ST, GSSu, KT	2.6	1.6	0.055
	1 class	7	113	120	9.5	Su, S, Nal, T	1.4	1.6	0.4573
Reference	19	430	449	35.7	Pan-susceptible	Reference			
Total	315	943	1258	100					
SN	7 classes	87	80	167	28.2	ACSSuTAmcCaz	2.9	1.2	<0.0001
	6 classes	74	13	87	14.7	ASSuTAmcCaz, ASSuSxTAmcCaz	15.1	1.4	<0.0001
	5 classes	1	5	6	1.0	Infinite ^a	0.5	3.0	0.5638
	4 classes	0	2	2	0.3	Infinite ^a	Infinite ^a		
	3 classes	1	6	7	1.2	Infinite ^a	0.4	3.0	0.4517
	2 classes	0	2	2	0.3	Infinite ^a	Infinite ^a		
	1 class	7	49	56	9.4	Su, Nal	0.4	1.5	0.0225
	Reference	73	193	266	44.9	Pan-susceptible	Reference		
	Total	243	350	593	100				

^aFrequency of isolates too few to carry out analysis.

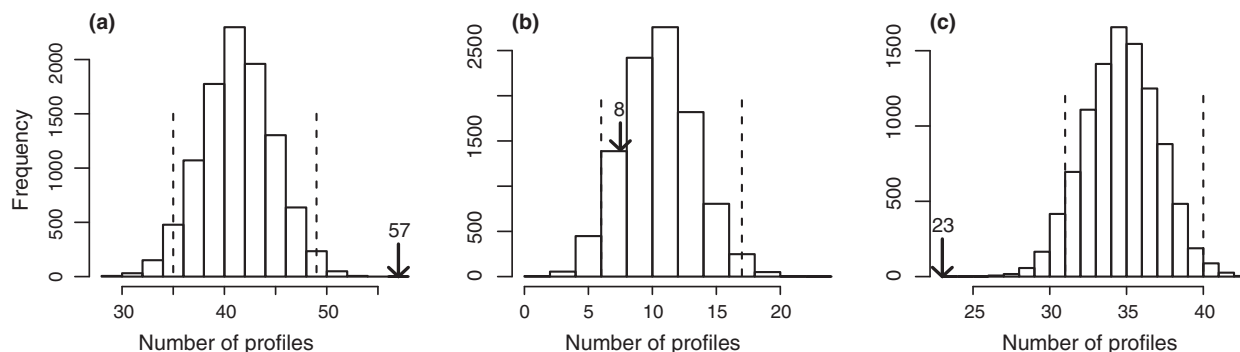


Fig. 3. Frequency distributions of the expected number of antimicrobial resistance profiles in *Salmonella* Typhimurium found in (a) humans only, (b) cattle only and (c) common to humans and cattle; in Northwestern United States, 2004–2011. The observed number of resistance profiles is marked with an arrow and those that fall within the first and last 2.5th percentile of the bootstrapped distribution (dashed lines) are significantly different.

came from Idaho and Oregon because the Washington Animal Disease Diagnostic laboratory serves the Pacific Northwest region. These isolates were considered to be sympatric with the human isolates as there is movement of dairy cattle between farms in the Pacific Northwest and reflect a common cattle pool.

There were shared and unique serovars between human and cattle sources. The distribution of serovars in humans in our study is similar to NARMS CDC reports for the same time period (<http://www.cdc.gov/narms/reports/index.html>), where SE and ST were the two most common serovars and SN the third most common (CDC, 2013). SH and SM, the fourth and fifth most common serovars in our

study, were among the ten most common serovars isolated from humans according to NARMS reports for the same period. Serovar distribution in cattle in our study is comparable to NARMS animal component reports for 2005–2010 (<http://www.ars.usda.gov/saa/bear/narms>) where SM was the most prevalent serovar. Furthermore, SN, SD and ST were among the top ten serovars reported by NARMS in cattle. However, SS, the fifth most common serovar in cattle in our study, did not feature among common serovars in the NARMS reports.

We noticed similarities and differences in AMR phenotypic structure in serovars that were common to humans and cattle. The high probability of resistance to multiple

anti-microbials in ST and SN from cattle could be consistent with the belief that cattle are a source of resistant *Salmonella* for people (Varma et al., 2006; Silbergeld et al., 2008; Hoelzer et al., 2010). As most of our cattle isolates came from apparently healthy animals, drug-resistant *Salmonella* had the potential to enter the human food chain. However, the occurrence of AMR profiles unique to ST and SN of cattle origin and not seen in temporally related human clinical cases indicates these profiles appear to be circulating in cattle populations only. In addition, the common profiles were mainly not shared and/or had different abundances. For example, the two predominant profiles in ST from cattle, AKSSuT and AKSSuTAmcCaz, occur at low frequencies in ST from humans.

