



ORIGINAL ARTICLE

Antimicrobial resistance dissemination associated with intensive animal production practices in Argentina: A systematic review and meta-analysis



Barbara Prack McCormick^{a,*}, María P. Quiroga^b, Verónica E. Álvarez^b, Daniela Centrón^{b,*}, Pablo Tittone^{c,d}

^a Universidad Nacional de Lomas de Zamora, Facultad de Ciencias Agrarias, RP N° 4 km 2 (1836), Llavallol, Buenos Aires, Argentina

^b Laboratorio de Investigaciones en Mecanismos de Resistencia a Antibióticos, Instituto de Investigaciones en Microbiología y Parasitología Médica, Facultad de Medicina, Universidad de Buenos Aires - Consejo Nacional de Investigaciones Científicas y Técnicas (IMPAM, UBA-CONICET), Paraguay 2157 (PC 1121), Ciudad Autónoma de Buenos Aires, Argentina

^c Agroecology, Environment and Systems Group, Instituto de Investigaciones Forestales y Agropecuarias de Bariloche, Instituto Nacional de Tecnología Agropecuaria - Consejo Nacional de Investigaciones Científicas y Técnicas (IFAB, INTA-CONICET), Modesta Victoria 4450 - CC 277 (8400), San Carlos de Bariloche, Río Negro, Argentina

^d Groningen Institute of Evolutionary Life Sciences, Groningen University, PO Box 11103, 9700 CC Groningen, The Netherlands

Received 27 September 2021; accepted 7 July 2022

Available online 19 September 2022

KEYWORDS

Food-borne disease;
Microbial drug
resistance;
Multidrug resistance;
Livestock;
Farming systems

Abstract Abuse and misuse of antimicrobial agents has accelerated the spread of antimicrobial-resistant bacteria. The association between antimicrobial-resistant infections in humans and antimicrobial use in agriculture is complex, but well-documented. This study provides a systematic review and meta-analysis of the dissemination of antimicrobial resistance (AMR) to antimicrobials defined as critically important by the WHO, in swine, chicken, and cattle from intensive and extensive production systems in Argentina. We conducted searches in electronic databases (MEDLINE-PubMed, Web of Science, SciELO, the National System of Digital Repositories from Argentina) as well as in the gray literature. Inclusion criteria were epidemiological studies on AMR in the main food-transmitted bacteria, *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp., and mastitis-causing bacteria, isolated from swine, chicken, dairy and beef cattle from Argentina. This study gives evidence for supporting the hypothesis that AMR of common food-transmitted bacteria in Argentina is reaching alarming levels. Meta-analyses followed by subgroup analyses confirmed the association between the prevalence of AMR and (a) animal species ($p < 0.01$) for streptomycin, ampicillin and tetracycline or (b) the animal production system ($p < 0.05$) for streptomycin, cefotaxime, nalidixic acid, ampicillin and tetracycline. Moreover, swine (0.47 [0.29; 0.66]) and intensive production (0.62 [0.34; 0.83]) showed the highest pooled prevalence of multidrug resistance while dairy (0.056 [0.003; 0.524]) and extensive production (0.107 [0.043; 0.240]) showed the lowest. A research

* Corresponding authors.

E-mail addresses: b.mcprack@gmail.com (B. Prack McCormick), dcentron@gmail.com (D. Centrón).

<https://doi.org/10.1016/j.ram.2022.07.001>

0325-7541/© 2022 Asociación Argentina de Microbiología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

gap regarding beef-cattle from feedlot was identified. Finally, there is an urgent need for political measures meant to coordinate and harmonize AMR surveillance and regulate antimicrobial use in animal production.

© 2022 Asociación Argentina de Microbiología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

PALABRAS CLAVE

Enfermedad transmitida por los alimentos;
Resistencia microbiana a drogas;
Multidrogorresistencia;
Ganadería;
Sistema de cría

Diseminación de la resistencia a antimicrobianos asociada a prácticas de producción animal intensiva en Argentina: Una revisión sistemática y metaanálisis

Resumen El abuso y mal uso de los antimicrobianos aceleró la propagación de bacterias resistentes. La asociación entre las infecciones que presentan resistencia a antimicrobianos (RAM) en humanos y el uso de antimicrobianos en la producción agropecuaria es compleja, pero está bien documentada. Proporcionamos una revisión sistemática y metaanálisis sobre la diseminación de la resistencia a antimicrobianos designados como críticamente importantes por la Organización Mundial de la Salud (OMS) en cerdos, aves y bovinos de producción intensiva y extensiva en Argentina. Se buscó información en bases de datos electrónicas (Medline-PubMed, Web of Science, SciELO, Sistema Nacional de Repositorios Digitales de Argentina) y en la literatura gris. Se incluyeron estudios epidemiológicos sobre la RAM en las principales bacterias transmitidas por los alimentos – *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* y *Enterococcus* spp. – y bacterias causantes de mastitis aisladas de cerdos, pollos y bovinos. Los resultados de este estudio apoyan la hipótesis de que la RAM de las bacterias transmitidas por los alimentos alcanza niveles alarmantes. Los metaanálisis seguidos de análisis por subgrupos mostraron asociación entre la RAM y (a) el animal ($p < 0,01$) para estreptomicina, ampicilina y tetraciclina o (b) el sistema productivo ($p < 0,05$) para estreptomicina, cefotaxima, ampicilina, ácido nalidixico y tetraciclina. La mayor prevalencia conjunta de multirresistencia se detectó en cerdos (0,47 [0,29; 0,66]) y producción intensiva (0,62 [0,34; 0,83]), mientras que la menor correspondió a bovinos de leche (0,056 [0,003; 0,524]) y producción extensiva (0,107 [0,043; 0,240]). Se observó un vacío de información respecto de los bovinos de *feedlot*. Es urgente adoptar medidas políticas para coordinar y armonizar la vigilancia de la RAM y regular el uso de antimicrobianos en animales.

