



Antibiotic resistance in *Salmonella enterica* isolated from dairy calves in Uruguay

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Abstract

Salmonella enterica is an important animal and human pathogen that can cause enteritis and septicemia in calves. Generally, antibiotics are prescribed for the treatment of salmonellosis in dairy calves. Here, we report the isolation of antibiotic resistant *S. enterica* serotypes from calves, including multidrug-resistant isolates. A total of 544 faecal samples from live healthy and diarrheic dairy calves from 29 commercial dairy farms and organ samples from 19 deceased calves that succumbed to salmonellosis in 12 commercial dairy farms in Uruguay were processed for selective *S. enterica* culture. In total, 41 isolates were serotyped, and susceptibility to 14 antibiotics, from 9 classes of compounds, was evaluated by disk-diffusion test. The minimum inhibitory concentration (MIC) was determined by microdilution. *Salmonella* Typhimurium was the most frequent serotype, followed by *S. Dublin* and *S. Anatum*. Whether determined by diffusion assay or microdilution, resistance to tetracycline, streptomycin and ampicillin were the most frequently pattern found. Based on MIC, 5 isolates were resistant to at least one antibiotic, 21 were resistant to 2 antibiotics, and 14 were multidrug-resistant (resistant to at least one antibiotic in 3 different categories of antibiotics). Eleven different resistance patterns were found. Multidrug resistance in *S. enterica* is a concern for animal and public health not only because of its zoonotic potential but also due to the possibility of transfer resistance determinants to other bacterial genera. This represents the first report of the antibiotic resistance in *S. enterica* in dairy farms in Uruguay.

Keywords *Salmonella* Typhimurium · *Salmonella* Dublin · *Salmonella* Anatum · Antibiotic resistance · Dairy calves

Salmonella enterica is an important pathogen that affects a wide range of animal species and humans. More than 2500 serotypes are documented within *Salmonella* spp. but only a few affect cattle [1]. In this species, *Salmonella* Dublin and *Salmonella* Typhimurium are by far the most frequent serotypes [2, 3], and can cause enteritis, diarrhoea and septicemia [4, 5].

Salmonellosis in calves is often treated with antibiotics and β -lactams, and sulphonamides are recommended in cases of septicemia [6, 7]. When resistance to these antibiotics is suspected or confirmed, quinolones are the next therapeutic option, but emergence of resistance to this group of antibiotics has also been reported [8]. Moreover, antibiotics have been used as feed additives for decades [9, 10], which has promoted the occurrence and selection of resistant and multidrug-resistant (MDR) strains, affecting the therapeutic performance of antibiotics in both animals and humans [9]. The World Health Organization (WHO) recommendations point toward the preservation of antibiotics for human use, reducing their use in animals, and the promotion of sanitation and hygienic practices to avoid disease and, therefore, the use of antibiotics [10].

Multidrug resistance is an emerging issue worldwide, and the transference of resistance mechanisms and the potentially zoonotic pathogens presence bound not only the therapeutic options in animals, but also in humans [11]. The main objective of this work is to report the antibiotic resistance profiles of *S. enterica* isolated from diarrheic and non-diarrheic calves, and from deceased dairy calves diagnosed at postmortem with salmonellosis in commercial dairy farms in Uruguay.

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Salmonella enterica isolation was attempted from two different sources. Firstly, individual faeces were taken directly from the rectal ampule of 544 live calves ≤ 30 days old, from 29 different dairy farms in Uruguay from March to November 2016. In this survey, 282 calves were non-diarrheic (healthy) and 262 were diarrheic based on the faecal score [12, 13]. Secondly, from March 2016 to October 2017, various organs from 19 autopsied calves ≤ 60 days of age, that had succumbed to salmonellosis in commercial dairy farms in Uruguay, were processed. These animals were from 12 different fatal outbreaks of spontaneous salmonellosis, submitted to the diagnostic service of the “Plataforma de Investigación en Salud Animal”, INIA- La Estanzuela, Colonia, Uruguay.