We used Hill's numbers to assess AMR diversity along a continuum depending on the relative contribution of rare versus common profiles (Hill, 1973; Mather et al., 2012). Of the three serovars common to humans and cattle, SM was the only one in which AMR diversity was greater in human versus cattle isolates across all diversity measures used. In ST and SN, AMR profile richness was greater in isolates obtained from humans than cattle. The greater profile richness in human isolates could be attributed to exposure to diverse environments and behaviours such as eating foods from diverse geographical origins, contact with pets and travel (Hoelzer et al., 2011; Scallan et al., 2011; Mather et al., 2012). Another explanation for the high AMR richness in human source *Salmonella* is evolution and maintenance of AMR across complex environments with differential and diverse selection (including anti-microbial selection) when compared to dairy cattle environments which are more uniform across farms. For instance, the adhesin gene in *Escherichia coli* from the genitourinary tract (sink) shows increased diversity due to richness instead of evenness compared to those from the large intestines (source), and the authors conclude this pattern is consistent with continuous emergence and extinction of alleles adaptive in a sink environment (Chattopadhyay et al., 2007). The high number of rare AMR profiles in human isolates suggests human communities or environments may favour continuous evolution and extinction of AMR phenotypes.

When measures which place more weight on common (Simpson's index) or predominant (Berger-Parker) profiles were used, AMR diversity in ST and SN was slightly higher in the cattle isolates. This finding could be attributed to the fact that in contrast to humans, cattle are kept in herd or farm settings with uniform exposures to resistant bacteria and resistance determinants circulating in their environment. This creates an environment that supports few but dominant stable AMR profiles. A study that examined herd-level resistance reported a median of two AMR patterns (pan susceptible and resistant) typically circulates

within a farm although a single pattern may often be dominant (Ray et al., 2007).

Among serovars common to cattle, AMR diversity was high in SD and ST followed by SN, and these serovars were associated with important MDR phenotypes. Conversely, SM and SS were predominantly pan susceptible. Our findings are consistent with other studies that found differences in resistance in serogroups or serovars from similar cattle herds (Edrington et al., 2004; Ray et al., 2007). It appears some serovars may be less efficient in the acquisition and/or maintenance of resistance genes and traits. The cattle isolates are under similar general management constraints, and serovars have remarkably unique patterns and unique range of AMR from mainly pan susceptible to highly resistant. While most cattle serovars had low resistance to both nalidixic acid (quinolone) and ceftazidime (third-generation cephalosporin), the occurrence of 3% resistance to these clinically important classes of drugs in SD is of concern.

When serovars common to humans were compared, diversity was highest in ST followed by SN and SE. Assuming serovars common to humans are exposed to similar drug, detergent and heavy metal selection pressures and other factors related to human behaviours, we would expect to find similar AMR diversity and resistance patterns in *Salmonella* serovars isolated from humans, but this was not the case.

The greater AMR diversity in clinical compared to non-clinical cattle *Salmonella* may be due to anti-microbial selection pressure in diseased cattle that received treatment or an AMR association with increased virulence. Greater AMR diversity has been reported in ST DT104 from disease-associated pig herds than asymptomatic herds, and the authors argued anti-microbial selection pressure might be less in the pigs carrying asymptomatic isolates than in disease-associated herds where treatment is carried out (Peron et al., 2007). No information regarding treatment was provided with our clinical isolates.

