

Prevalence, main serovars, and antimicrobial resistance profiles of Non-typhoidal *Salmonella* in poultry samples from the Americas: A systematic review and meta-analysis

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Abstract

Poultry and poultry-derived products such as meat and eggs are among the main sources of non-typhoidal *Salmonella* (NTS) transmission to the human. Therefore, we performed a systematic review and used random-effects meta-analyses to 1) estimate the prevalence of NTS in poultry samples from birds, products and subproducts, and environmental samples, 2) examine the diversity and frequency of their serovars, and 3) estimate the prevalence and profiles of antimicrobial resistance (AMR) in NTS isolates reported in studies from the Americas. We included 157 studies from 15 countries comprising 261,408 poultry samples and estimated an overall pooled prevalence of 17.9% (95% CI: 10.8–26.3) in birds, 21.8% (17.7–26.1) in products and subproducts, and 29.5% (24.2–35.1) in environmental samples. At the national level, the prevalence of NTS was heterogenous across countries with the highest values in Mexico, the USA, and Canada. In total, 131 serovars were identified from 13,388 isolates, Heidelberg, Kentucky, Enteritidis, and Typhimurium were the most prevalent in the overall top 10 ranking (range 6.5–20.8%). At the national level, Enteritidis and Typhimurium were identified in most of the countries, though with national differences in their ranks. The prevalence of AMR increased from 24.1% for 1 antibiotic, to 36.2% for 2-3 antibiotics, and 49.6% for [?] 4 antibiotics. Kentucky, Heidelberg, Typhimurium, and Enteritidis were the serovars with the highest prevalence of AMR and tetracycline, ampicillin, streptomycin, ceftiofur, and amoxicillin-clavulanic acid were the top five antibiotics to which NTS isolates were resistant. In conclusion, NTS was distributed through the avian production chain with high and heterogenous values of prevalence in poultry samples. Besides, there were distinctive patterns of serovars distribution across countries and an alarming prevalence of AMR among zoonotic serovars.

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Abstract

Poultry and poultry-derived products such as meat and eggs are among the main sources of non-typhoidal *Salmonella* (NTS) transmission to the human. Therefore, we performed a systematic review and used random-effects meta-analyses to 1) estimate the prevalence of NTS in poultry samples from birds, products and subproducts, and environmental samples, 2) examine the diversity and frequency of their serovars, and 3) estimate the prevalence and profiles of antimicrobial resistance (AMR) in NTS isolates reported in studies from the Americas. We included 157 studies from 15 countries comprising 261,408 poultry samples and estimated an overall pooled prevalence of 17.9% (95% CI: 10.8–26.3) in birds, 21.8% (17.7–26.1) in products and subproducts, and 29.5% (24.2–35.1) in environmental samples. At the national level, the prevalence of NTS was heterogenous across countries with the highest values in Mexico, the USA, and Canada. In total, 131 serovars were identified from 13,388 isolates, Heidelberg, Kentucky, Enteritidis, and Typhimurium were the most prevalent in the overall top 10 ranking (range 6.5–20.8%). At the national level, Enteritidis and Typhimurium were identified in most of the countries, though with national differences in their ranks. The prevalence of AMR increased from 24.1% for 1 antibiotic, to 36.2% for 2-3 antibiotics, and 49.6% for [?] 4 antibiotics. Kentucky, Heidelberg, Typhimurium, and Enteritidis were the serovars with the highest prevalence of AMR and tetracycline, ampicillin, streptomycin, ceftiofur, and amoxicillin-clavulanic acid were the top five antibiotics to which NTS isolates were resistant. In conclusion, NTS was distributed through the avian production chain with high and heterogenous values of prevalence in poultry samples. Besides, there were distinctive patterns of serovars distribution across countries and an alarming prevalence of AMR among zoonotic serovars.

Keywords: Infectious diseases, Foodborne disease, Food safety, Multi-drug resistance, Salmonellosis, Zoonosis.

1. INTRODUCTION

Salmonella are Gram negative rod-shaped bacilli that belongs to the family *Enterobacteriaceae*. The *Salmonella* genus includes only two species, one of which is *Salmonella enterica* that is divided into six subspecies that includes *S. enterica* subsp. *enterica* (Popoff, Bockemuhl, & Gheesling, 2004). According to the Kauffmann-White scheme, *Salmonella* strains are serologically classified into more than 2,610 serovars based on their specific antigenic reaction (Guibourdenche et al., 2010). *S. enterica* subsp. *enterica* is of medical interest because causes an infectious disease that can be classified into: enteric fever (typhoidal) that affects only humans and non-typhoidal *Salmonella* (NTS) that affects both humans and animals (Barrow & Methner, 2013). Indeed, NTS is considered among the main pathogen bacteria that cause foodborne disease (FBD), which causes a significant public health, economic and social burden worldwide, particularly in low- and middle-income countries (World Health Organization, 2021).

Non-typhoidal salmonellosis is commonly manifested as mild to moderate gastroenteritis characterized by vomiting, nausea, diarrhea, and abdominal pain (Foley & Lynne, 2008). Usually, these symptoms developed 6-72 h after ingestion of the bacteria (Centers for Disease Control and Prevention, 2004) and are resolved within 2-7 days because they are self-limiting and thus do not require treatment. However, NTS can develop into a more severe illness that invade normally sterile sites that results in bacteremia, meningitis, and other focal infections, which are denominated invasive NTS (Crump, Sjolund-Karlsson, Gordon, & Parry, 2015). Only in 2017, there were 535,000 cases of invasive NTS worldwide that caused 77,500 deaths worldwide that affected mostly children under five years of age, elderly people, and people with HIV infection (Stanaway et al., 2019).

In the human, NTS is acquired mainly through contaminated food of animal origin such as poultry products and poultry-derived products, which are recognized as common sources of transmission (Goncalves-Tenorio, Silva, Rodrigues, Cadavez, & Gonzales-Barron, 2018). In poultry, this pathogen bacteria can be found in the carcasses, raw meat, and eggs (eggshell, salk, and yolk) (Foley, Lynne, & Nayak, 2008), as well as in live birds from poultry farms (El-Sharkawy et al., 2017), and in the environment related to poultry production and slaughter (Manoj & Singh, 2015). Thus, NTS is widely distributed in the poultry production chain and serves as an important reservoir for the dissemination of the pathogen to the humans (Howard, O'Bryan, Crandall, & Ricke, 2012).