Organs and faecal samples were aerobically cultured in tetrathionate broth (37 °C, 24 to 48 h). After this selective enrichment, 100 μ l of grown media were plated onto xylose lysine deoxycholate (XLD) agar, *Salmonella*-suspect colonies were selected, and identified to the species level (*S. enterica*) by routine biochemical tests [14]. To determine the *S. enterica* serotype for each isolate, the Kauffman-White-Le Minor serotyping scheme was performed at the bacteriology service of the “Instituto de Higiene, Facultad de Medicina, UdelaR”, in Montevideo, Uruguay, following a previously described procedure [1].

Antimicrobial susceptibility profiles were assessed using the disk diffusion assay following the procedures outlined by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [15–17]. The agar disk diffusion is an accessible, low-cost and reproducible technique that provides rapid results. It is very widespread and easily available in most veterinary diagnostic laboratory. Commercial disks (Oxoid) containing fourteen antibiotics covering nine antimicrobial classes were employed, as follows: β -lactams -ampicillin (10 μ g), amoxicillin-clavulanic acid (20 μ g/10 μ g), cefotaxime (30 μ g); sulphonamide-diaminopyrimidine-sulfamethoxazole/trimethoprim (23.75/1.25 μ g); quinolones -nalidixic acid (30 μ g), ciprofloxacin (5 μ g), enrofloxacin (5 μ g); phenicol -chloramphenicol (30 μ g); aminoglycosides -streptomycin (10 μ g), gentamicin (10 μ g); tetracyclines -tetracycline (30 μ g); polypeptides -fosfomicin-trometamol (200 μ g); nitrofurans -nitrofurantoin (300 μ g); and macrolides -azithromycin (15 μ g). *Escherichia coli* ATCC 25922 and *E. coli* ATCC 35218 were used for quality control. *Salmonella enterica* isolates were classified as susceptible: sensitive (S); or non-susceptible: intermediate (I) or resistant (R) to the antimicrobial compound tested according to EUCAST breakpoints [17], except for nalidixic acid, enrofloxacin, streptomycin, tetracycline and azithromycin, for which CLSI guides were followed, as there were no EUCAST breakpoints described. [15, 16].

Additionally, for every *S. enterica* isolate, the minimum inhibitory concentration (MIC) profiles were determined by

the broth microdilution method, using a Gram-negative Sensititre plate (CMV3AGNF, Thermo Scientific, USA). The determination of MIC is the gold-standard methods for interpret the antimicrobial resistance. The panel of 14 antimicrobials tested included amoxicillin-clavulanic acid, ampicillin, azithromycin, cefoxitin, ceftiofur, ceftriaxone, chloramphenicol, ciprofloxacin, gentamicin, nalidixic acid, streptomycin, sulfisoxazole, trimethoprim-sulfamethoxazole and tetracycline. The MICs were determined, and breakpoints were interpreted based on EUCAST guidelines where possible [17]. For nalidixic acid, sulfisoxazole, tetracycline, azithromycin, ceftiofur and cefoxitin CLSI guidelines were followed [15, 16] and for streptomycin, NARMS breakpoints were considered [18]. *Escherichia coli* ATCC 25922 was used as a quality control strain. According to the MIC, isolates were classified as multidrug-resistant (MDR) when they were resistant to at least one antibiotic in three or more antimicrobial classes [19].

To ordinate the antimicrobial susceptibility profiles for each isolate, and to infer similarities among them, a principal component analysis (PCA) was performed using the PAST software version 3.18 [20]. For this exploratory analysis, the diameters of the inhibition halos measured in mm were used as inputs.

Salmonella enterica was isolated from 22 faeces, from 16 diarrheic and 6 non-diarrheic calves (Table S1). These samples were from 9 of the 29 (31%) farms studied. In 8 of these farms, *S. Typhimurium* was the identified serotype, while *S. Anatum* was isolated in only one (3%) (Table S1). Also, 19 isolates were obtained, one from each calf from the 12 different mortality outbreaks. In this group, *S. Typhimurium* was isolated from 16 deceased calves in 10 outbreaks and *S. Dublin* from 3 calves in 2 outbreaks (Table S1). For further antimicrobial susceptibility assays, one isolate of each calf was selected (17 from mesenteric lymph node, one from the liver and one from intestine).