© 2022 Asociación Argentina de Microbiología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The discovery of antimicrobials has been one of the main advances in the history of medicine³⁰. The appropriate use of antimicrobials is important in ensuring human and animal health as well as welfare, food safety and food security^{27,64}. However, abuse and misuse of antimicrobials has allowed the global dissemination of antimicrobial resistance (AMR) in clinical and non-clinical species^{61,96}.

A well-known case of inappropriate use of antimicrobials is represented by livestock farming where much of its global use is to fulfill non-therapeutic purposes such as growth promotion and infection prevention^{2,7,9}. The world population growth coupled with a higher purchasing power in low- and middle-income countries has driven an increase in the demand for high-value animal protein⁸⁸. Therefore, the main food-producing countries, including Argentina, have opted for highly profitable and vertically integrated intensive production systems, which rely on the use of antimicrobials to maintain productivity and animal health⁷⁸.

There is compelling scientific evidence available to support that antimicrobial use on farms imposes a public health burden due to infections with resistant pathogens³⁷. Moreover, transference of AMR genes to the human gut microbiome can also occur through the food chain^{17,38,69}. Despite these risks, the use of antimicrobials in animals has remained largely unregulated⁴⁹.

If no political measures are taken to stop the spread of AMR, it is expected to cause 10 million deaths per year toward 2050, more than cancer-related deaths^{60,63}. Given the dry pipeline for new antimicrobials, we must expertly manage the drugs that are currently available³⁰. Therefore, the World Health Organization (WHO) in collaboration with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) have declared AMR an issue of global concern which does not recognize geographical nor human/animal boundaries and therefore, requires a holistic and multi-sectoral approach⁹⁵.

In June 2015, the Argentine Ministries of Health and Agriculture, Livestock and Fisheries approved the Argentine Strategy for Control of Antimicrobial Resistance, and

the National Commission for the Control of Antimicrobial Resistance was created (CONACRA, <https://www.argentina.gob.ar/tags/conacra>). As part of the action plan, an AMR surveillance program has begun. It started to analyze the prevalence of AMR of importance for public health, among commensal and pathogenic bacteria isolated from fecal samples obtained in slaughterhouses. In addition, the national registrations and certificates for the use and commercialization of animal feed containing antibiotics, antiparasitics or coccidiostats were automatically deregistered as of January 2019 (SENASA Resolution No. 1119/18). Moreover, since that year, the production, distribution, imports, use and possession of veterinary products containing colistin were also banned in Argentina (RESOL-2019-22-APN-PRES#SENASA). However, the use of certain antimicrobials as growth promoters for animal production is still allowed in this country (Luna F., personal communication, 2022, SENASA).

To date, there are no comprehensive studies that systematically document the dissemination of AMR in the rapidly growing, intensive animal production industry being developed in Argentina³³, a country with a longstanding tradition of extensive animal production systems (MAGYP, <https://www.magyp.gob.ar/sitio/areas>). Given the leading role of livestock industries in the economy of Argentina, representing approximately USD 4000 million exported to different markets yearly⁴⁰, the revision of AMR mechanisms in this area is mandatory.

Therefore, our objective was to document the dissemination of AMR to antimicrobials ranked as critically important for human medicine by the WHO, among commensal and pathogenic bacteria isolated from food-producing animals from Argentina, contrasting intensive and extensive production systems. These findings may help to develop highly relevant policies and regulations not just for Argentina but for other countries undergoing similar intensive animal production growth.

Methodology

Search strategy

A systematic search was conducted in the international databases MEDLINE-PubMed (ncbi.nlm.nih.gov/pubmed/), Web of Science ([webofknowledge.com](https://www.webofknowledge.com)), SciELO (scielo.org/en/), and the National System of Digital Repositories of Argentina (repositoriosdigitales.mincyt.gob.ar/vufind/). The search strategy included the terms “cattle”, “dairy”, “swine”, “pig”, “chicken”, “anti-infective agent resistance”, “antimicrobial resistance”, and “Argentina”. The last search was performed on January 24th 2022.

In addition, generic and academic searches were conducted in the Internet in order to identify relevant gray literature including conference papers and government documents. When necessary, the authors were contacted to obtain further information about their studies. Key informants from the National Service of Agri-Food Health and Quality (SENASA) were also contacted.

Study selection

Study selection was performed following the flowchart reported by Moher et al.⁵³ (Fig. 1). The first screening was performed at a title and abstract level, and the full texts of the records retained were assessed for eligibility. Those included were epidemiological studies about AMR in *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp., the main four food-transmitted bacteria isolated from swine, chicken, dairy and beef cattle, whose products were intended for human consumption, published in English or Spanish and which included the assessment of animals coming from farms in Argentina. Given that clinical mastitis was reported to be the most prevalent disease in adult dairy cows, which together with dry cow therapy, represent 85.4% of total drug usage at herd level³⁴, when the report was on dairy, mastitis-causing bacteria were also included. To be as inclusive and comprehensive as possible, there were no limits placed on study quality, with study quality issues handled through sensitivity analyses instead.

