FOODBORNE PATHOGENS AND DISEASE
Volume 14, Number 2, 2017

DOI: 10.1089/fpd.2016.2228

# Antimicrobial Resistance in Nontyphoidal *Salmonella* Isolated from Human and Poultry-Related Samples in Brazil: 20-Year Meta-Analysis

Daiane Voss-Rech,[1,2] Luciana Potter,[3] Clarissa Silveira Luiz Vaz,[2] Daniela Isabel Brayer Pereira,[4] Luís Antonio Sangioni,[1] Águeda Castagna Vargas,[1] and Sônia de Avila Botton[1,*]

## Abstract

Nontyphoidal *Salmonella* are one of the leading causes of foodborne diseases in the world. As poultry products are recognized as main sources of human salmonellosis, nontyphoidal *Salmonella* control has become a global issue for the poultry industry. The increasing antimicrobial resistance in poultry-related nontyphoidal *Salmonella* serovars is a global matter of concern. By monitoring the evolution of antimicrobial resistance, alternative treatments can be identified and possible restrictions in the treatment of systemic human salmonellosis foreseen. A meta-analysis was conducted to assess the profile and temporal evolution of the antimicrobial resistance of nontyphoidal *Salmonella* of poultry and human origin in Brazil, isolated in the period from 1995 to 2014. Four databases were researched; twenty-nine articles met the eligibility criteria and were included in the meta-analysis. In the nontyphoidal isolates of poultry origin, the highest levels of antimicrobial resistance were verified for sulfonamides (44.3%), nalidixic acid (42.5%), and tetracycline (35.5%). In the human-origin isolates, the resistance occurred mainly for sulfonamides (46.4%), tetracycline (36.9%), and ampicillin (23.6%). Twenty-two articles described results of antimicrobial resistance specifically for *Salmonella* Enteritidis, also enabling the individual meta-analysis of this serovar. For most antimicrobials, the resistance levels of *Salmonella* Enteritidis were lower than those found when considering all the nontyphoidal serovars. In the poultry-origin isolates, a quadratic temporal distribution was observed, with reduced resistance to streptomycin in *Salmonella* Enteritidis and in all nontyphoidal serovars, and a linear increase of resistance to nalidixic acid in *Salmonella* Enteritidis. In the human-origin isolates, a linear increase was identified in the resistance to nalidixic acid in *Salmonella* Enteritidis and in all the nontyphoidal isolates, and to gentamicin in *Salmonella* Enteritidis. Continuous monitoring of the development and spread of antimicrobial resistance could support the measurement of the consequences on poultry and human health.

**Keywords:** antimicrobial resistance, *Salmonella,* human, poultry, meta-analysis, systematic review

## Introduction

*Salmonella* is an enterobacteria found in several species of animals and one of the main microorganisms transmitted by food worldwide. It is responsible for the second most reported zoonosis in humans in Europe (EFSA, 2015b) and the most reported in the United States (CDC, 2014). *Salmonella enterica* subspecies *enterica* is the most frequently involved and comprises >1500 serovars (EFSA, 2015b). More broadly speaking, the *Salmonella* genus can be split into two large groups: typhoidal, which includes the host-restricted serovars, and the nontyphoidal, comprising the other host ubiquitous serovars (Hur *et al.*, 2012). Infection by nontyphoidal *Salmonella* can present different clinical manifestations in humans. Gastroenteritis is the most common manifestation and most cases are self-limiting (Jasson

[1]Programa de Pós-Graduação em Medicina Veterinária (PPGMV), Departamento de Medicina Veterinária Preventiva, Centro de Ciências Rurais (CCR), Universidade Federal de Santa Maria (UFSM), Santa Maria, Brazil.
[2]Laboratório de Sanidade e Genética Animal, Embrapa Suínos e Aves, Concordia, Brazil.
[3]Departamento de Zootecnia, CCR, UFSM, Santa Maria, Brazil.
[4]Departamento de Microbiologia e Parasitologia, Instituto de Biologia (IB), Universidade Federal de Pelotas (UFPel), Pelotas, Brazil.
*Adviser.

and Butaye, 2012). However, in immunocompromised elderly and child patients, or in cases of serious systemic infection, antimicrobial treatment is essential. In this context, broad-spectrum fluoroquinolones and cephalosporins are fundamental for the treatment of salmonellosis, and the emergence of antimicrobial resistance directly affects treatment evaluation (Ruiz *et al.*, 2004; EFSA, 2015a).

Antimicrobials have been key in controlling bacterial infections; however, over the course of time, use of these drugs has promoted the selection of resistant bacteria. The choice of unsuitable antimicrobials, dosage, and treatment times has fomented the emergence of resistant strains. The spread of resistant microorganisms has been supported by inefficient infection control measures, improper sanitary conditions, and inappropriate manipulation of foodstuffs (WHO, 2015). Contaminated poultry products are considered important sources of human *Salmonella* infection. As a rule, poultry colonized by nontyphoidal *Salmonella* do not develop clinical signs of illness and do not require antimicrobial treatment, but they do offer fertile conditions for the bacteria to disseminate in the flock (EFSA, 2015a). In this condition, the bacteria remain under the selective pressure of any other antimicrobial that is administered.

Brazil is the world's leading exporter of chicken meat, and a portion of its table eggs production is sold to foreign markets (ABPA, 2015), this is why the impact of antimicrobial resistance could have international reach. Therefore, epidemiological surveillance of microorganisms resistant to antimicrobials is essential to gather information about the magnitude and trends of such resistance, allowing for alternative treatments to be planned and identified and the possible limitations in the treatment of severe cases of salmonellosis to be foreseen. Several studies about antimicrobial resistance in *Salmonella* have been independently accomplished in Brazil, representing different geographic areas and periods of time (Wilson, 2004; Oliveira *et al.*, 2005, 2012; Vaz *et al.*, 2010; Campioni *et al.*, 2012, 2014; Voss-Rech *et al.*, 2015). Consequently, the results obtained in each study are variable and hinder an all-encompassing interpretation. In such cases, meta-analysis represents an important tool to support retrospective studies into antimicrobial resistance. Integrated analysis of data from previous studies can allow one to adopt a more realistic perspective of the antimicrobial resistance of *Salmonella* spp. and its temporal evolution in Brazil. This information is important for establishing strategies to prevent the emergence and spreading of resistant strains in the country. We, therefore, carried out a systematic review and meta-analysis study with the aim of evaluating the profile and temporal evolution of the antimicrobial resistance of nontyphoidal *Salmonella* from humans and poultry over the past 20 years in Brazil.