Based on the agar disk diffusion method, the most widespread resistance was against tetracycline (87.8%, 36/41 isolates), streptomycin (85.4%, 35/41 isolates) and ampicillin (22%, 9/41 isolates) (Table 1). The PCA analysis allowed to group the isolates according to their resistance-susceptibility profiles. Three different groups were formed corresponding to the three detected serotypes. In addition, the most resistant isolates were located in the left quadrants (Fig. 1). The three first principal components explained more than 70% of the variability observed.

The determination of MIC showed that antimicrobial resistance was a common feature among the isolates; 92.7% (38/41 isolates) were resistant to tetracycline and 80.5% (33/41 isolates) to streptomycin (Table 2). In addition, resistance to ampicillin 24.4% (10/41) and ciprofloxacin 22% (9/41) was observed. Five isolates were resistant to at least one antibiotic and 21 were resistant to 2 antibiotics. Also, 14 isolates were

Table 1 Number of *S. enterica* isolates (total = 41) susceptible, resistant or with intermediate susceptibility to 14 antibiotics by serotype

Antibiotics	Serotype								
	Typhimurium			Dublin			Anatum		
	S	I	R	S	I	R	S	I	R
AMP	28	0	7	3	0	0	1	0	2
AMC	32	0	3	3	0	0	1	0	2
CTX	34	0	1	3	0	0	2	1	0
C	34	0	1	3	0	0	3	0	0
NA	15	2	5	3	0	0	3	0	0
CIP	12	22	1	2	1	0	0	3	0
ENR	14	2	0	2	0	1	3	0	0
SXT	35	0	0	3	0	0	1	0	2
S	1	1	33	2	1	0	0	1	2
CN	34	1	0	3	0	0	3	0	0
TE	1	0	34	3	0	0	1	0	2
AZM	35	0	0	2	0	1	3	0	0
FOT	35	0	0	3	0	0	3	0	0
F	26	8	1	3	0	0	2	1	0

AMP, ampicillin; AMC, amoxicillin-clavulanic acid; CTX, cefotaxime; C, chloramphenicol; NA, nalidixic acid; CIP, ciprofloxacin; ENR, enrofloxacin; SXT, trimethoprim-sulfamethoxazole; S, streptomycin; CN, gentamicin; TE tetracycline; AZM, azithromycin; FOT, fosfomycin-trometamol; F, nitrofurantoin; S, susceptible; I, intermediate; R, resistant according to the EUCAST and CLSI [15–17]

classified as MDR [19], being resistant to at least three and up to six antimicrobial compound categories (Table 3). Eleven of these MDR isolates were *S. Typhimurium* and 3 were *S. Anatum*. No MDR was detected in *S. Dublin* isolates. The MDR isolates showed 11 different resistance pattern profiles being S/TE/CIP the most frequent combination, with six isolates (Table 3).

In this study, *S. Typhimurium* was isolated from calves with diarrhoea, septicaemia and mortality, as reported in previous works [7, 21]. The serotype *S. Anatum* was only isolated from faecal samples from only one dairy farm (Table S1). These samples were from two diarrhoeic and one non-diarrhoeic calves. *Salmonella Anatum* has been isolated from dairy and beef calves [22, 23] but the role of this serotype as a causative agent of diarrhoea in neonate calves still needs to be elucidated. Recently, a human salmonellosis outbreak was reported due to food contamination with this serotype [24]. *Salmonella Dublin* was only isolated from 3 autopsied calves and was associated to the cause of death based on the pathologic examination (data not shown). The affected calves, around 60 days old, were from 2 different dairy farms and were suffering mild diarrhoea and most of them died (data not shown). This serotype, adapted to cattle, generally causes septicaemia in calves and recently had been reported as a causative agent of urocystitis and ureteritis [25–27].