Finally, for the meta-analyses, studies that presented recovery strategies with antimicrobial selection or, selection based on the presence of an AMR genetic determinant were not considered eligible. Moreover, exclusively for the meta-analyses of food-transmitted bacteria, studies involving targeted sampling of animals with clinical symptoms were not considered eligible either.

Data extraction and definitions

When different animal species or bacterial genera had been included in a scientific article, each animal species or bacterial genus was included separately in the review as a particular “study”. Similarly, when a scientific article reported the results derived from different animal production systems, each one was considered as an individual study. Therefore, a single scientific article could represent several included studies. By contrast, when a scientific article reported results from different stages of animal breeding in the same farm, it was considered as a single study.

Data from the full text of the selected primary studies were extracted by using Excel spreadsheet, and graphics were made using Excel, Power Point, and the statistical software R-4.1.2 (2021-11-01). Information about geographical distribution, year of publication, food-producing animals sampled, animal production system (intensive, confined, extensive, family farming), type of samples, number of samples, sampling period, bacteria assessed, methodology to determine AMR, and the outcomes (number of isolates resistant to critically important antimicrobials and total isolates analyzed) were extracted from each article.

The definitions followed throughout the article were, prevalence: number of isolates over total samples analyzed; prevalence of resistance to critically important antimicrobials: number of isolates resistant over total isolates analyzed; and multidrug resistance (MDR): number of isolates resistant to three or more antimicrobial classes over total isolates analyzed⁴⁸. Isolates with intermediate

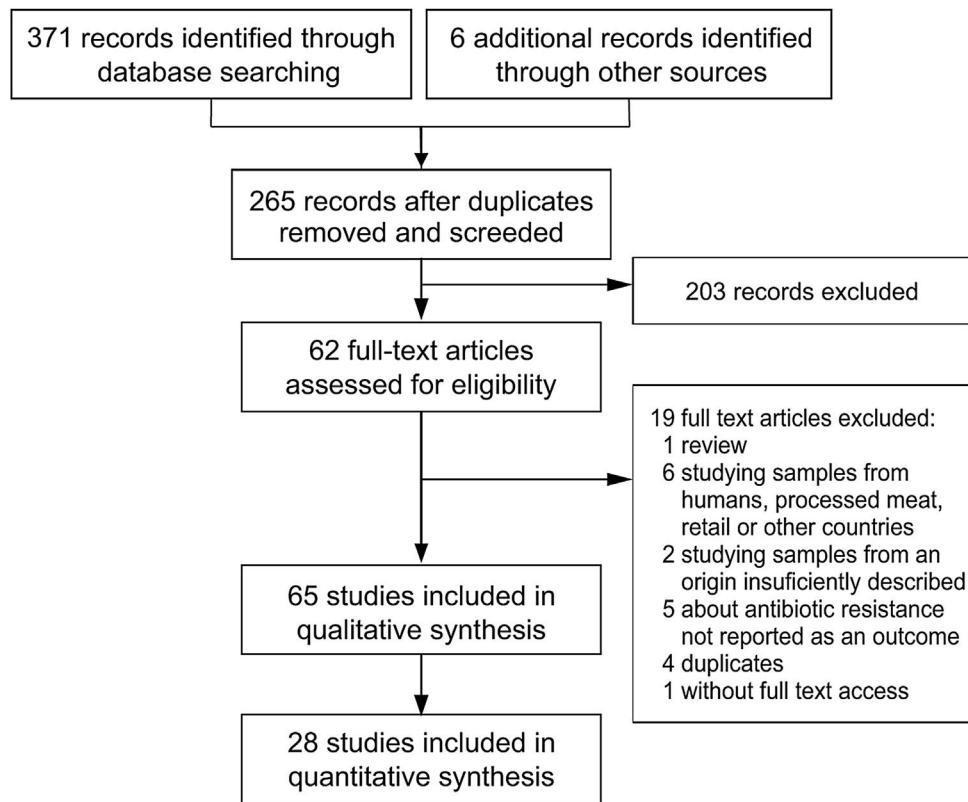


Figure 1 Flow diagram of selected studies included in the systematic review and meta-analyses.

susceptibility were classified as susceptible. When the definitions followed by the studies differed from the ones presented here, if possible, the outcomes were recalculated.

For production system comparison, systems were classified as 'intensive', 'extensive' or 'not described'. A study was assigned to the category 'intensive' if animal husbandry was classified by authors as intensive, industrialized and/or where animals spend most of their life confined indoors. On the contrary, a study was assigned to the category 'extensive' if animal husbandry was classified by the authors as extensive, free-range, backyard, family farming and/or where animals spend most of their life grazing outdoors. Studies with not enough information to classify their systems as 'intensive' or 'extensive' were considered 'not described'.

To simplify the AMR report we adopted the following terms to describe the levels of AMR occurrence: 'rare: <0.1%', 'very low: 0.1% to 1.0%', 'low: >1% to 10.0%', 'moderate: >10.0% to 20.0%', 'high: >20.0% to 50.0%', 'very high: >50.0% to 70.0%', 'extremely high: >70.0%'.

Statistical analysis

A statistical analysis was performed using the statistical software R-4.1.2 (2021-11-01) with the {meta}⁶ and {dmetar}⁵⁰ packages. Meta-analyses were conducted separately for each group of bacteria and each antimicrobial. Particularly

for food transmitted bacteria, meta-analyses were followed by subgroup analyses to explore the sources of heterogeneity. Each meta-analysis was only performed if there were six or more studies, and each subgroup analysis was only done if there were 10 or more studies, to reduce the risk of obtaining biased pooled estimates³⁵.