## Materials and Methods

### *Search strategy*

To obtain the data to be included in the research, an extensive systematic review of the literature was performed to identify the studies that have assessed the antimicrobial resistance of *Salmonella* spp., published between January 1995 and May 2015. This review was conducted in four stages: identification, screening, eligibility, and inclusion, as recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—PRISMA (Moher *et al.*, 2009). The following online databases were consulted: Web of Science, PubMed, SciELO, and Science Direct. The keywords searched for in the articles included (''antimicrobial resistance'' or ''microbial resistance'' or ''bacterial resistance'' or ''resistance pattern'' or resistance or susceptibility) and *Salmonella* and Brazil or Brasil.

### *Study selection*

The initial selection prioritized the identification of articles related to the study scope, based on the title and abstract. All selected articles were read in full for a second selection stage, in accordance with the following eligibility criteria: (1) isolated in Brazil, (2) isolated from poultry and/or human origin, (3) isolated between 1995 and 2014, (4) number of isolates and year of isolation identified, (5) results separated by origin, (6) not directed at multiresistance, and (7) employed the disk diffusion susceptibility test. Furthermore, the references cited in the selected articles were also analyzed and included in the study, when pertinent. The information extracted from the articles was systematized in a spreadsheet (Microsoft Excel, 2010). Studies that present data from different years separately were included in the database as different observations. For articles in which the results of multiple years were presented together, the average year of the period was considered.

### *Quality assessment*

The studies included in the database were categorized by quality, in accordance with the following set of criteria: informed the criterion for interpreting zones of inhibition, used a standard strain for quality control of the tests, employed the international methodology approved by the Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST), and evaluated >20 nontyphoidal *Salmonella* isolates. The articles received a score from 0 to 4 according to the number of criteria met.

### *Statistical analysis*

The data were analyzed using the statistical software SAS, version 9.4. The antimicrobial resistance of the nontyphoidal *Salmonella* isolates was assessed in function of the percentage of resistance by serovar and the origin. Resistance against the most commonly used antimicrobials was compared, for both humans and poultry. The comparisons were made by means of the Kruskal–Wallis test and, when any differences were found between antimicrobials, the Bonferroni test was applied to compare the mean averages.

Regression analysis was conducted to assess the temporal evolution of the antimicrobials, in which the choice of the models was based on the significance of the linear, quadratic, and cubic coefficients, using the Student's *t*-test at 5% probability. This analysis only considered those antimicrobials that were assessed for at least five different years. For regression analysis, square root transformation was applied to the antimicrobials that failed to present normality. The temporal distributions graphs of the antimicrobial resistance were generated by plotting the level of resistance of each observation.

To classify the levels of antimicrobial resistance, the following parameters were used: rare, <0.1%; very low, 0.1% to 1%; low, >1% to 10%; moderate, >10% to 20%; high, >20% to 50%; very high, >50% to 70%; extremely high, >70% (EFSA, 2015b).

## Results

### Systematic review

The systematic review of the literature process is presented in Figure 1. Initially, 473 articles were identified, of which 29 met all the eligibility criteria and were included in the meta-analysis. Of those, 17 articles assessed nontyphoidal *Salmonella* isolated from poultry, 8 from humans, and 4 from both humans and poultry (Table 1).

### Quality assessment

Of those articles included in the meta-analysis, 22 articles (75.8%) met two or more pre-established criteria and were considered of higher quality. Only 4 articles clearly mentioned the criteria for interpreting zones of inhibition, 14 articles described the use of strains for quality control of the antimicrobial susceptibility tests, 24 articles used and/or informed the international methodology (CLSI or EUCAST), and 23 articles tested >20 isolates. All the categorized articles were analyzed, irrespective of the score achieved.

### Antimicrobial resistance

In the 29 articles included in the study, a total of 2119 nontyphoidal *Salmonella* isolates were assessed, 1272 of which were recovered from poultry (drag swab, cloacal swab, viscera, stools, meconium, carcasses, chicken portions, feed, broiler litter, and table eggs) and 847 recovered from humans (stools, blood, and other fluids). Of these, 22 articles showed positive results for *Salmonella* Enteritidis, enabling individual analysis of this serovar.

Forty-five different antimicrobials were tested for at least one of the studies included in the database. The most frequently tested antimicrobials were selected for meta-analysis: ampicillin, cefalotin, chloramphenicol, ciprofloxacin, enrofloxacin, gentamicin, nalidixic acid, norfloxacin, streptomycin, sulfonamides, trimethoprim/sulfamethoxazole, and tetracycline. Furthermore, cefotaxime and ceftriaxone were also included, because of their clinical importance. Analysis of these 14 antimicrobials comprised 556 observations. Observations corresponded to the frequency (%) of antimicrobial resistance found in each given article according to the source (poultry or human).

### Antimicrobial resistance in human isolates

In the nontyphoidal *Salmonella* isolates from human, the highest resistance levels were found against sulfonamides (46.4%), tetracycline (28%), and ampicillin (24.5%). For *Salmonella* Enteritidis, the highest resistance levels were