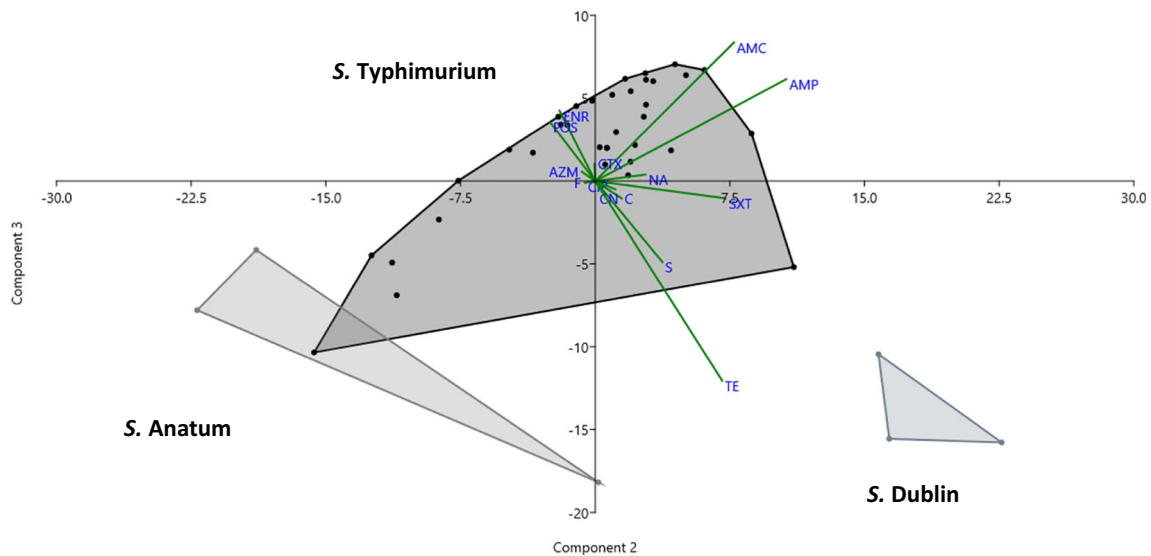


Fig. 1 Principal components analysis (PCA) biplots. The graphic was constructed with the diameter of the inhibition halos in mm for 14 antimicrobials of the 41 tested *Salmonella enterica* isolates. Components 2 and 3 are graphed. The different isolates of a same serotype (*S. Dublin*, *S. Anatum*, *S. Typhimurium*) are contained in one convex hull. The contribution of each variable (diameter of the inhibition

halo) to each component is graphed as a vector. Ampicillin, AMP; amoxicillin-clavulanic acid, AMC; cefotaxime, CTX; chloramphenicol, C; nalidixic acid, NA; ciprofloxacin, CIP; enrofloxacin, ENR; trimethoprim-sulfamethoxazole, SXT; streptomycin, S; gentamicin, CN; tetracycline, TE; azithromycin, AZM; fosfomycin FOS and nitrofurantoin, F

Table 2 MIC distribution for *S. enterica* isolated from calves ($n = 41$)

ATB ^a	Number of isolates with MIC ($\mu\text{g/mL}$) of														
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
AZM				0	0	0	0	2	32	5	2				
C								0	2	38	1	0			
FOX						0	0	29	9	2	0	1			
TE									3	0	1	37			
AXO					36	3	0	0	1	0	0	1	0		
AMC ^b							28	2	0	7	3	1			
CIP	20	11	1	0	2	5	1	0	1						
CN					0	31	4	4	0	2	0				
NA						0	0	2	29	3	4	3			
XNL				0	0	5	32	2	1	1					
FIS											0	1	2	38	0
SXT ^b				16	18	0	2	0	5						
AMP							29	2	0	0	0	10			
S								0	0	0	4	4	33		

Grey cells represent the concentration of each ATB in the Gram-negative Sensititre plate (CMV3AGNF, ThermoScientific, USA). Vertical black lines in each row represent the clinical breakpoint used [15–18]. Bold numbers are the concentration for each ATB. ^aATB antibiotic; AZM, azithromycin; C, chloramphenicol; FOX, ceftiofur; TE, tetracycline; AXO, ceftriaxone; AMC, amoxicillin/clavulanic acid (2:1); CIP, ciprofloxacin; CN, gentamicin; NA, nalidixic acid; XNL, ceftiofur; FIS, sulfisoxazole; SXT, trimethoprim/sulfamethoxazole; AMP, ampicillin; S, streptomycin. ^bFor AMC dilutions rank from 1/0.5 to 32/16 $\mu\text{g/mL}$; for SXT dilutions rank from 0.12/2.38 to 4/76 $\mu\text{g/mL}$.