From the perspective of public health, the subspecies *enterica* concentrates the most important zoonotic serovars of NTS that include Typhimurium and Enteritidis, which are frequently reported as a cause of FBD associated to the consumption of poultry products (Park et al., 2014). Previous studies have reported contrasting patterns of serovars predominance across the regions of the world: in poultry from Asia, Latin America, Europe, and Africa, Enteritis was predominant, and Kentucky and Sofia were most prevalent in North America and Oceania (Ferrari et al., 2019), whereas in poultry samples from Europe, Enteritidis, Infantis, and Typhimurium were the most frequent serovars (Antonelli, Belluco, Mancin, Losasso, & Ricci, 2019). Nevertheless, the pattern of predominance and distribution of the serovars might be prone to change due to the increase in the international trading of poultry and poultry-derived products (Manoj & Singh, 2015) in conjunction with the implementation of control measures that have induced the expansion of previously less common serovars (Antunes, Mourao, Campos, & Peixe, 2016). Besides, the emergence and spread of NTS serovars with antimicrobial resistance (AMR) is a major public health concern given that the abusive use of antibiotics in intensive livestock systems increase the rate of appearance of AMR (Antunes et al., 2016) and because antibiotics are crucial for successful treatment of invasive infections.

In consequence, it is necessary to implement effective intervention strategies focused on reducing and controlling the dissemination of NTS from poultry to humans. Besides, estimating the burden of the most important FBD, such as NTS that cause a great impact on public health, is an essential component in the effort to reduce its negative effect (World Health Organization, 2021). In this context, identifying and estimating

the magnitude of *Salmonella* serovars with AMR in poultry and their products capable of causing FBD in humans might provide an initial step in the identification of sources of exposure for the dissemination of NTS because these products are recognized as the main source of foodborne salmonellosis (Antunes et al., 2016) . This is particularly important in regions of the world with a high level of poultry production and consumption, such is the case of the Americas that concentrates 42.3% of the poultry meat production at the global level (FAO, 2019). Therefore, we conducted a systematic review and meta-analysis to 1) estimate the prevalence of NTS in poultry samples from birds, products and subproducts, and environmental samples, 2) determine the diversity and frequency of their serovars, and 3) estimate the prevalence and profiles of AMR in NTS isolates reported in studies from the Americas.

2. METHODS

2.1 Protocol and objectives

A protocol, available from the corresponding author upon reasonable request, was developed *a priori* in accordance to the Preferred Reporting Items for Systematic reviews and Meta-analysis Protocol (PRISMA-P) statement (Moher et al., 2015). The study was conducted according to the Cochrane handbook for systematics reviews (Higgins et al., 2019) and it is reported in agreement with the PRISMA statement (Liberati et al., 2009). We conducted a systematic review and meta-analysis to address the following questions: What is the prevalence of NTS in samples of poultry from the Americas? Which are the main serovars of NTS identified in each type of sample? What is the prevalence and profile of antimicrobial resistance in NTS isolates of poultry?

2.2 Eligibility criteria

We defined the eligibility criteria for the studies according to the POS (Population, Outcome, and Study) approach of the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analysis) statement (Liberati et al., 2009). In **Table 1** are summarized the definitions used. In brief, we included publications that met the following inclusion criteria: 1) the studies reported the presence of NTS in samples from poultry birds (included subpopulations such as layers, broilers, and breeders at the individual or flock/collective level), samples from products and subproducts of poultry, or environmental samples from the ambient related to poultry production, 2) the studies assessed the prevalence of NTS, the frequency and diversity of the serovars, or the antimicrobial resistance profiles, and 3) the studies were full text primary publications from the Americas published in English, Spanish, or Portuguese in peer-reviewed journals from 1980 to March 2020. Reasons for exclusion were 1) reporting turkeys, ducks, ostriches, pigeons, quails, or wild, song or, ornamental birds, 2) not reporting any of the three types of samples defined, 3) reporting NTS isolates previously obtained, 4) not reporting at least one of the defined outcomes, 5) re-used data from a previous study, 6) study outside the Americas. We did not include any grey literature (i.e., unpublished studies, thesis, conference proceedings, or reports) to assure an adequate and comparable level of methodological quality among the selected studies.

2.3 Information sources and search methodology

A single reviewer consulted PubMed, CAB Abstracts, Virtual Health Library (VHL), Science Direct, Scopus, and Web of Science from 24 February to 02 March 2020 to find scientific literature. To find the most relevant and specific publications, the reviewer conducted separated searches for each outcome (prevalence, serovars, and antimicrobial resistance). For this, we defined a common search term for the population [(salmonell* OR salmonella OR salmonellosis) AND (avian OR poultry OR broiler OR laying hen OR fowl OR chick)] that was used in conjunction with search terms for prevalence (prevalence OR incidence), serovars (genotype OR serotyping OR serovar), and antimicrobial resistance (resistance OR resistant). Full searches and the number of recovered records for each database are presented in **Supplementary Table 1** of the supplementary material. After completing the searches, all the retrieved records were downloaded and stored in a single library in EndNote x9 (Thompson Reuters, USA).

2.4 Study selection process and data extraction

To select the studies to be included in the narrative synthesis, one reviewer first removed the duplicates automatically from the EndNote library and then revised the records manually. Next, the same reviewer performed the screening of all the remaining records by checking whether the publications were related to the reviewed subject, first based on the title, and second, based on the abstract. Once the screening was completed, the selected publications were retrieved in full text to assess their eligibility for final inclusion in the systematic review and meta-analysis. To account for this, two independent reviewers used a standardized questionnaire that was based on the eligibility criteria (**Supplementary Table 2**) and was piloted in 10% of the publications selected at random. Each time there was a discrepancy between the reviewers, a third reviewer served as referee until consensus was reached.

A single reviewer used a standardized questionnaire to extract data from all the selected publications. Prior to be used, the extraction sheet format was piloted in 10% of the studies selected at random. The extracted data included a) the main characteristics of the publication (first author, country, publication year, and study design), b) the main characteristics of the assessed population (poultry subgroup, sex, and age), c) the type of sample reported (birds, products and subproducts, or environmental), d) the diagnostic technique for NTS, and e) the reported outcomes (prevalence, serotyping, or antimicrobial resistance). For the publications that reported both data on the individual and flock/collective level, we selected for extraction only data at the individual level to avoid duplication of estimates for a single publication and because we found less variation in the estimations made at the individual when compared to the flock/collective level. Besides, for the publications that assessed more than one type of sample, each one of them was extracted separately and counted as one independent study within a single publication. All the extracted data were registered into an Excel spreadsheet (Microsoft, USA) and a codebook was created to facilitate its handling.

2.5 Assessment of the risk of bias in individual studies

One reviewer assessed the risk of bias using an adapted version of the method published by Higgins et al. (2019). Each study was rated as having or not (Yes or Not) risk of bias according to the following criteria: for all the studies, 1) samples that tested positive to NTS were confirmed by at least two diagnostic techniques; for the studies that reported serovars, 2) all the NTS-positive samples were serotyped and 3) the study presents a complete report of all the serovars that were found; for the studies that reported antimicrobial resistance, 4) all the NTS isolates were assessed for antimicrobial resistance, and 5) the study presents the complete antimicrobial resistance profile. For the studies that did not report the three outcomes, each criterion was scored as not applicable (NA). To summarize the results, we present the percentage of studies that had or not risk of bias per each criterion.