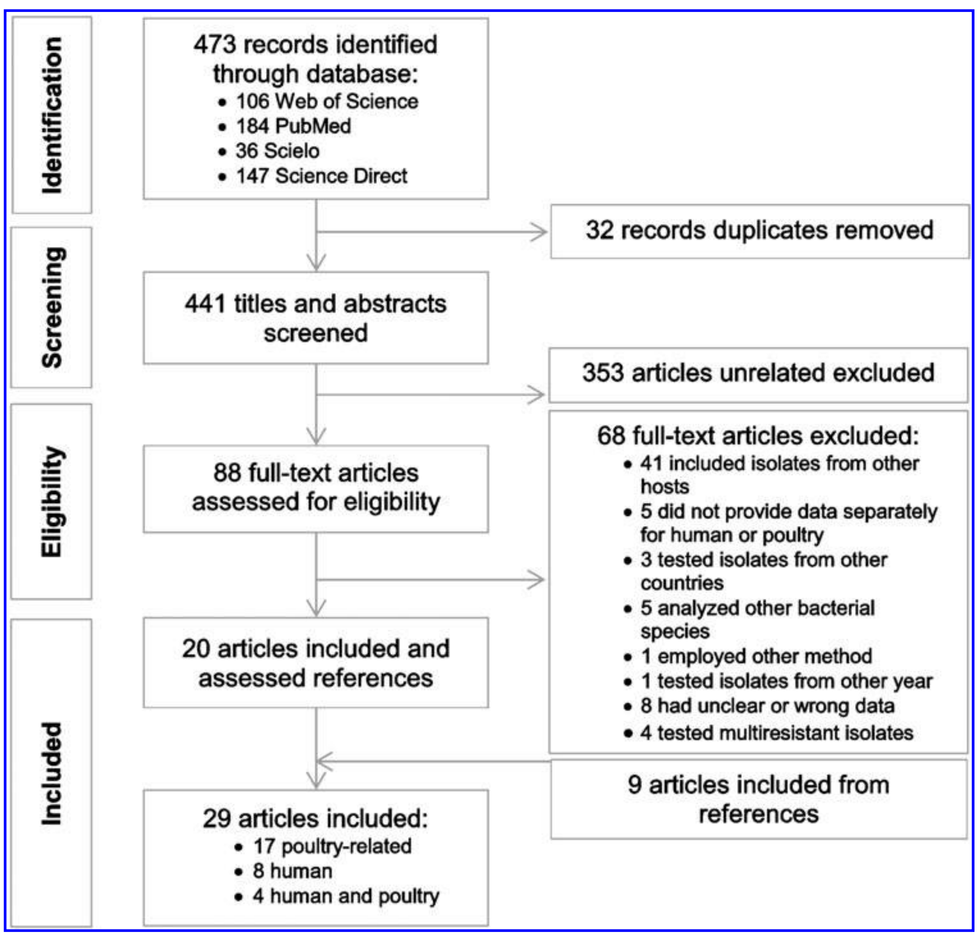


**FIG. 1.** Flow diagram of articles selection.

Table 1. Characteristics of the Selected Articles

| *Reference* | *Region of Brazil* | *Isolation period* | *Average year* | *Origin of isolate* | *No. of* Salmonella *Enteritidis* | *No. of other serovars* | *Total no. of isolates* |
|---|---|---|---|---|---|---|---|
| Peresi *et al.* (1998) | Southeast | 1993–1997 | 1995 | Poultry | 5 | 0 | 5 |
| | | | 1995 | Human | 18 | 0 | 18 |
| Santos *et al.* (2000) | Southeast | 1996–1997 | 1997 | Poultry | 29 | 19 | 48 |
| Oplustil *et al.* (2001) | South, Southeast, Mid-West, Northeast | 1998–1999 | 1999 | Human | 0 | 57 | 57 |
| Baú *et al.* (2001) | South | 1997–1998 | 1998 | Poultry | 10 | 3 | 13 |
| Castro *et al.* (2002) | Southeast | 1985–1999 | 1994 | Human | 128 | 0 | 128 |
| Delicato *et al.* (2004) | South | 1999–2000 | 2000 | Human | 14 | 7 | 21 |
| Wilson (2004) | NI | 1998–2000 | 1999 | Poultry | 15 | 11 | 26 |
| Oliveira *et al.* (2005) | South | 1995–1996 | 1996 | Human | 17 | 0 | 17 |
| | | | 1996 | Poultry | 43 | 0 | 43 |
| Cortez *et al.* (2006) | Southeast | 2003–2004 | 2004 | Poultry | 0 | 29 | 29 |
| Cardoso *et al.* (2006) | South | 1995–1996 | 1996 | Poultry | 80 | 0 | 80 |
| Fonseca *et al.* (2006) | Southeast | 1996–2001 | 1999 | Human | 0 | 35 | 35 |
| Pereira *et al.* (2007) | NI | 1999–2003 | 2001 | Human | 0 | 10 | 10 |
| Ribeiro *et al.* (2007) | South | 1996 | 1996 | Poultry | 21 | 4 | 25 |
| Ribeiro *et al.* (2008) | South | 1999 | 1999 | Poultry | 32 | 0 | 32 |
| | | 2000 | 2000 | Poultry | 28 | 0 | 28 |
| | | 2001 | 2001 | Poultry | 19 | 0 | 19 |
| Lima *et al.* (2009) | NI | 1994–2006 | 2000 | Poultry | 153 | 67 | 220 |
| Duarte *et al.* (2009) | Northeast | 2004 | 2004 | Poultry | 5 | 14 | 19 |
| Vaz *et al.* (2010) | South | 1995–2003 | 1999 | Poultry | 53 | 0 | 53 |
| | | 1995–1996 | 1996 | Poultry | 9 | 0 | 9 |
| | | 1995–1996 | 1996 | Human | 14 | 0 | 14 |
| Kottwitz *et al.* (2011) | NI | 2002–2006 | 2004 | Poultry | 7 | 0 | 7 |
| | | 2002–2006 | 2004 | Human | 4 | 0 | 4 |
| Medeiros *et al.* (2011) | South, Southeast, Mid-West, North, Northeast | 2004–2006 | 2005 | Poultry | 122 | 128 | 250 |
| Reis *et al.* (2011) | NI | 1990–1999 | 1995 | Human | 0 | 70 | 70 |
| | | 2000–2008 | 2004 | Human | 0 | 327 | 327 |
| Campioni *et al.* (2012) | Southeast | 1992–1995 | 1994 | Human | 11 | 0 | 11 |
| | | 1996–2000 | 1998 | Human | 22 | 0 | 22 |
| | | 2001–2005 | 2003 | Human | 21 | 0 | 21 |
| | | 2006–2010 | 2008 | Human | 12 | 0 | 12 |
| Oliveira *et al.* (2012) | South | 1999–2006 | 2003 | Human | 80 | 0 | 80 |
| Kottwitz *et al.* (2012) | South | 2002–2006 | 2004 | Poultry | 38 | 0 | 38 |
| Kottwitz *et al.* (2013) | South | 2003–2006 | 2005 | Poultry | 22 | 4 | 26 |
| Scur *et al.* (2014) | South | 2006–2010 | 2008 | Poultry | 16 | 102 | 118 |
| Campioni *et al.* (2014) | South, Southeast, Mid-West, Northeast | 2004–2010 | 2007 | Poultry | 60 | 0 | 60 |
| Albuquerque *et al.* (2014) | Northeast | 2013–2014 | 2014 | Poultry | 3 | 0 | 3 |
| Pandini *et al.* (2014) | South | 2010–2011 | 2011 | Poultry | 0 | 39 | 39 |
| Voss-Rech *et al.* (2015) | South | 2010–2011 | 2011 | Poultry | 0 | 82 | 82 |

NI, not informed.

against nalidixic acid (21.1%), ampicillin (13%), and tetracycline (9.4%) (Table 2).