The binary parameter 'proportion' (with 95% confidence intervals) was the one selected to measure effect size³⁵. We pooled logarithmic proportion of resistant isolates by antimicrobial, using the Hartung-Knapp correction for random-effects model with the function *metaprop*. The method specified was inverse-variance pooling. The function *forest.meta* was used to construct Forest Plots.

Between-study heterogeneity was assessed using Cochran's Q test and the inconsistency index (I^2 -statistic). Sensitivity analyses were performed with the function *InfluenceAnalysis* from {dmetar}⁵⁰ to test for highly influential studies. The function performs the same analysis, but leaving-one-out in each iteration. Subgroup analyses were performed using the random-effects model, assuming common τ^2 in the subgroups³⁵. For food-transmitted bacteria, *a priori* subgroup analyses were planned to assess the association between AMR and (1) food-producing animals or (2) food-producing systems. *A posteriori*, a subgroup analysis for (3) bacteria was included, which was necessary because, based on the reduced number of studies, results from *Salmonella* spp. and *E. coli* were pulled together under the category *Enterobacteriaceae*.

The presence of publication bias was assessed using funnel plots with the function *funnel.meta* from {meta}⁶. Funnel plot asymmetry was tested using the Egger's regression test with the function *metabias*²³. This test was only performed in meta-analyses with 10 or more studies.

Results

Excluded studies

The literature search yielded two hundred and sixty-five records after duplicates were removed (Fig. 1). Reviews, studies on parasites or viruses, studies about samples from humans, processed meat, retail or other countries, studies on the development of new drugs or new treatments, studies about alternative growth promoters or methods and studies where AMR was not tested or tested only by PCR, were excluded.

Overview of included studies

Forty-three articles of two hundred and sixty-five screened were eligible for qualitative synthesis (Fig. 1). Among these articles, the first one was published in 1997, two were subsequently published until 2000, nine between 2001 and 2010, twenty-seven between 2011 and 2020, and the remaining four in 2021 (Fig. 1).

Within the eligible articles a total of sixty-five studies was identified, differing in geographical distribution, subjects studied, animal production systems and, methods and guidelines followed to identify AMR (Fig. 1). Of Argentina's twenty-three provinces, the data came mainly from those in the center region of the country. Buenos Aires province was the most represented one, followed by the provinces of Cordoba, Santa Fe and Entre Ríos (Fig. 1A).

At least one study was found about each food-producing animal (chicken, swine, beef-cattle and dairy), food-transmitted bacteria (*E. coli*, *Enterococcus* spp., *Salmonella* spp., *Campylobacter* spp.) and the main mastitis-causing bacteria (Fig. 2B and C). The largest proportion of studies assessed swine^{3,8,12,13,24,39,42,45,56–59,65,66,89,91–93}, followed by dairy^{11,12,16,31,32,36,44,52,55,58,67,68,71,73,79–83,89}, chicken^{14,18–20,62,65,72,86,98} and beef cattle^{12,44,52,65,79,89} (Fig. 2B). Among mastitis-causing bacteria, all isolates belonged to genera *Staphylococcus*^{11,31,32,55,68,71,73,80–83} and *Streptococcus*^{16,36}. While *E. coli* was the most frequently studied food-transmitted bacteria^{3,8,12,18,19,24,44,45,52,56–59,65,67,79,86,89} (Fig. 2C), *Staphylococcus* was the most studied mastitis-causing genus (Fig. 2C).

With respect to the methods applied to test susceptibility to antimicrobials, disk diffusion was the one preferred by almost all authors (Fig. 2D). The main exception was broth microdilution^{3,18,19,55,71}, which was particularly needed to test susceptibility to colistin. Conversely, the E-test was used as a complement, but never as an only option^{16,62,73,82}. Similarly, when comparing guidelines, all authors followed NCCLS guidelines – before 2008 – or CLSI guidelines – after 2008 – except for particular antimicrobials (Fig. 2E). For example, CASFM guidelines were followed by some authors

when assessing susceptibility to streptomycin⁶⁵ and EUCAST guidelines when assessing susceptibility to colistin^{18,19}.

Overview of antimicrobial resistance

Reports on AMR were initially divided into five groups which included the following bacteria (Fig. 3). Group 'Campylobacter' included *Campylobacter* spp.^{65,98} and *Campylobacter jejuni*⁶²; group 'Enterococcus' only included *Enterococcus* spp.^{14,65,91}; group 'E. coli' included *E. coli*^{3,18,24,56,58,59,65,79,86,89}, Shiga toxin-producing *E. coli*^{12,44,52}, enterotoxigenic *E. coli*⁵⁷, colistin-resistant *E. coli*¹⁹ and integron positive *E. coli*^{12,45}; group 'Salmonella' included *Salmonella* spp.^{13,65,72,86,92,93}, *Salmonella enterica*^{42,66}, *Salmonella enterica* subspecies *enterica*³⁹ and *Salmonella* Heidelberg^{13,20}; and group 'dairy' included *E. coli*^{79,89}, Shiga toxin-producing *E. coli*^{12,44}, enterotoxigenic *E. coli*⁶⁷, integron positive *E. coli*¹², and mastitis-causing bacteria *Staphylococcus aureus*^{31,55,68,73,80,81,83}, coagulase-negative staphylococci^{32,71,80,82,83}, coagulase-positive staphylococci¹¹, *Streptococcus* spp.¹⁶ and *Streptococcus agalactiae*³⁶.