2.6 Summary measures and statistical analysis

We estimated the overall pooled prevalence of NTS and the prevalence of antimicrobial resistance in poultry samples with a meta-analysis of proportions using the Freeman-Tukey double arcsine transformation with 95% exact confidence intervals (95% CI) (Chaidez-Ibarra et al., 2021). Due to expected heterogeneity across studies, we defined *a priori* a random effects model (DerSimonian & Kacker, 2007). To estimate the prevalence of NTS: first, we performed independent meta-analyses according to the type of sample (birds, products, and environmental) with subgroup analysis aggregating the studies by the level of sampling (individual or flock/collective), and second, we performed independent meta-analysis according to the type of sample aggregating the studies by country (considering both individual and flock/collective data). To estimate the prevalence of antimicrobial resistance, we performed independent meta-analyses according to the number of antibiotics (1, 2-3, or [?]4) to which the NTS isolates were resistant and aggregated the studies by the type of sample. The overall effect of the model was assessed with the z statistic assuming an effect size = 0, whereas the Cochran's Q statistic (X^2 test) was used to assess significant heterogeneity across trials and the I^2 statistic was used to measure the proportion of variation in the effects caused by heterogeneity in the true effects rather than sampling error (Diaz et al., 2019; Romo-Barron et al., 2019). All analyses were performed on Stata 12 (StataCorp, TX, USA) and the graphs were constructed on Prism 9 (GraphPad Inc., CA, USA). In all the cases, we considered a value of $p < 0.05$ as significant.

3. RESULTS

3.1 Study selection

As shown in **Figure 1** , a total of 12,279 records were retrieved from the electronic databases, of which 84.5% were provided by VHL, Scopus, and PubMed. In total, 4,815 publications remained after duplicates were removed and once the screening of titles and abstract was completed, 340 publications were retrieved in full text for final eligibility. A total of 157 publications that met the inclusion criteria were included in the quantitative synthesis. Among the 183 full text publications that were excluded, the main reasons were: assessed SNT isolates previously obtained (56.8%), lacked the defined population (21.3%), and not a full text or other type of study different than the defined (10.9%). A list of the publications that were excluded and the primary reason for exclusion are provided in **Supplementary Table 2** and a full reference list with all the included publications is presented in **Supplementary Table 3** .

3.2 Main characteristics of the studies

The 157 publications included in our study were conducted in 15 countries from the Americas, of which 81.5% (128/157) were from the United States of America (USA), Brazil, and Canada. Colombia, Argentina, and Mexico provided 4-6 studies each, whereas Trinidad and Tobago contributed with three studies and Costa Rica, Ecuador, and Paraguay provided two studies each. Finally, we found only one publication from Chile, Guatemala, Puerto Rico, Uruguay, and Venezuela (**Fig. 2a**). English was the predominant language of publication with 94.9% (149/157) and according to the study design, cross-sectional studies were the most frequent with 77.7% (122/157) of the publications, followed by surveys, surveillance studies, and experiments (19, 7, and 4 publications, respectively) (**Fig. 2b**). The cumulative distribution according to the year of publication showed that 53.3% of the studies were published during the last decade since 2010 (**Fig. 2c**). As depicted in **Figure 2d** , the publications used a mixture of diagnostic techniques to detect NTS in the samples, 43.9% (69/157) of them reported up to three diagnostic tools, whereas 37.6% (59/157) used at least two different diagnostic techniques. Among the publications, bacterial culture was the most frequent diagnostic tool with 95.5% (150/157), followed by serological and biochemical tests (117 and 83). Only 22.3% (35/157) of the publications reported the use of PCR for the molecular confirmation of NTS in the positive samples and used the following genes: *inv A*, RNAr 16S, *bla*_{CMY}, *bla*_{CMY-2}, *SpvC* , *mdh y ompC* .

The main characteristics of the 157 publications included in the quantitative synthesis are summarized in **Supplementary Table 4** . The publications were characterized by reporting a mixture of the three defined outcomes: 149/157 reported the prevalence of NTS, 94/157 included the serotyping of the isolates, and 46/157 assessed the antimicrobial resistance profiles of the NTS isolates. Besides, the 149 publications that reported the prevalence of NTS included up to three types of samples and we extracted each sample as an independent study within a publication; therefore, there were 194 independent studies that were distributed according to the type of sample in products and subproducts (90), environmental (61), and birds (43).

3.3 Risk of bias assessment

As shown in **Figure 2e** , 81.5% of the publications reported at least two diagnostic tools to detect NTS-positive samples and thus were judges as not having risk of bias. Among the 94 publications that serotyped the NTS isolates, 87.2% were judges as not having risk of bias because the studies serotyped all the isolates. For these same publications, 74.5% reported the complete diversity of serovars found and thus were free of risk of bias. A total of 84.8% of the 46 publications that assessed the antimicrobial resistance profile of the isolates were free of risk of bias because they included all the NTS-positive samples. However, 54.3% of these 46 publications had risk of bias because they did not report the complete antimicrobial resistance profiles for all the assessed isolates.

3.4 What is the prevalence of NTS in samples of poultry from the Americas?

As summarized in **Table 2** , the prevalence of NTS varied both according to the type of the sample assessed and the country. The pooled overall prevalence of NTS was 17.9% (95% CI: 10.8 to 26.3) in 43 studies that reported 24,113 samples of birds from 11 countries with a significant test of effect size ($Z=7.5$, $p =0.00$) and

substantial heterogeneity as judged by the I^2 (99.5%, $p = 0.00$). For these samples, the subgroup analysis revealed a lower prevalence of NTS in individual data (3.8 to 18.2, $n=25$) in comparison to the value of 33.8% (16.6 to 53.3, $n=18$) estimated in flock data (**Supplementary Figure 1**). At the national level, the prevalence of NTS ranged from 23.2 to 50% in samples of birds reported in studies from Mexico, the USA, Uruguay, and Venezuela. In contrast, the prevalence of NTS was lower in studies from Brazil, Chile, Paraguay, and Trinidad and Tobago where the estimations varied between 0.8 and 3.7% (**Table 2**).