It was found that the nontyphoidal serovars of human origin displayed a growing linear temporal evolution of the antimicrobial resistance against nalidixic acid ($p = 0.0004$, $R^2 = 80.5\%$) (Fig. 2A). For *Salmonella* Enteritidis, resistance against nalidixic acid ($p = 0.0005$, $R^2 = 88.5\%$) and gentamicin ($p = 0.0005$, $R^2 = 88.5\%$) also increased over the course of the years (Fig. 2B, C). No temporal effect was identified for any of the other antimicrobials.

### *Antimicrobial resistance in poultry isolates*

In the nontyphoidal *Salmonella* isolated from poultry, the highest levels of resistance were found for sulfonamides (44.3%), nalidixic acid (42.5%), and tetracycline (35.6%).

Table 2. Average Antimicrobial Resistance of Nontyphoidal *Salmonella* and *Salmonella* enteritidis Isolated from Poultry and Humans from 1995 to 2014

| | | *Poultry,* % (n) | | *Human,* % (n) | |
|---|---|---|---|---|---|
| *Class* | *Antimicrobial* | Salmonella *Enteritidis* | *All* | Salmonella *Enteritidis* | *All* |
| Aminoglycosides | Streptomycin | 20.3 (564) | 22.5 (1000) | 3.3 (177) | 12.4 (609) |
| | Gentamicin | 6.7 (643) | 6.6 (1141) | 3.8 (271) | 13.3 (323) |
| Cephems | Ceftriaxone | NA | NA | 0 (80) | 11.2 (189) |
| | Cefotaxime | 0 (82) | 12.1 (132) | NA | NA |
| | Cefalotin | 15.5 (275) | 24.2 (592) | 2.1 (243) | 12.6 (295) |
| Phenicols | Chloramphenicol | 1.3 (620) | 2.9 (1026) | 1.8 (327) | 15.2 (833) |
| Folate pathway inhibitors | Sulfonamide | 43.8 (478) | 44.3 (684) | NA | 46.4 (428) |
| | Trimethoprim/ sulfamethoxazole | 2.8 (459) | 8.2 (879) | 6.2 (324) | 14.8 (398) |
| Penicillin | Ampicillin | 9 (628) | 14.8 (1048) | 13 (327) | 24.5 (833) |
| Quinolones | Nalidixic acid | 48.2 (631) | 42.5 (989) | 21.1 (305) | 18.9 (350) |
| | Ciprofloxacin | 1.4 (609) | 1.4 (1060) | 0.7 (133) | 0.5 (242) |
| | Enrofloxacin | 9.6 (479) | 7.3 (876) | NA | NA |
| | Norfloxacin | 0.8 (254) | 1.8 (498) | NA | NA |
| Tetracycline | Tetracycline | 32 (638) | 35.6 (1136) | 9.4 (305) | 28 (747) |

All, nontyphoidal serovars, including *Salmonella* Enteritidis; NA, not analyzed (less than four articles have tested these antimicrobials).

For *Salmonella* Enteritidis, the antimicrobial resistance was more prominent against nalidixic acid (48.2%), sulfonamides (43.8%), and tetracycline (32%) (Table 2).

The antimicrobial resistance of the poultry nontyphoidal *Salmonella* serovars and *Salmonella* Enteritidis against streptomycin showed a quadratic temporal distribution ($p=0.029$, $R^2=33.9\%$) (Fig. 3A) and ($p=0.029$, $R^2=33.9\%$) (Fig. 3B), respectively. Furthermore, *Salmonella* Enteritidis displayed a growing linear temporal evolution against nalidixic acid ($p=0.015$, $R^2=35.3\%$) (Fig. 3C). No temporal effect was identified for any of the other antimicrobials. In general, *Salmonella* Enteritidis in isolation showed lower levels of antimicrobial resistance than all the nontyphoidal serovars ($p=0.036$).

## Discussion

In the isolates recovered from poultry, the highest levels of antimicrobial resistance were against sulfonamides, nalidixic acid, and tetracycline, respectively. For the human isolates, sulfonamides, tetracycline, and ampicillin showed the highest levels of resistance (Table 2). Similar results have also been found in other countries (Jasson and Butaye, 2012; Van *et al.*, 2012; CDC, 2015; EFSA, 2015a). These antimicrobial agents are among the oldest groups used in the treatment of bacterial infections, both in human and in veterinary medicine. The tetracyclines and sulfonamides were used as additives in animal feeds in Brazil until 1998, when their use was restricted to therapeutic purposes. However, these drugs still exert selection pressure on the microorganisms. Despite the high levels of resistance found, these antimicrobials are not among those considered critical for the treatment of human salmonellosis (WHO, 2011).