The overview of antimicrobials tested included almost every class classified as critically important for human medicine by the 5th WHO ranking (Fig. 3). While some antimicrobials were tested against all bacteria, others were only tested in certain bacteria. Particularly, not enough information was gathered to perform the meta-analyses for *Campylobacter* spp. and *Enterococcus* spp. The five groups defined in the previous paragraph were tested for susceptibility to aminoglycosides, macrolides, penicillins and tetracyclines. 'E. coli', 'Salmonella', 'Campylobacter' and 'dairy' were also tested for susceptibility to quinolones. Additionally, 'E. coli'^{19,24,45} and 'Salmonella'^{13,20,42} surveillance included carbapenems, 3rd and 4th generation cephalosporins, monobactams, phosphonic acid derivatives and polymyxins. Moreover, glycopeptides and oxazolidinones were tested in 'Enterococcus'^{14,65,91}. Three recent papers included ansamycins^{55,67} (*S. aureus* and *E. coli*) and glycolcyclines²⁴ (*E. coli*). Finally, reports about 5th generation cephalosporins and lipopeptides, were not identified.

Qualitative synthesis of antimicrobial resistance

This section intends to qualitatively summarize the data on AMR available in Argentina for those bacteria and antimicrobials for which there is yet not enough information to conduct a meta-analysis. It also includes data from studies based on samples from animals with clinical symptoms and isolates obtained using selective pressure or molecular selection. Therefore, it should be considered with caution.

Campylobacter spp.

Five studies extracted from three articles reported prevalence of resistance within this group; one study in swine⁶⁵ and four^{62,65,98} in chicken, with no reports from beef cattle (Fig. 3 and Suppl. table* S2).

In swine, Pantozzi et al. analyzed prevalence of resistance of *Campylobacter* spp. strains isolated from animals from intensive production⁶⁵. Resistance to tetracycline (80%), nalidixic acid (80%), ciprofloxacin (60%),

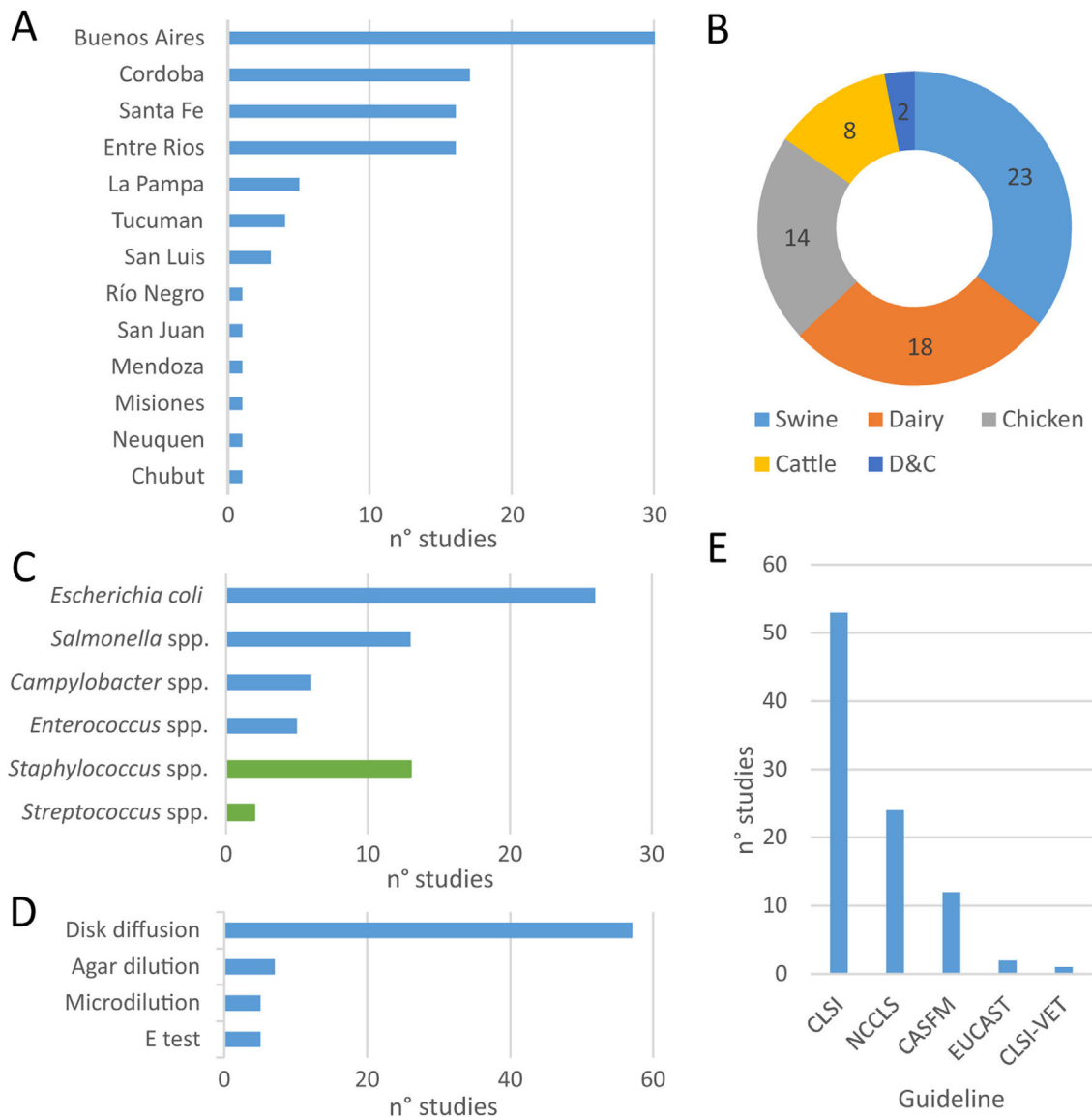


Figure 2 Geographic distribution of studies on antimicrobial resistance included in this review (A), coverage of food-producing animals (B) and bacteria (C), methods used (D) and guidelines followed (E) for antimicrobial resistance testing and interpretation of results. More information about each of the studies is available in [Suppl. table* S1](#).

erythromycin (20%) and ampicillin (20%) was found, and absence of resistance only to gentamicin.