In 90 studies that reported 173,354 samples of products and subproducts from 10 countries, the overall pooled prevalence of NTS was 21.8% (17.7 to 26.1) with a significant test of effect size ($Z=16.8$, $p = 0.00$) and a significant variation attributable to heterogeneity ($I^2=99.6\%$, $p = 0.00$). According to subgroup analysis, the prevalence estimations were consistent between the individual (21.2%, 17.7 to 26.1, $n=78$) and collective data (28.1%, 12.6 to 46.4, $n=12$) of these samples (**Supplementary Figure 2**). The studies from Canada showed the highest pooled prevalence of NTS in samples from products and subproducts, while prevalence values ranging from 31.2 to 34.4% were estimated in studies from Guatemala, Mexico, and Puerto Rico. Finally, Argentina, Brazil, Costa Rica, and Trinidad and Tobago had prevalence values below-average (**Table 2**).

Regarding the environmental samples, the pooled prevalence of NTS was 29.5% (24.2 to 35.1) in 61 studies that comprised 63,941 samples from eight countries. There was a significant test of effect size ($Z=17.1$, $p = 0.00$) and substantial heterogeneity across studies ($I^2=94.4\%$, $p = 0.00$), and the subgroup analysis showed a contrasting difference of 21.9 and 52.4% at the individual (17.6 to 26.6, $n=43$) and collective (41.7 to 62.9, $n=18$) level, respectively (**Supplementary Figure 3**). At the national level, the studies from Canada and the USA had prevalence values above the overall estimation, whereas with estimations varying 3.3 to 9.0%, the studies from Argentina and Costa Rica showed the lowest prevalence of NTS in environmental samples (**Table 2**).

Which are the main serovars of NTS identified in each type of sample?

In total, 131 NTS serovars were identified from 13,388 isolates from poultry samples reported in 94 publications from 13 countries (**Fig. 3**). The USA and Canada contributed both with the highest percentage of isolates (84.0%) and the greatest diversity of NTS serovars (68 and 57, respectively). Likewise, Brazil and Colombia provided a great diversity of serovars (53 and 40, respectively), whereas the remaining countries reported a lower diversity of NTS serovars (range 1-19). A detailed list of the distribution of the 131 NTS serovars per country is provided in **Supplementary Table 5**.

Overall, 84.3% of the isolates were distributed among 10 NTS serovars, Heidelberg, Kentucky, and Enteritidis were the most prevalent (20.8, 20.6, and 17.6%, respectively), whereas Mbandaka, Schwarzengrund, and Montevideo were less prevalent with values ranging from 2.2 to 2.4%. Outside the top 10 serovars, the category “Others” comprised the remaining 121 serovars that were found in 2,103 isolates. As shown in **Figure 3**, there was a heterogeneous pattern in the top 10 ranking of the NTS serovars across countries, which additionally had several serovars not included in the overall top 10 ranking. Additionally, in Costa Rica, Ecuador, Mexico, and Trinidad and Tobago their 1st top serovar was not included in the overall top 10 ranking list. Even though the serovars Heidelberg and Kentucky were ranked as 1st and 2nd overall, these serovars were reported only in 5 and 6 countries, respectively, where their ranks varied across countries. In contrast, serovars Enteritidis and Typhimurium (3rd and 4th overall) were identified in most of the countries (10 and 8 respectively); thus, these two serovars had the broadest distribution in poultry samples across countries from the Americas. Furthermore, Enteritidis was the 1st top-ranked serovar in the USA, Brazil, Colombia, Paraguay, and Uruguay where its prevalence ranged from 23.4 to 100% and the 2nd top-ranked serovar in Argentina, Chile, and Ecuador. Similarly, Typhimurium was the 1st top-ranked serovar in Chile and the 3rd ranked in Colombia. Despite the serovars Hadar, Thompson, and Montevideo were ranked in the top 10 overall, they were reported only in two countries each and thus showed a narrow geographical distribution.

We constructed Sankey diagrams to examine and compare the distribution of the top five NTS serovars

according to the type of poultry sample (**Fig. 4**). Laying hens, broilers, and a mixture category that grouped chicks and hens were the main sources of NTS isolates in animal samples, whereas carcasses, eggs, and subproducts for consumption (such as meat and processed products) provided most of the isolates for the products and subproducts group. Finally, among environmental samples, most of the isolates were obtained from production wastes (such as litter and feces), breeding facilities, and production supplies (such as water, feed, and litter). Serovars Enteritidis and Heidelberg were identified in all the poultry samples, whereas the samples from products and subproducts and environmental shared 4 out of 5 serovars (Enteritidis, Kentucky, Heidelberg, and Typhimurium). Among the samples from birds and products and subproducts, Enteritidis was the most prevalent serovar with 32.4 and 22.8%, respectively, followed by Senftenberg and Kentucky (10.6% for birds and 21.5% for products and subproducts). Heidelberg and Kentucky were the most prevalent serovars in environmental samples (32.1 and 28.8%, respectively).

What is the prevalence and the profile of antimicrobial resistance in NTS isolates of poultry?

Of the 46 publications that assessed the AMR of the NTS isolates, 38/46 reported the prevalence in 3,078 isolates of which 2,223 were resistant to at least one antibiotic. As depicted in **Figure 5a**, the prevalence of AMR tended to be higher according to the increase in the number of antibiotics to which the NTS isolates were resistant: 1 antibiotic, 24.1% (14.7 to 34.9%, n=440); 2-3 antibiotics, 36.2% (24.5 to 48.6%, n=758); and [?] 4 antibiotics, 49.6% (36.9 to 62.2%, n=1,025). Besides, there was a heterogenous pattern of prevalence to AMR among the three types of samples because in samples from birds and products and subproducts, resistance to [?] 4 antibiotics was highly prevalent (61.2 and 48.7%), whereas resistance to 2-3 antibiotics was highly prevalent in environmental samples (47.1%) (**Supplementary Figure 4**).

A total of 26/46 publications reported 50 serovars from 1,688 NTS isolates that were resistant to at least one antibiotic. As shown in **Figure 5b**, 10 serovars contributed with 79.2% of the total, among which Kentucky (29.5%), Heidelberg (16.7%), Typhimurium (9.8%), and Enteritidis (7.1%) were the top four serovars most frequently reported as resistant to at least one antibiotic. Outside the top 10 ranking, the category “Others” comprised 40 serovars from 331 NTS isolates of which Typhimurium var. 5-, 4,5, 12:1:, Pullorum, Anatum, Lithfield, Montevideo, Hadar, Ohio, Newport, and Senftenberg were reported in 10 to 33 isolates each. In contrast, serovars such as Havana, Idikan, Ouakam, Bredeney, Alachua, Corvallis, Istanbul, Livingstone, Worthington, and I 4,5, 12: - were reported only once across the publications.