The resistance to nalidixic acid of the poultry isolates and the *Salmonella* Enteritidis isolates from humans was high (>20% to 50%) (Table 2) in the analyzed period; the resistance levels increased significantly over the course of time, for nontyphoidal *Salmonella* isolated both from humans and from poultry (Figs. 2A, B and 3C). The increased resistance

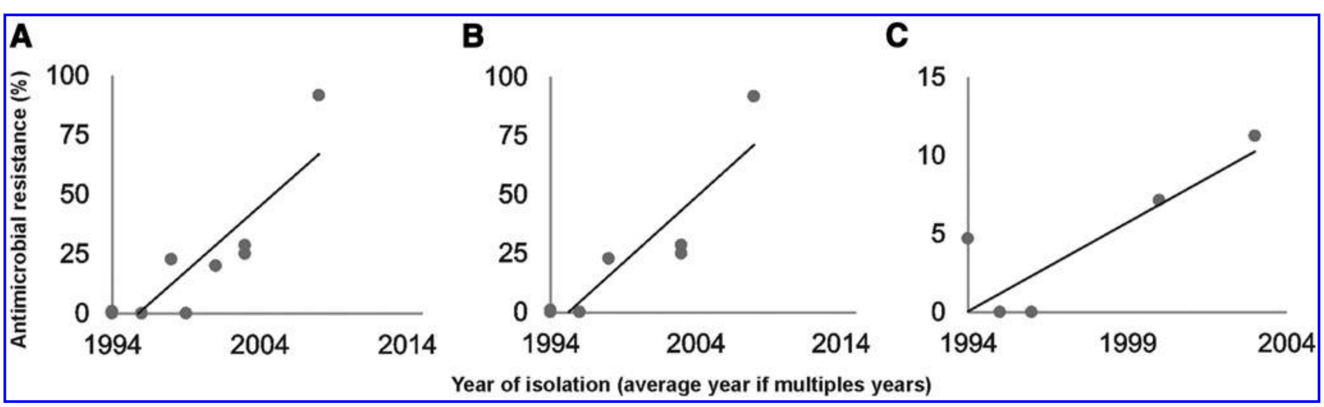


**FIG. 2.** Temporal evolution of the antimicrobial resistance of *Salmonella* of human origin. **(A)** Resistance of nontyphoidal *Salmonella* to nalidixic acid (*n*: 350; *a*: 7). **(B)** Resistance of *Salmonella* Enteritidis to nalidixic acid (*n*: 305; *a*: 5). **(C)** Resistance of *Salmonella* Enteritidis to gentamicin (*n*: 271; *a*: 6). *n*, number of isolates; *a*, number of articles.

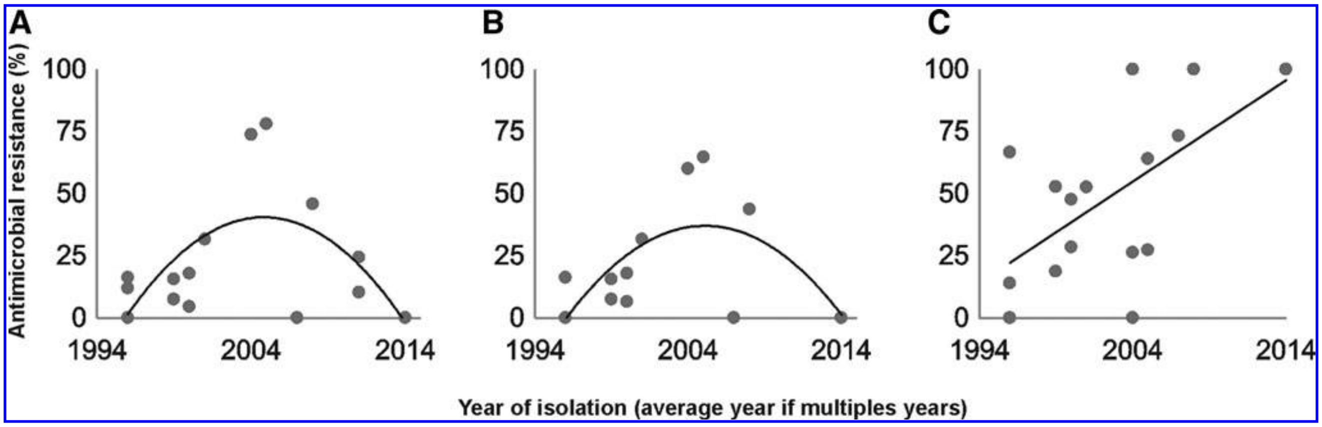


**FIG. 3.** Temporal evolution of the antimicrobial resistance of *Salmonella* of poultry origin. **(A)** Resistance of nontyphoidal *Salmonella* to streptomycin (*n*: 1000; *a*: 11). **(B)** Resistance of *Salmonella* Enteritidis to streptomycin (*n*: 564; *a*: 9). **(C)** Resistance of *Salmonella* Enteritidis to nalidixic acid (*n*: 631; *a*: 11). *n*, number of isolates; *a*, number of articles.

to quinolones has also been found in nontyphoidal *Salmonella* of human origin in the United States since 1996 (Stevenson *et al.*, 2007; WHO, 2015) and in China between 2009 and 2012 (Lai *et al.*, 2014). Isolates from poultry displayed an increase in resistance to nalidixic acid in Austria, Czech Republic, Germany, Poland, and Slovakia (EFSA, 2015a). For some antimicrobials, differences in the occurrence of resistance are observed between countries. However, this increase has been attributed to the broad use of these antimicrobials in both human and veterinary medicine (Angulo *et al.*, 2004; Stevenson *et al.*, 2007).

Despite nalidixic acid not being one of the critical antimicrobials in human treatment, the resistance of this drug in Enterobacteriaceae is generally correlated to reduced susceptibility to ciprofloxacin (Lai *et al.*, 2014). Ciprofloxacin, a second-generation quinolone (fluoroquinolone), is the medication of choice for treating serious cases of human salmonellosis. Treatments with fluoroquinolones have failed in patients infected with *Salmonella* spp. resistant to nalidixic acid (Dimitrov *et al.*, 2007; Stevenson *et al.*, 2007). This resistance is primarily attributed to point mutations in the gene regions where resistance to quinolones is determined, including the gyrase and topoisomerase IV genes (Cavaco *et al.*, 2009; EFSA, 2015a), as well as by active efflux mechanisms (Hur *et al.*, 2012). In this study, we found low resistance levels to ciprofloxacin, <1.5%, regardless of the origin of the isolates (Table 2). Low resistance levels to quinolones have been found in nontyphoidal *Salmonella* of human origin in the United States (3.5%) (CDC, 2015) and the European Union (EU) (3.8%) (EFSA, 2015a). However, in the EU, highest levels of microbiological resistance were found in isolates from chickens (53.8%), although lower levels (<10.0%) were recorded in Denmark, France, Ireland, and the United Kingdom.