In chicken, Pantozzi et al. (2010) assessed one strain of *Campylobacter* spp., Notario et al. (2011) *C. jejuni* isolated from broilers and laying hen belonging to industrial and family farming, and Zbrum et al. (2015) *Campylobacter* spp. from hens and broilers from six poultry meat supply chains. The only strain reported by Pantozzi et al. (2010) was resistant to tetracycline and nalidixic acid and sensitive to gentamicin, ciprofloxacin, erythromycin and ampicillin⁶⁵. On the other hand, Notario et al. (2011) reported that all strains isolated from industrial farming were resistant to ciprofloxacin, differing from family farming chicken where only 38.9% were resistant to this antimicrobial⁶². Finally, Zbrum et al. (2015) reported resistance to all antimicrobials tested including aminoglycosides, quinolones, macrolides, penicillins and tetracyclines. Among those, extremely high

prevalence of AMR was reported for nalidixic acid and ciprofloxacin and very high for doxycycline and ampicillin⁹⁸ (Fig. 3 and [Suppl. table* S2](#)).

***Enterococcus* spp.**

Five studies extracted from three articles reported results involving AMR of strains from the genus *Enterococcus*, coming from swine^{65,91}, chicken^{14,65} and beef cattle⁶⁵ (Fig. 3 and [Suppl. table* S2](#)).

In swine and chicken, studies on *Enterococcus* spp. present similar AMR patterns. Extremely high prevalence of resistance was reported for tetracycline and erythromycin, while complete susceptibility was reported for ampicillin and linezolid. With regard to vancomycin, isolates assessed by Pantozzi et al. (2010) had complete susceptibility. However, Delpech et al. (2018) and Vallejo et al. (2021) found low prevalence of resistance to vancomycin and teicoplanin in isolates from swine and chicken.