In total, 40/46 publications reported 15 groups of antibiotics that included 57 antibiotics to which 8,911 NTS isolates were resistant. Each group included between 1 and 11 antibiotics that varied in the frequency of report (**Supplementary Table 6**). In **Figure 5c** are depicted the main six groups of drugs and their corresponding antibiotics to which 90.6% of the isolates were resistant. Cephalosporins, penicillins, tetracyclines, and aminoglycosides were the top four groups, which concentrated 71.9% of the resistant isolates of NTS. As shown in **Figure 5d**, with a prevalence that ranged from 5.8 to 16.2%, tetracycline, ampicillin, streptomycin, ceftiofur, and amoxicillin-clavulanic acid were among the top 10 antibiotics with the highest overall prevalence of resistance in *Salmonella* isolates. In the bottom rank, gentamicin and trimethoprim-sulfamethoxazole were the antibiotics with the lowest prevalence of resistance in NTS. Regarding the three poultry samples, the profile of antimicrobial resistant was heterogenous. Except for tetracycline, which was the 1st top-ranked antibiotic among resistant isolates, the remaining antibiotics varied in their position within the rank. For instance, streptomycin that was the second most prevalent in birds, ranked 4th and 5th in environmental samples and products and subproducts. Likewise, ampicillin ranked 5th in environmental samples, whereas in the two other samples this antibiotic was among the top three, nalidixic acid that was the third to last most prevalent overall, in environmental samples was ranked 3rd. Besides, in the three samples of poultry there were 1-2 antibiotics that were not included in the overall top 10 ranking.

4. DISCUSSION

Summary and implications of the evidence

Despite the increased global awareness regarding food safety in recent decades, FBD still cause a substantial public health burden (World Health Organization, 2021) and NTS stands among the main foodborne pathogens that contribute to this burden, particularly by the consumption of contaminated poultry and poultry-derived products. In consequence, it is fundamental to assess the prevalence and characteristics of this foodborne pathogen throughout the poultry productive chain. The current systematic review and meta-analysis provide a comprehensive synthesis of evidence regarding the prevalence, the diversity and frequency of serovars, and the AMR profiles of NTS reported in poultry samples from the Americas.

The meta-analyses showed that the prevalence of NTS was the highest in environmental samples. We performed an additional meta-analysis grouping together studies that reported internal (farm installations and infrastructure, poultry houses, eggshells, bedding, feces, dust, and litter) or external (supplies, transport cages, slaughterhouse installations, and processing facilities) sources from where the environmental samples were taken. The results showed a similar prevalence of NTS in internal (31.5%, 25.1 to 38.3) and external (29.4%, 11.1 to 51.9) sources of environmental samples and thus demonstrate that NTS is both broadly distributed and highly frequent throughout the environment related to poultry production in the Americas. This result agrees with previous studies that have demonstrated a consistent presence of NTS in environmental samples including poultry feed (Magwedere, Rauff, De Klerk, Keddy, & Dziva, 2015), farm infrastructure (Bhatia & McNabb, 1980), slaughterhouse installations and processing facilities (Rivera-Perez, Barquero-Calvo, & Zamora-Sanabria, 2014), and leftovers such as litter or feces (Vaz, Voss-Rech, de Avila, Coldebella, & Silva, 2017).

With prevalence values ranging from 3.3 to 36.7%, SNT was isolated in the environmental samples from 8 out of 15 countries included in the study. Even though the variability was high in the estimates among the countries, this is an important result because the presence of NTS in the internal and external environment related to poultry production might facilitate the reintroduction of the pathogen to the productive chain and thus become a persistent source of exposition for further contamination (Mueller-Doblies, Sayers, Carrique-Mas, & Davies, 2009). In a recent longitudinal study, Voss-Rech et al. (2019) found that once NTS was detected in the litter samples during the harvest of the first flock, then the pathogen was isolated from the environment of subsequent flocks, whereas Marin, Balasch, Vega, and Lainez (2011) reported that all the different environmental samples related with poultry production were contaminated with NTS and that the prevalence of the pathogen remained high even after cleaning and disinfection. Several studies have assessed different control measures to prevent and reduce the incidence of NTS in the environment of poultry production. For instance, preventing contamination of the facilities where the animal feed is produced and killing the pathogens by pelleting the feed (Jones, 2011), inactivation of residual microorganisms in recycled litter by shallow fermentation or windrowing (Vaz et al., 2017), and cleaning and disinfection to avoid persistent contamination in the broiler houses (Davies, Breslin, Corry, Hudson, & Allen, 2001). However, the ability of NTS to persist for long periods means that every available tool must be used to control the organism, and efforts must be sustained (Jones, 2011) and constant sampling of the environment should be performed.

Additionally, the presence of NTS in the environment related to poultry production and processing increases the probability of cross-contamination of the carcasses and poultry meat during slaughtering (Volkova et al., 2010). In this regard, Carraminana et al. (1997) reported that the percentage of poultry carcasses contaminated with NTS increased from 56.7% to 70% after the processing, whereas Tozser et al. (2019) found that the 0% positivity to NTS in the body surface of the birds before transportation increased up to 100% after the slaughter and processing stages. Given that poultry meat is one of the most frequent sources of the exposure of NTS to the human, the cross-contamination from the poultry environment to the carcasses and meat poses a serious threat to public health, thus the interventions aimed at reducing the contamination with pathogenic bacteria are fundamental and require appropriate knowledge regarding the presence and dissemination of these pathogens at various steps during the processing stage (Berrang et al., 2007). Nevertheless, more studies are needed to fully understand which interventions are effective against

NTS contamination of the poultry-derived products in countries from the Americas.

We found substantial heterogeneity in the estimates at the national level. The disparate number of studies included for each country and the difference in the number of samples assessed could have increased the uncertainty of the estimations and thus cause part of the heterogeneity, this variability might reflect different husbandry practices and the absence of effective control measures across the poultry production chain (Antunes et al., 2016; Brochu et al., 2021). Despite successful control of NTS has involved actions such as culling and vaccination, the currently available vaccines have played a minor role in the control of fowl typhoid as they offer short-lived protection against clinical disease and limited or variable protection against infection with field strains (World Organization for Animal Health, 2018). Therefore, other containment methods including improved hygiene, increased biosecurity, segregated hatching, competitive exclusion treatment, and monitoring and removal of infected flocks could also be applied (EFSA Panel on Biological Hazards et al., 2019). Nevertheless, the differential implementation of these control measures caused by the variability in the poultry husbandry practices across countries from the Americas could explain part of the heterogeneous prevalence seen in these countries. In this regard, in several countries from South America the imposition of strict controls on the environment and hygiene of poultry husbandry is restricted due to high ambient temperatures (Barrow, Jones, Smith, & Wigley, 2012), thus causing differences in the incidence of NTS concerning countries with improved hygiene and management practices. Finally, national programs of poultry health, current legislation, and farmers' perceptions are also factors capable of affecting the monitoring and control of the pathogens in poultry as well as the biosecurity measures needed to avoid their spreading (de Oliveira Sidinei, Marcato, Perez, & Bankuti, 2021; Reis et al., 2021).