Although in Uruguay enrofloxacin is a very used quinolone in veterinary medicine, the *Salmonella* isolates from this work showed low frequency of resistance. Tetracycline and streptomycin are two antimicrobials with extended use worldwide in veterinary medicine [11]. Resistance to both antibiotics can be transferred concurrently in conjugative plasmids [28]. All

MDR salmonellae were both tetracycline and streptomycin resistant (Table 3). Our results indicate that there is an association between resistances to these antibiotics, which might have a genetic basis. Additional molecular characterization of these strains is warranted.

Table 3 Antimicrobial resistance profiles of MDR-*S. enterica* isolates ($n = 14$)

Number of classes of antibiotics	Classes of antibiotics	Antibiotics	n
6	AG-T-Q-BL-PH-S	S-TE-CIP-FOX-AXO-AMC-C-SXT	1
4	AG-T-Q-BL	S-TE-CIP-AXO	1
	AG-T-BL-S	S-TE-AMP-SXT	3
	AG-T-Q-BL	S-CN-TE-NA-XNL	1
	AG-T-Q-BL	S-TE-NA-XNL	1
	AG-T-BL-S	S-TE-FOX-AMP-SXT	1
	AG-T-Q-BL	S-TE-CIP-AMP-AMC	1
	AG-T-Q-BL	S-TE-CIP-NA-AMP-XNL	1
3	AG-T-BL	S-TE-AMC	1
	AG-T-BL	S-TE-AMP-AMC	1
	AG-T-Q	S-TE-CIP	2

Antibiotic resistance classified according compounds categories, AG aminoglycosides; T tetracyclines; Q, quinolones; BL, β -lactams; PH, phenicols; S, folate pathway inhibitor. Antibiotic resistance classified according to single antibiotics: AMP, ampicillin; AMC, amoxicillin-clavulanic acid; FOX, ceftiofur; AXO, ceftriaxone; XNL ceftiofur; SXT, trimethoprim-sulfamethoxazole; NA, nalidixic acid; CIP, ciprofloxacin; C, chloramphenicol; S, streptomycin; CN, gentamicin; TE, tetracycline

As shown in Fig. 1, the three different *S. enterica* serotypes grouped separately, with *S. Typhimurium* isolates showing an ample diversity of antibiotic resistance profiles. This diversity is probably biased by the greater representation of this serotype in the collection of isolates analysed in this study. Despite of this bias, the antimicrobial resistance profiles seem to be influenced by the serotype. This has been observed in previous works [29, 30], where serotypes Typhimurium and Dublin were more resistant in cattle. In opposition, *S. Dublin* isolates in this study were the least resistant representatives of the collection, being susceptible to most of antibiotics assayed (Table 1, Fig. 1).

Several isolates, distributed in the left quadrants of the PCA graph (Fig. 1), were resistant to more than three classes of antibiotics. Resistance to ampicillin, amoxicillin-clavulanic acid, trimethoprim/sulfamethoxazole, tetracycline and streptomycin explains most of the grouping observed in Fig. 1.

As mentioned, MDR was common, and 31.4% of the *S. Typhimurium* isolates were included in this subset, while the three *S. Anatum* isolates were MDR, showing resistance to four antimicrobial classes. The occurrence of MDR bacteria has increased in the last years, [31] and worldwide public concern in this topic has been established [32]. *Salmonella enterica* infections have an important impact on animal and public health as a food-borne pathogen [33]. Misuse of

antibiotics and subtherapeutic dosage had promoted pressure and selection on bacteria and transference of resistance determinants [34].

The three serotypes described in dairy calves in this study have also been reported in humans, highlighting their zoonotic potential. In South America, *S. Typhimurium* has been isolated from food-borne cases and resistance to β -lactams has been reported [35, 36]. Additionally, *S. Dublin* can cause invasive infection in humans and has been reported in the same geographic region of the isolates of the present study [37].

In this study, 34% of salmonellae isolated from diseased and healthy dairy calves showed MDR profiles, and all of them had the putative potential to infect humans. The diversity of antibiotic resistance profiles in this collection of isolates recovered in a relatively short period of time highlights the importance of this issue. Probably multiple diverse antibiotic resistance mechanisms coexist and represent a potential of transference to other bacteria. Efforts should be done to control MDR dissemination focusing in the implications for public health.

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Data availability statement The datasets generated during and/or analysed during the current study are available from the corresponding author on request.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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