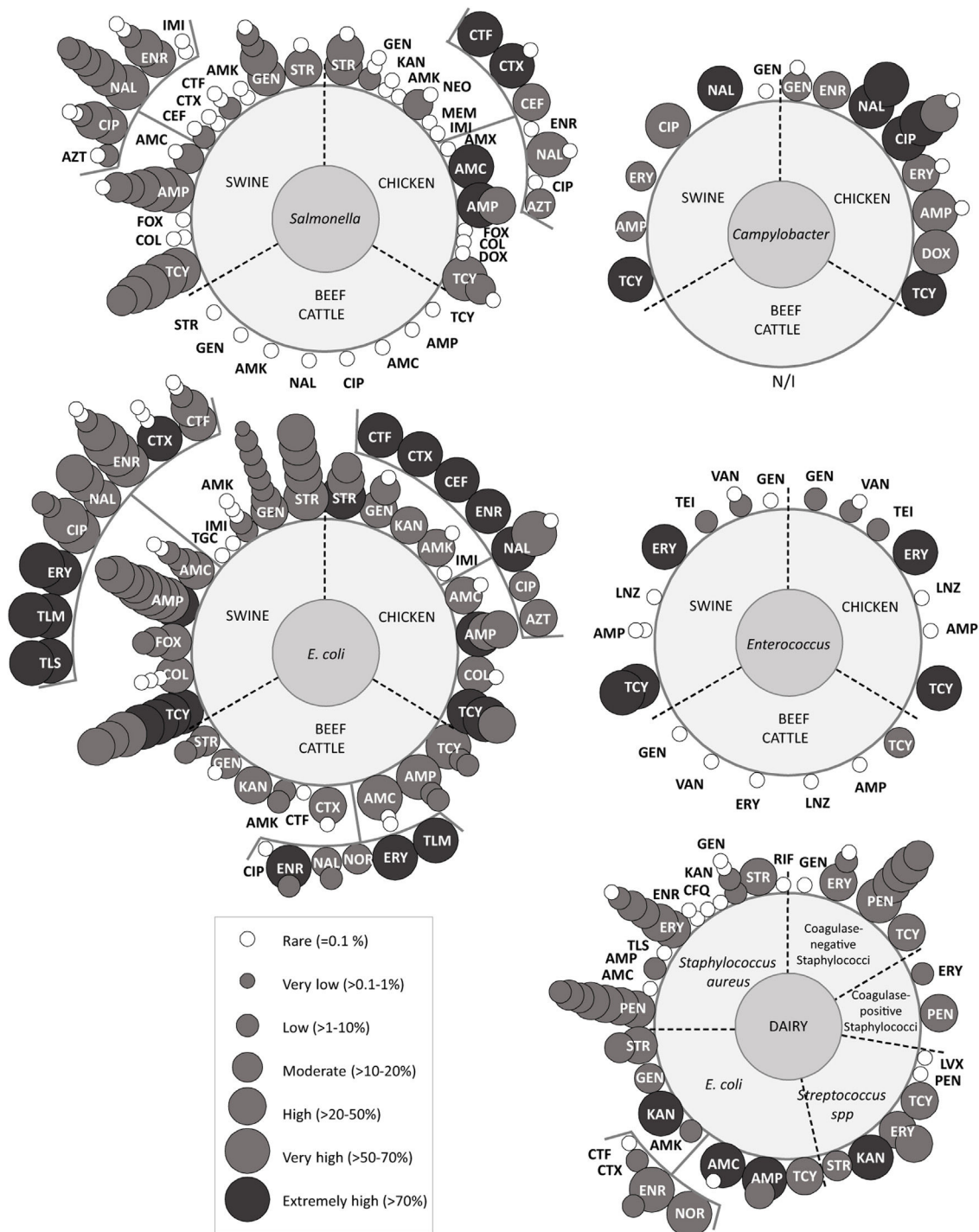


Figure 3 Antimicrobial resistance rates to critically important antimicrobials reported for each bacteria and food-producing animal included; overlapped spheres represent AMR reported by different studies. AMK: amikacin; AMP: ampicillin; AMX: amoxicillin; AMC: amoxicillin + clavulanic acid; AZT: aztreonam; CEF: cefepime; CFQ: cefquinome; CIP: ciprofloxacin; COL: colistin; CTF: ceftiofur; CTX: cefotaxime; DOX: doxycycline; ENR: enrofloxacin; ERY: erythromycin; FOX: fosfomycin; GEN: gentamicin; IML: imipenem; KAN: kanamycin; LVX: levofloxacin; LZD: linezolid; MEM: meropenem; NAL: nalidixic acid; NEO: neomycin; NOR: norfloxacin; PEN: penicillin; POL: polymyxin; RIF: rifampin; STR: streptomycin; TEI: teicoplanin; TGC: tigecycline; TLM: tilimicosin; TLS: tylosin; TCY: tetracycline; VAN: vancomycin. This figure includes data from articles that presented recovery strategies with antimicrobial selection or, selection by the presence of a genetic determinant of AMR, or targeted sampling of animals with clinical symptoms. Studies about *E. coli* with less than 4 isolates were not represented in the figure. More information is available in [supplementary data](#).

In beef cattle from extensive production, Pantozzi et al. (2010) reported moderate prevalence of resistance to tetracycline and complete susceptibility to all other antimicrobials tested, including vancomycin.

Escherichia coli

E. coli was the most studied bacteria in the reports included in this review. Results from the meta-analyses for streptomycin, gentamicin, amikacin, cefotaxime, enrofloxacin, nalidixic acid, ciprofloxacin, amoxicillin with clavulanic acid, ampicillin, and tetracycline are shown in Section “*Enterobacteriaceae*”.

In swine, three studies assessed *E. coli* strains from animals with no clinical signs^{56,65,89}, others assessed *E. coli* isolated from swine with diarrhea^{3,8,58,59}, or diarrheic piglets and healthy pigs²⁴, enterotoxigenic *E. coli*³⁵ and integron positive *E. coli*⁴⁵ or Shiga-toxin producing *E. coli*¹². For this food-producing animals, AMR to almost all antimicrobial agents evaluated was observed, except for carbapenems and glycolcyclines. Isolates assessed in the initial reports were susceptible to colistin^{56,57,65,66} until 2019; Faccone et al. (2019) reported extremely high levels of AMR to cefotaxime and high levels of AMR to colistin²⁴, when isolating *E. coli* using plates containing cefotaxime, colistin or both. Moreover, at least one study reported very high resistance to enrofloxacin^{3,8,45} and ciprofloxacin^{24,58}. In swine with diarrhea, extremely high prevalence of AMR to erythromycin, tilmicosin and tylosin was found^{3,8}.

In chicken, Tessi et al. (1997), Pantozzi et al. (2010) and Dominguez et al. (2017) studied *E. coli*, while Dominguez et al. (2018) studied colistin-resistant *E. coli*, most of them from intensive farming^{18,19,65} or not described⁸⁶. With respect to colistin, 49% of *E. coli* strains were resistant to this antimicrobial¹⁸. Furthermore, colistin-resistant *E. coli* testing showed higher prevalence of resistance than *E. coli* to all antimicrobials except amikacin¹⁹. Thus, extremely high prevalence of AMR was reported for streptomycin, ceftiofur, cefotaxime, cefepime, enrofloxacin, nalidixic acid, ampicillin and tetracycline¹⁹. Finally, complete susceptibility to imipenem and meropenem was reported¹⁹ (Fig. 3 and Suppl. table* S2).

In beef cattle, Pantozzi et al. (2010) and Torres et al. (2017) assessed *E. coli* strains in healthy animals raised in extensive production^{65,89}. Absence of AMR was reported for ceftiofur⁸⁹ (Fig. 3). In *E. coli*⁷⁹ and Shiga toxin-producing *E. coli*^{12,44,52} from diarrheic dairy and beef-cattle calves, authors reported high resistance to polymyxin B⁵², very high resistance to gentamicin⁵², amoxicillin/clavulanic acid⁷⁹ and extremely high AMR to neomycin^{52,79}, enrofloxacin⁷⁹ and tetracycline⁵² (Fig. 3 and Suppl. table* S2).

In dairy, studies assessed *E. coli* from healthy cows or diarrheic calves. Torres et al. (2017) assessed *E. coli* isolated from vaginal samples of healthy cows. The authors reported complete susceptibility to ceftiofur. Results from healthy cows (see Section “*Enterobacteriaceae*”) contrast with those obtained when assessing *E. coli*⁷⁹, enterotoxigenic *E. coli*⁶⁷, and Shiga-toxin producing *E. coli*⁴⁴ from diarrheic calves. Prevalence of AMR in diarrheic calves ranged from rare to extremely high for streptomycin, kanamycin, and amoxicillin with clavulanic acid. Pasayo et al. (2019) reported resistance to rifampicin in the three isolates

assessed⁶⁷, while most authors reported complete susceptibility to cefotaxime (Fig. 3 and Suppl. table* S2).