Our summary of evidence showed that Enteritidis and Typhimurium were identified in most of the countries, where they ranked among the top three serovars, thus coinciding with several studies that report Typhimurium and Enteritidis as the main serovars in poultry samples (Carraminana, Rota, Agustin, & Herrera, 2004; El-Sharkawy et al., 2017). The serovar distribution and prevalence found in countries from the Americas differ with the pattern reported in some European countries, which report as main serovars Infantis in Hungary (Tozser et al., 2019), Hadar, Anatum, and Mbandaka in France (Le Bouquin et al., 2010), and Enteritidis, Hadar, Virchow, and Ohio in Spain (Marin et al., 2011). However, the variety and prevalence of NTS serovars are expected to differ among the studies from different regions and types of farms (Andino & Hanning, 2015). Despite the great amount of NTS isolates included in the studies, the serovar diversity was rather low because only 131 serovars were identified; therefore, more studies are necessary to increase our knowledge regarding the NTS serovar diversity and frequency present in the poultry production chain of the countries from the Americas. Especially given that many serovars are restricted to a single region of the world that generates distinct profiles both within and between regions (Galanis et al., 2006).

Enteritidis was the serovar most prevalent in birds samples (mainly laying hens) and products and sub-products (mainly eggs and carcasses), which concurs with previous reports of salmonellosis outbreaks caused by consumption of eggs and poultry meat contaminated with this NTS serovar in the USA (Jackson, Griffin, Cole, Walsh, & Chai, 2013) and Europe (EFSA, 2019). Besides Typhimurium and Enteritidis, Heidelberg and Newport have also been highlighted as NTS serovars capable of causing a great burden of FBD due to poultry and poultry-derived products (Jajere, 2019) and our results confirm this for Heidelberg because this serovar was consistently found among the top five serovars in each of the three samples assessed in our study. Even more, Heidelberg was the most prevalent serovar found in environmental samples taken from production wastes and breeding facilities. Thus, the pattern of NTS serovars found across the different sources for each type of sample demonstrates the presence of the three most common serovars frequently associated with FBD caused by poultry and poultry-derived products.

Despite the global tendency to both reduce the indiscriminate use of antibiotics and increase awareness regarding their negative effect, our results demonstrate a high and alarming prevalence of multiresistance to antibiotics in NTS isolates. The pooled prevalence of AMR to 2-3 antibiotics was 36.2% with the highest values in birds and environmental samples, whereas resistance to [?] 4 antibiotics reached a pooled estimate of 49.6% with even a higher prevalence of 61.2% in birds. These results not only determine the magnitude

of the current AMR status in the poultry husbandry in the Americas but also emphasize the major public health issue linked to the presence and dissemination of NTS multiresistant strains throughout the poultry production chain that ultimately might reach to the human. This pattern of multiresistance could be a consequence of the combined use of antibiotics, which although is prohibited in several countries, remains as a common practice in several regions and countries.

Kentucky, Heidelberg, Typhimurium, Enteritidis, and Infantis were the top five NTS serovars with the highest prevalence of AMR in the poultry samples from the Americas, which partially coincide with several studies in which the highest prevalence of AMR was found in the serovars Enteritidis, Typhimurium, and Infantis (Carraminana et al., 2004; El-Sharkawy et al., 2017; Kunadu, Otwey, & Mosi, 2020). The presence of these isolates with AMR in the poultry production chain is a concern given that several actors from this husbandry and supply chain frequently handle equipment, animals, and products without the necessary protections and thus increase the risk of resistance transfer and spread to commensal bacteria (Reis et al., 2021). Besides, even though the serovar Heidelberg is not frequently reported among the main resistant serovars, we found that Heidelberg was the 2nd top-ranked serovar with AMR in the Americas and this is an important result for public health given that Heidelberg is one of the serovars that can induce systemic complications in people, especially children, the elderly or immunocompromised people (Silva, Milbradt, Zamae, Andreatti Filho, & Okamoto, 2016).

Cephalosporins, penicillins, tetracyclines, and aminoglycosides concentrated 71.9% of the resistant isolates and thus were the four main groups of antibiotics to which NTS was resistant in poultry samples from the Americas. This profile partially contrast with recent secondary studies, which reported that quinolones and beta-lactams in Europe (Antonelli et al., 2019) and sulphonamides, quinolones, and tetracyclines in Brazil (Voss-Rech et al., 2017) were the main groups of antibiotics to which NTS isolated from poultry and poultry-derived products were resistant. Even though the specific pattern of AMR was distinct among the poultry samples, tetracycline was consistently the 1st top-ranked, whereas ampicillin varied between the 2nd and 5th top-ranked. Such a result should probably reflect the fact that tetracyclines and penicillins were the largest selling antimicrobials, but their use gradually reduced while cephalosporins increased (Kim, Seo, Jeon, Lim, & Lee, 2018), thus causing an increase in AMR to cephalosporins in NTS from poultry as have been reported in NTS serovar Typhimurium, though with concurrent resistance to ciprofloxacin and ceftriaxone increasing in other serovars (Wong, Zeng, Liu, & Chen, 2013). AMR to ceftriaxone and ciprofloxacin in NTS isolates from poultry is of major interest to public health, because these two antibiotics in conjunction with azithromycin are the key drugs of choice for the treatment of invasive NTS infections. However, according to our profile of AMR, except for the samples from birds in which ceftriaxone was 8th top-ranked, none of these three antibiotics were among the top 10 antibiotics to which NTS was resistant.

4.2 Limitations

We detect several limitations in our study: 1) unpublished studies were not included to maintain a comparable level of methodological quality among the studies, which could introduce bias because only published studies were searched and included, 2) despite several databases were searched, we only found studies for 15/35 countries from the Americas, in consequence the epidemiological landscape found might not be representative for the countries that were not included, 3) our study only included poultry samples from broilers, laying hens, and reproducers and thus the epidemiological landscape for NTS in ducks, turkeys, quails, and ostriches still needs to be assessed in countries from the Americas, and 4) to provide an overall summary of the studies, we grouped a broad variety of poultry samples into three discrete categories that avoided the meta-analysis of the specific sources of NTS contamination within each particular stage or condition.

4.3 Conclusion

Our systematic review and meta-analysis both confirm the presence of NTS throughout the poultry productive chain in countries from the Americas and determines the magnitude of the prevalence of this pathogen that causes a high burden of FBD. Despite we found a reduced diversity of NTS serovars among the three types of poultry samples, the presence of zoonotic serovars capable of causing outbreaks was consistent across

countries. Besides, the results demonstrated a high and alarming prevalence of AMR in the NTS isolates from poultry samples, which in addition showed an increasing trend towards higher prevalence of multiresistance. Furthermore, we found that the serovars with the higher prevalence of AMR were those commonly reported in salmonellosis outbreaks associated with poultry. Taken together, these results confirm the growing concern of NTS as a public health problem caused by the consumption and exposure to contaminated poultry and poultry-derived products. Additionally, our results highlight the need for appropriate control measures against NTS in the entire poultry productive chain to prevent further emergence and dissemination of multiresistant serovars to the human, which threatens the successful treatment of invasive infections caused by this pathogen.