The second most important group for treating human salmonellosis is the third-generation cephalosporins, especially for serious infections in children, in whom the use of fluoroquinolones can cause side effects (EFSA, 2015a). In the antimicrobials assessed in this work, this group is represented by ceftriaxone and cefotaxime. Resistance to these antimicrobials results from the presence of genes, usually found on plasmids, encoding extended-spectrum $\beta$-lactamase enzymes or AmpC enzymes, which can degrade the chemical structure of the antimicrobial (Miriagou *et al.*, 2004). Our results demonstrated that resistance to cefotaxime and to ceftriaxone was moderate (>10% to 20%) in the nontyphoidal isolates and rare (<0.1%) in *Salmonella* Enteritidis, regardless of the origin (Table 2). Lower levels of antimicrobial resistance in the nontyphoidal *Salmonella* have been described in the United States and the EU. In the United States, 2.5% of resistance was related to ceftriaxone in human isolates (CDC, 2015), and in the EU, this level was 1.4% and 3.2% to cefotaxime in human and poultry, respectively (EFSA, 2015a).

A temporal evolution of the antimicrobial resistance was also observed for streptomycin and gentamicin, belonging to the class of aminoglycosides. Resistance to members of this class is associated with enzymes production, changes in uptake and efflux, action of membrane proteases, and target modification (Becker and Cooper, 2013). The *Salmonella* Enteritidis isolates of human origin displayed increased resistance to gentamicin until 2003, the last year of assessment in the articles (Fig. 2C). This antimicrobial is widely used in human treatment, which may have promoted the selection of resistant isolates. For streptomycin, the isolates of nontyphoidal *Salmonella* and *Salmonella* Enteritidis of poultry origin presented a quadratic distribution effect of antimicrobial resistance. We observed an increase in resistance until 2005, followed by a sharp decline until the end of the studied period (Fig. 3A, B). Streptomycin is commonly used in treating infectious diseases in animals, it is a low-cost drug, discovered more than 70 years ago, which may have contributed toward the increased resistance in the first decade of assessment. The decline observed in recent years has also been demonstrated in other countries (CDC, 2015) and could have resulted from reduced use of streptomycin in poultry.

In Brazil, *Salmonella* Enteriditis was the most frequently reported serovar in the poultry industry for more than two decades. Indeed, the majority of the studies reviewed in this study presented specific data about *Salmonella* Enteriditis (Table 1). A national program for vaccination and control was implemented in breeders (Brazil, 2003), as well as the establishment of continuous monitoring of broiler chicken and turkey flocks at farm level (Brazil, 2009), and, recently, a decline has been reported in this serovar in broiler chickens (Pandini *et al.*, 2014; Voss-Rech *et al.*, 2015). However, *Salmonella* Enteritidis is among the serovars most commonly involved in human infections in Brazil (Baú *et al.*, 2001; Delicato *et al.*, 2004; Capalonga *et al.*, 2014) and also in other countries (CDC, 2014; EFSA, 2015b). Therefore, monitoring the antimicrobial resistance of *Salmonella* Enteritidis is indispensable. In this study, *Salmonella* Enteritidis, when individually analyzed, was more susceptible to the majority of the antimicrobials than all the nontyphoidal serovars (Table 2). In contrast to its prevalence in human infections, *Salmonella* Enteritidis is reported as a more susceptible serovar to antimicrobials (Hur *et al.*, 2012; Van *et al.*, 2012; EFSA, 2015a).

### *Study limitation*

Several studies were excluded from the meta-analysis because of inconsistencies in the presentation of the results, conflicting information in different sections of the article, or because they failed to separate the results by origin, and others (Fig. 1). Despite this critical evaluation, some limitation could not be overcome in this study: (1) it was not possible to standardize interpretation of the results, because of modifications to the diameter ranges of the zones of inhibition used over the years or because of an absence of information of the interpretation criteria adopted; (2) the number of isolates from each geographic region varied over the years, tending to the greater representation of some regions at certain periods of time; and (3) in the articles that presented the results of multiple years together, the average year of the period was considered in the temporal evaluation.

Similar difficulties were observed by Moodley *et al.* (2014), and we can corroborate their recommendation that, for new meta-analysis studies, it would be important for the resistance interpretation criteria to be harmonized, as well as the presentation of standardized results.

## Conclusions

The results demonstrated that the highest resistance levels were found for the oldest antimicrobials. The resistance to the majority of the antimicrobials was not changed over the course of time, except for streptomycin, nalidixic acid, and gentamicin, the observed effect of which varied in accordance with the origin or serovar of the isolates. In addition, *Salmonella* Enteritidis displayed lower levels of antimicrobial resistance than all the nontyphoidal serovars. These results reinforce the importance of epidemiological surveillance and the need to limit the continued evolution of antimicrobial resistance to preserve the action of available drugs.

## Disclosure Statement

No competing financial interests exist.

## References

[ABPA] Associação Brasileira de Proteína Animal. Relatório Anual de Atividades 2014. São Paulo, 2015. Available at: http://abpa-br.com.br/files/publicacoes/c59411a243d6dab1da8e605be58348ac.pdf Accessed June 15, 2016.

Albuquerque AH, Maciel WC, Lopes ED, Teixeira RSD, Salles RPR, Machado DN, Bezerra WGA, Vasconcelos RH, Mendonça SV, Carbó CB. Presence of *Salmonella* spp. in one-day-old chicks from hatcheries in the metropolitan region of Fortaleza, Brazil. Acta Sci Vet 2014;42:1222.

Angulo F, Nargund V, Chiller T. Evidence of association between use of antimicrobial agents in food animals and antimicrobial resistance among bacteria isolated from humans and the human health consequences of such resistance. J Vet Med 2004;51:374–379.

Baú AC, Carvalhal JB, Aleixo JAG. Prevalência de *Salmonella* em produtos de frangos e ovos de galinha comercializados em Pelotas, RS, Brasil. Cienc Rural 2001;31:303–307.

Becker B, Cooper MA. Aminoglycoside antibiotics in the 21st century. ACS Chem Biol 2013;8:105–115.