It is logical to assume that if *Salmonella* from cattle are a main source of resistance for human *Salmonella*, then the profiles in humans would be a subset of what is found in cattle. When we assessed whether the resistance phenotypes in ST, SN and SM from humans and cattle were part of a single mixed community of resistance phenotypes, our data showed that the number of resistance profiles exclusive to humans was higher than expected, those exclusive to cattle were as expected, while the number of profiles common to humans and cattle was fewer than expected. Our results indicate that although there are profiles found in isolates from both host populations, ST, SN and SM from humans and cattle also have unique resistance phenotypes. These findings are consistent with a study that compared phenotypic resistance in ST DT104 from humans and animals in Scotland. The authors concluded that local animals,

predominantly cattle, may not be the major source of resistance for humans for this bacterium (Mather et al., 2012). The fewer number of profiles common to humans and cattle than expected may suggest that resistance associated with *Salmonella* is mainly confined to their source populations with modest amount of sharing. A partial explanation for this observation is that *Salmonella* mainly circulates within each population as a consequence of movement and persistence. A study utilizing bovine non-clinical isolates demonstrates resistant *Salmonella* can persist as unobserved infections in cattle, and cattle movement is a risk factor for herd infection (Adhikari et al., 2009). There is some evidence for *Salmonella* circulation within the human population. For instance, a study culturing human source wastewater influent consistently recovered *Salmonella* at each sampling time. At each sampling, multiple serovars were recovered, geographical differences in serovar abundance were detected, and recovered serovars were more diverse than those associated with clinical cases (Berge et al., 2006). Another study, using human wastewater influent, detected *Salmonella* Heidelberg before, during and after an outbreak in a small closed community (Vincent et al., 2007). In that survey, *S. Heidelberg* was detected before the outbreak and the authors suggested that it was circulating in the community as undetected infection and possibly became an outbreak through an infected food handler. The higher number of observed profiles in human source *Salmonella* than expected may also reflect global food sourcing and diversity of food from non-bovine sources such as swine, poultry and seafood (Varma et al., 2006; FDA, 2010) that introduce diverse AMR *Salmonella* into the human population.

In this study and others (Mather et al., 2012), lack of AMR data from diverse foods consumed by humans makes it difficult to examine AMR diversity seen in humans. Future analysis of long-term and comprehensive data sets such as those collected by NARMS could resolve some of the controversies defining sources of AMR diversity and dissemination of AMR between humans and food animals. NARMS has conducted surveillance on AMR in enteric bacteria from food animals, foods and humans in the United States since 1996. The United States Department of Agriculture characterizes AMR in animal carcasses at slaughter, the Food and Drug Administration is responsible for characterizing resistance in isolates from retail meats, and CDC characterizes resistance in human clinical cases. Currently, NARMS data are presented as resistance to individual anti-microbials, and resistance to multiple drugs is portrayed in terms of four phenotypes (ACSSuT, ACSSuT-AuCx, ACT/S and CxNal). To conduct similar diversity analyses such as those presented here, information on all resistances demonstrated by each isolate within the NARMS data would be required.

Conclusions

There were similarities and differences in AMR phenotypic structure among human and cattle isolates as well as serovar-specific AMR structures within source. Some AMR profiles in the three common serovars (ST, SN and SM) were similar, but also unique profiles were observed in each host population. In addition, AMR profile richness was greater in the common serovars from humans, although both source data sets were dominated by relatively few profiles. Also, AMR diversity was greater in clinical compared to non-clinical cattle *Salmonella*, and this may be due to anti-microbial selection pressure in diseased cattle that receive treatment or an AMR association with increased virulence. ST and SN from cattle had greater probability of resistance to multiple classes of anti-microbials than ST and SN from humans. While this could be consistent with the notion that cattle are a source of resistance for people, occurrence of these profiles as unique to cattle and not seen in temporally related human isolates indicates these profiles may be circulating in cattle only. Our findings suggest AMR diversity in humans likely has multiple origins; hence, multiple control points may be beneficial.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Antimicrobial resistance profiles observed in *Salmonella* Typhimurium from humans and cattle in Northwestern United States, 2004–2011.

Table S2. Antimicrobial resistance profiles in *Salmonella* Newport from humans and cattle in Northwestern United States, 2004–2011.

Table S3. Antimicrobial resistance profiles in *Salmonella* Montevideo from humans and cattle in Northwestern United States, 2004–2011.

Table S4. Diversity of antimicrobial resistance profiles in the five most common *Salmonella* serovars in humans.

Table S5. Diversity of antimicrobial resistance profiles in the five most common *Salmonella* serovars in cattle.

Fig. S1. Effective number of AMR profiles in (a) *Salmonella* Typhimurium, (b) *Salmonella* Newport and (c) *Salmonella* Montevideo from humans and cattle and 95% CI in Northwestern United States, 2004–2011.

Fig. S2. Frequency distributions of the expected number of antimicrobial resistance profiles in *Salmonella* Newport found in (a) humans only; (b) cattle only; and (c) common to humans and cattle in Northwestern United States, 2004–2011.