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ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data and material are available from the supplementary material that can be accessed online at the journal website.

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Figure Legends

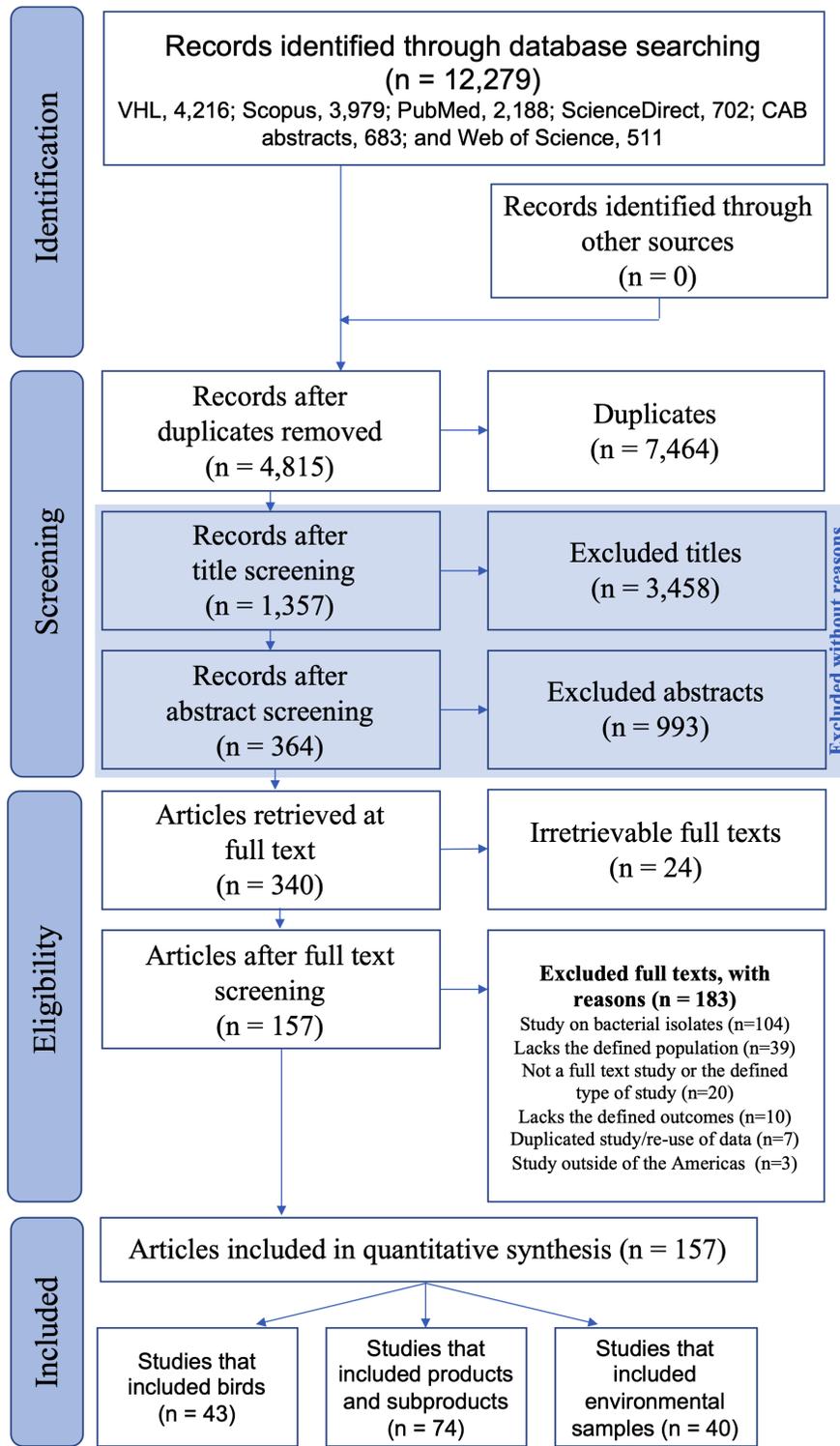
Fig. 1. PRISMA flow chart for the selection of studies included in the systematic review and meta-analysis.

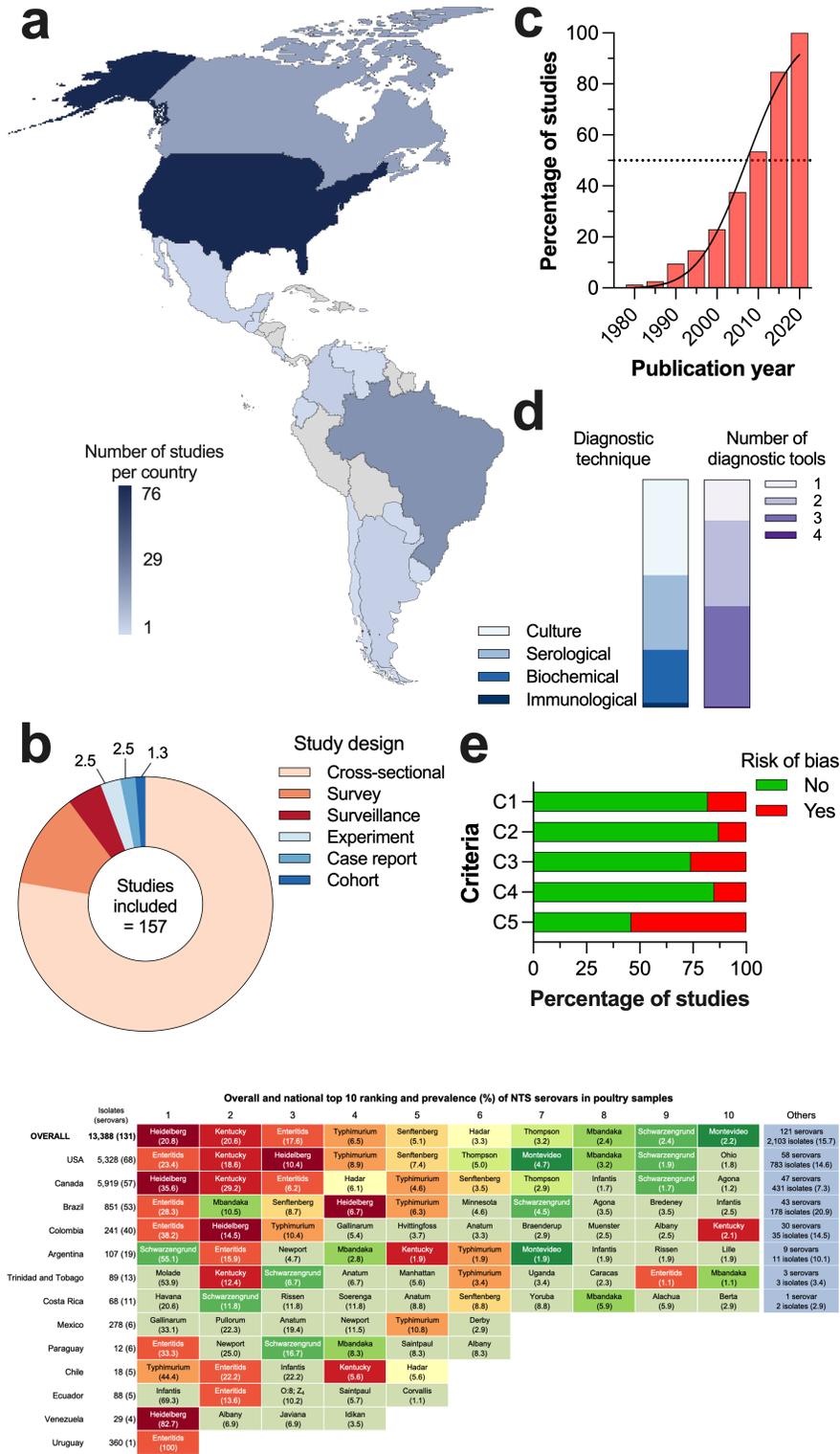
Fig. 2 . a) geographical distribution of the 157 studies included, b) distribution of the design of the study, c) cumulative frequency according to the year of publication, d) distribution of the diagnostic technique and the number of diagnostic tools used to detect NTS in poultry samples, and e) summary of the individual risk of bias assessment.