Brazil. Ministry of Agriculture, Livestock and Food Supply. Normative Instruction SDA no. 78, of 3 November 2003. Normas técnicas para controle e certificação de núcleos e estabelecimentos avícolas como livres de *S*. Gallinarum e de *S*. Pullorum e livres ou controlados para *S*. Enteritidis e para *S*. Typhimurium. Diário Oficial da União 2003;1:3.

Brazil. Ministry of Agriculture, Livestock and Food Supply. Joint Official Communication DSA/DIPOA no. 001/2009 of 15 January 2009. Procedimentos para monitoramento de estabelecimentos de frango de corte e perus para Salmoneloses aviarias. Departamento de Saude Animal 2009;1–4.

Campioni F, Moratto Bergamini AM, Falcão JP. Genetic diversity, virulence genes and antimicrobial resistance of *Salmonella* Enteritidis isolated from food and humans over a 24-year period in Brazil. Food Microbiol 2012;32:254–264.

Campioni F, Zoldan MM, Falcao JP. Characterization of *Salmonella* Enteritidis strains isolated from poultry and farm environments in Brazil. Epidemiol Infect 2014;142:1403–1410.

Capalonga R, Ramos RC, Both JM, Soeiro ML, Longaray SM, Haas S, Tondo EC. *Salmonella* serotypes, resistance patterns, and food vehicles of salmonellosis in southern Brazil between 2007 and 2012. J Infect Dev Ctries 2014;8:811–817.

Cardoso MO, Ribeiro AR, dos Santos LR, Pilotto F, de Moraes HLS, Salle CTP, Rocha SLS, do Nascimento WPD. Antibiotic resistance in *Salmonella* Enteritidis isolated from broiler carcasses. Braz J Microbiol 2006;37:368–371.

Castro FA, Santos VR, Martins CHG, Fernandes SA, Zaia JE, Martinez R. Prevalence and antimicrobial susceptibility of *Salmonella* serotypes in patients from Ribeirão Preto, São Paulo, Brazil, between 1985 and 1999. Braz J Infect Dis 2002;6:244–251.

Cavaco LM, Hasman H, Xia S, Aarestrup FM. qnrD, a novel gene conferring transferable quinolone resistance in *Salmonella enterica* serovar Kentucky and Bovismorbificans strains of human origin. Antimicrob Agents Chemother 2009;53:603–608.

[CDC] Centers for Disease Control and Prevention. *Foodborne Diseases Active Surveillance Network (FoodNet): FoodNet Surveillance Report for 2012 (Final Report)*. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC, 2014.

[CDC] Centers for Disease Control and Prevention. *National Antimicrobial Resistance Monitoring System (NARMS): Human Isolates Final Report, 2013*. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC, 2015.

Cortez A, Carvalho A, Ikuno A, Bürger K, Vidal-Martins A. Resistência antimicrobiana de cepas de *Salmonella* spp. isoladas de abatedouros de aves. Arq Inst Biol 2006;73:157–163.

Delicato ER, Mikcha JMG, Fernandes SA, Pelayo JS. Resistance profile to antimicrobials of *Salmonella* spp. isolated from human infections. Braz Arch Biol Technol 2004;47:193–197.

Dimitrov T, Udo EE, Albaksami O, Kilani AA, Shehab DM. Ciprofloxacin treatment failure in a case of typhoid fever caused by *Salmonella enterica* serotype Paratyphi A with reduced susceptibility to ciprofloxacin. J Med Microbiol 2007;56:277–279.

Duarte DAM, Ribeiro AR, Vasconcelos AMM, Santos SB, Silva JVD, Andrade PL, Falcão LSA. Occurrence of *Salmonella* spp. in broiler chicken carcasses and their susceptibility to antimicrobial agents. Braz J Microbiol 2009;40: 569–573.

[EFSA] European Food Safety Authority and [ECDC] European Centre for Disease Prevention and Control. EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013. EFSA J 2015a;13:4036, 178 pp.

[EFSA] European Food Safety Authority and [ECDC] European Centre for Disease Prevention and Control. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2014. EFSA J 2015b;13:4329, 191 pp.

Fonseca EL, Mykytczuk OL, Asensi MD, Reis EMF, Ferraz LR, Paula FL, Ng LK, Rodrigues DP. Clonality and antimicrobial resistance gene profiles of multidrug-resistant *Salmonella enterica* serovar Infantis isolates from four public hospitals in Rio de Janeiro, Brazil. J Clin Microbiol 2006; 44:2767–2772.

Hur JC, Jawale C, Lee JE. Antimicrobial resistance of *Salmonella* isolated from food animals: A review. Food Res Int 2012;45:819–830.

Jasson V, Butaye P. Report on susceptibility of *Salmonella* serotypes in Belgium. CODA-CERVA (Centrum voor Onderzoek in Diergeneeskunde en Agrochemie-Centre d'Etudeet des Recherches Vétérinaires et Agrochimiques). Federal Public Service Health, Food Chain Security and Environment. Belgium. 2012. Available at: www.amcra.be/sites/default/files/bestanden/Report%20Salmonella%20data%202012.pdf Accessed May 13, 2016.

Kottwitz LB, Leão JA, Back A, Rodrigues DP, Magnani M, Oliveira TC. Commercially laid eggs vs. discarded hatching eggs: Contamination by *Salmonella* spp. Braz J Microbiol 2013;44:367–370.

Kottwitz LBM, Scheffer MC, Dalla-Costa LM, Farah S, Moscalewski WSB, Magnani M, de Oliveira TCRM. Molecular characterization and resistance profile of *Salmonella* Enteritidis PT4 and PT9 strains isolated in Brazil. J Med Microbiol 2011;60:1026–1031.

Kottwitz LBM, Scheffer MC, Dalla Costa LM, Leitão JA, Back A, Rodrigues DP, Magnani M, de Oliveira TCRM. Perfil de resistência a antimicrobianos, fagotipagem e caracterização molecular de cepas de *Salmonella* Enteritidis de origem avícola. Semina: Ciências Agrárias 2012;33: 705–712.

Lai J, Wu C, Wu C, Qi J, Wang Y, Wang H, Liu Y, Shen J. Serotype distribution and antibiotic resistance of *Salmonella* in food-producing animals in Shandong province of China, 2009 and 2012. Int J Food Microbiol 2014;180: 30–38.

Lima ET, Andreatti Filho RL, Pinto JPAN. Perfil de susceptibilidade antimicrobiana de sorotipos de *Salmonella* isolados de produtos avícolas. Vet Zootec 2009;16:394–400.

Medeiros MAN, Oliveira DCN, Rodrigues DPR, Freitas DRC. Prevalence and antimicrobial resistance of *Salmonella* in chicken carcasses at retail in 15 Brazilian cities. Rev Panam Salud Publica 2011;30:555–560.

Miriagou V, Tassios PT, Legakis NJ, Tzouvelekis LS. Expanded-spectrum cephalosporin resistance in non-typhoid *Salmonella*. Int J Antimicrob Agents 2004;23:547–555.

Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6: e1000097.

Moodley A, Damborg P, Nielsen SS. Antimicrobial resistance in methicillin susceptible and methicillin resistant *Staphylococcus pseudintermedius* of canine origin: Literature review from 1980 to 2013. Vet Microbiol 2014;171: 337–341.

Oliveira FA, Pasqualotto AP, Silva WP, Tondo EC. Characterization of *Salmonella* Enteritidis isolated from human samples. Food Res Int 2012;45:1000–1003.

Oliveira SD, Siqueira Flores F, dos Santos LR, Brandelli A. Antimicrobial resistance in *Salmonella* Enteritidis strains isolated from broiler carcasses, food, human and poultry-related samples. Int J Food Microbiol 2005;97:297–305.

Oplustil CP, Nunes R, Mendes C; RESISTNET Group. Multicenter evaluation of resistance patterns of *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella* spp and *Shigella* spp isolated from clinical specimens in Brazil: RESISTNET surveillance program. Braz J Infect Dis 2001;5:8–12.

Pandini JA, da Silva Pinto FG, Muller JM, Weber LD, Moura AC. Ocorrência e perfil de resistencia antimicrobiana de sorotipos de *Salmonella* spp. isolados de aviários do Paraná, Brasil. Arq Inst Biol 2014. Available at: http://www.scielo.br/pdf/aib/v82/1808-1657-aib-1808-1657000352013.pdf Accessed May 13, 2016.

Pereira CS, Medeiros LM, Costa RG, Festivo ML, dos Reis EMF, Seki LM, Rodrigues DP. Phage typing and multidrug resistance profile in *S*. Typhimurium isolated from different sources in Brazil from 1999 to 2004. Braz J Microbiol 2007; 38:385–390.

Peresi JTMP, Almeida IAZC, Lima SI, Marques DF, Rodrigues ECA, Fernandes SA, Gelli DS, Irino K. Surtos de enfermidades transmitidas por alimentos causados por *Salmonella* Enteritidis. Rev Saúde Pública 1998;32:477–483.

Reis EMF, Rodrigues DP, Freitas-Almeida AC, Hofer E. Prevalence of R-type ACSSuT in strains of *Salmonella* serovar Typhimurium DT193 isolated from human infections in Brazil. Rev Panam Salud Publica 2011;29:387–392.

Ribeiro AR, Kellermann A, Santos LR, Bessa MC, Nascimento VP. *Salmonella* spp. in raw broiler parts: Occurrence, antimicrobial resistance profile and phage typing of the *Salmonella* Enteritidis isolates. Braz J Microbiol 2007;38:296–299.

Ribeiro AR, Kellermann A, Santos LR, Nascimento VP. Antimicrobial resistance in *Salmonella* Enteritidis isolated from clinical and environmental broiler chickens and breeders broiler. Arq Bras Med Vet Zootec 2008;60:1259–1262.

Ruiz M, Rodriguez JC, Escribano I, Royo G. Available options in the management of non-typhi *Salmonella*. Expert Opin Pharmacother 2004;5:1737–1743.

Santos DMS, Berchieri JA, Fernandes SA, Tavechio AT, Amaral LA. *Salmonella* em carcaças de frango congeladas. Pesq Vet Bras 2000;20:39–42.

Scur MC, Pinto FGS, De Bona EAM, Weber LD, Alves LFA, Moura AC. Occurrence and antimicrobial resistance of *Salmonella* serotypes isolates recovered from poultry of Western Paraná, Brazil. Afr J Agric Res 2014;9:823–830.

Stevenson JE, Gay K, Barrett TJ, Medalla F, Chiller TM, Angulo FJ. Increase in nalidixic acid resistance among non-Typhi *Salmonella enterica* isolates in the United States from

1996 to 2003. Antimicrob Agents Chemother 2007;51: 195–197.
Van TT, Nguyen HN, Smooker PM, Coloe PJ. The antibiotic resistance characteristics of non-typhoidal *Salmonella enterica* isolated from food-producing animals, retail meat and humans in South East Asia. Int J Food Microbiol 2012;154: 98–106.
Vaz CSL, Streck AF, Michael GB, Marks FS, Rodrigues DP, dos Reis EM, Cardoso MR, Canal CW. Antimicrobial resistance and subtyping of *Salmonella enterica* subspecies enterica serovar Enteritidis isolated from human outbreaks and poultry in southern Brazil. Poult Sci 2010;89:1530–1536.
Voss-Rech D, Vaz CSL, Alves L, Coldebella A, Leão JA, Rodrigues DP, Back A. A temporal study of *Salmonella enterica* serotypes from broiler farms in Brazil. Poult Sci 2015; 94:433–441.
[WHO] World Health Organization. Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). Critically important antimicrobials for human medicine. 3 ed. 2011. Available at: http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf Accessed May 26, 2016.
[WHO] World Health Organization. Antimicrobial resistance. Fact sheet No. 194. 2015. Available at: www.who.int/mediacentre/factsheets/fs194/en Accessed May 13, 2016.
Wilson IG. Antimicrobial resistance of *Salmonella* in raw retail chickens imported chicken portions, and human clinical specimens. J Food Prot 2004;67:1220–1225.

Address correspondence to:
*Daiane Voss-Rech, BSc*
*Laboratório de Sanidade e Genética Animal*
*Embrapa Suínos e Aves*
*Concordia 89700-991*
*Brazil*

*E-mail:* daiane.rech@embrapa.br