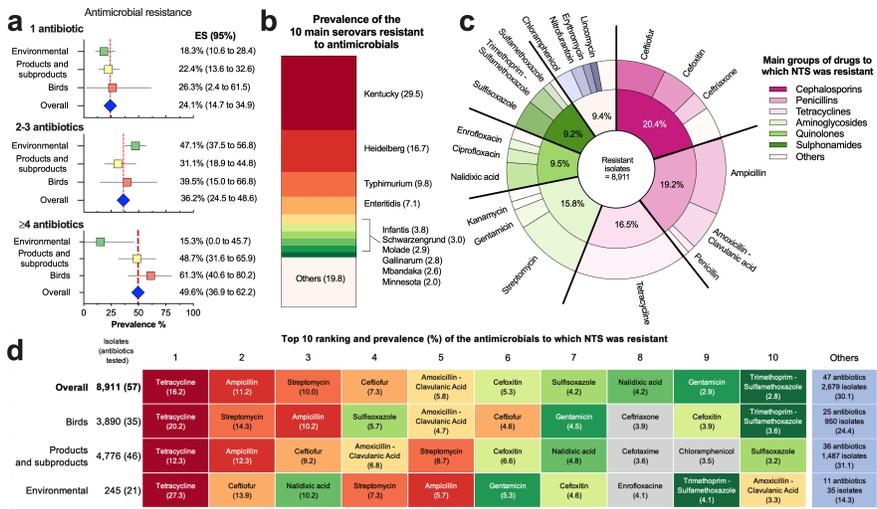
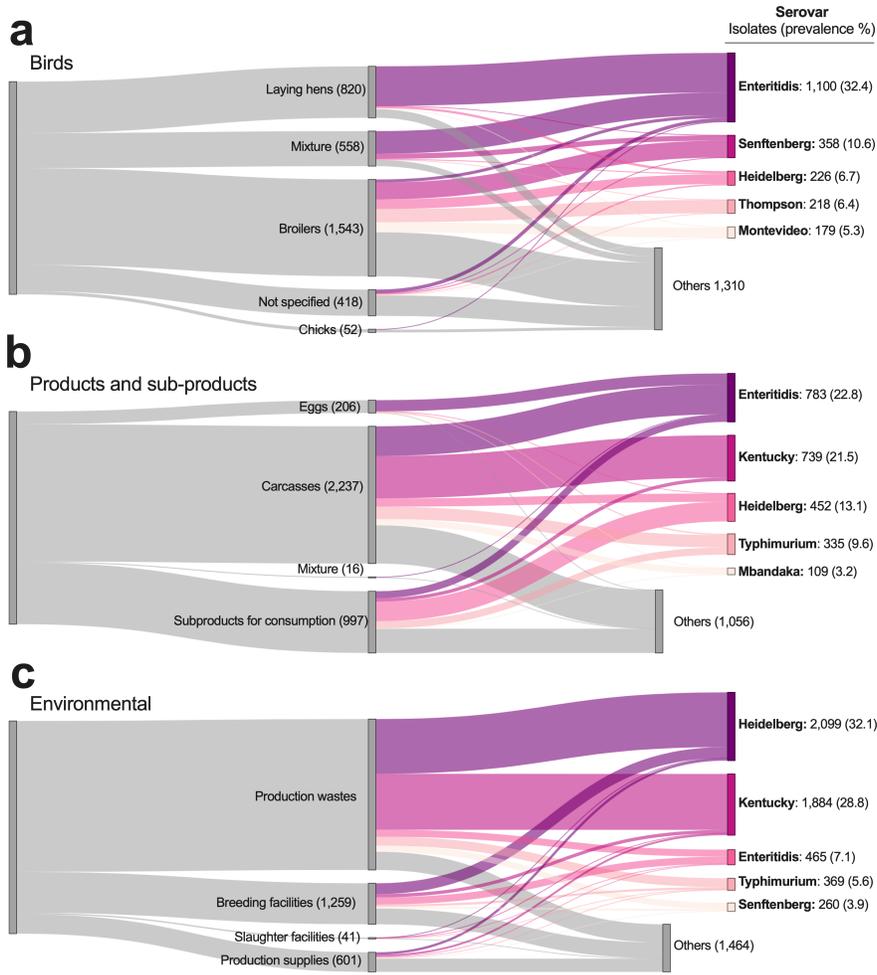
Fig. 3 . Top 10 ranking and prevalence of NTS in poultry samples from the Americas.

Fig. 4. Sankey diagrams for the distribution of the five main serovars of NTS in samples from a) birds, b) products and sub-products, and c) environmental.

Fig. 5. a) forest plot of the meta-analysis to estimate the prevalence of antimicrobial resistance in poultry samples, b) top 10 ranking of the NTS serovars that showed antimicrobial resistance, c) distribution of *Salmonella* isolates according to the group and antibiotic to which they showed resistance, and d) top 10 ranking of the antibiotics that were reported in resistant isolates.







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