Salmonella spp.

Eleven studies reported prevalence of AMR within this group; seven studies in swine^{13,39,42,66,92,93}, three in chicken^{20,72,86} and one in beef cattle⁶⁵ (Fig. 3 and Suppl. table* S2). Results from the meta-analyses for streptomycin, gentamicin, amikacin, cefotaxime, enrofloxacin, nalidixic acid, ciprofloxacin, amoxicillin with clavulanic acid, ampicillin, and tetracycline are shown in Section “*Enterobacteriaceae*”.

In swine, most studies evaluated AMR patterns in *Salmonella* spp. strains isolated from intensive production, including confined farrow-to-finish farms^{13,66,92,93}, while Joaquim et al. (2021) compared intensive production to backyard farms. Prevalence of AMR was rare to fosfomycin⁹³ and polymyxins^{92,93}. The most recent study (2021) showed low resistance to 3rd and 4th generation cephalosporins, ceftiofur and cefepime, in intensive production⁴². Extremely high AMR was reported for amoxicillin⁹² (Fig. 3 and Suppl. table* S2).

In chicken, Tessi et al. (1997) and Rodríguez et al. (2018) assessed *Salmonella* spp. while Dominguez et al. (2021) assessed *Salmonella* Heidelberg. On the one hand, all strains isolated from 657 tested-chicken from family farms were susceptible to all antimicrobials tested, including phosphonic acid derivatives⁷². On the other hand, when assessing *Salmonella* Heidelberg from intensive production, very high prevalence of AMR was reported for ceftiofur and cefepime²⁰.

Mastitis-causing bacteria

In dairy, the prevalence of AMR was tested for a lower number of antimicrobials. For *S. aureus*, all authors tested AMR to penicillin and erythromycin and results from the meta-analyses are presented in Section “*Staphylococcus aureus*”. The main fluoroquinolone tested was enrofloxacin and results showed rare prevalence of resistance for *S. aureus*^{55,73}. Other bacteria assessed were coagulase-negative staphylococci^{32,71,80,82,83}, coagulase-positive staphylococci¹¹ and *Streptococcus* spp.^{16,36} (Fig. 2). The highest AMR prevalence reported in mastitis-causing bacteria was 83.3% of kanamycin-resistant *Streptococcus agalactiae*³⁶.

MDR was low^{68,81} or absent^{16,55,73} in *Staphylococcus* spp. isolated from dairy, with the highest value being 5.9% reported for coagulase-negative staphylococci⁷¹. However, MDR was considerably higher in *S. agalactiae*, where 25% of the isolates were resistant to three or more antimicrobial classes³⁶.

Quantitative synthesis of antimicrobial resistance: meta-analyses

Twenty-eight studies, of sixty-five included in the qualitative synthesis, were finally included in the quantitative synthesis (Suppl. Fig. S1). Among food-transmitted bacteria, twenty-one studies involved *Enterobacteriaceae*, while not enough studies were available to perform meta-analyses for *Campylobacter* spp. or *Enterococcus* spp. Among

Table 1 Prevalence of multidrug resistance in bacteria isolated from food-producing animals in Argentina.

Antimicrobial	No. of studies	No. of isolates	Pooled estimate ^a	95% CI	<i>I</i> ^{2b}	Cochran Q <i>p</i> -value	Egger's <i>p</i> -value ^c
<i>Enterobacteriaceae</i>							
Streptomycin	17	646	0.2659	[0.1632; 0.4022]	82.0%	<0.0001	0.0345
Gentamicin	17	700	0.0753	[0.0328; 0.1635]	71.9%	<0.0001	0.0017
Amikacin	10	380	0.0649	[0.0196; 0.1939]	80.4%	<0.0001	0.0219
Amikacin*	9	331	0.0483	[0.0181; 0.1229]	31.9%	0.1629	NA
Cefotaxime	11	440	0.0327	[0.0064; 0.1516]	77.6%	<0.0001	0.0006
Cefotaxime*	10	420	0.0154	[0.0075; 0.0314]	0.0%	0.8745	0.0003
Enrofloxacin	11	390	0.1006	[0.0405; 0.2285]	76.4%	<0.0001	0.0177
Nalidixic acid	16	688	0.2425	[0.1103; 0.4527]	86.0%	<0.0001	0.0501
Ciprofloxacin	12	430	0.0890	[0.0380; 0.1944]	59.8%	0.0041	0.0188
Amoxi-cillin/clav. acid	14	445	0.0752	[0.0248; 0.2061]	79.2%	<0.0001	0.0243
Ampicillin	19	685	0.3275	[0.1880; 0.5061]	86.2%	<0.0001	0.3172
Tetracycline	20	697	0.4701	[0.2941; 0.6538]	87.7	<0.0001	0.3631
Multidrug resistance							0.6312
<i>Staphylococcus aureus</i>							
Penicillin	7	663	0.2556	[0.1412; 0.4177]	84.6%	<0.0001	NA
Erythromycin	6	633	0.1245	[0.0365; 0.3484]	85.5%	<0.0001	NA

* Meta-analysis excluding outliers or influential studies: amikacin excluding Pantozzi et al. (2010) cattle; cefotaxime excluding Dominguez et al. (2021). (a) Pooled estimate prevalence of isolates resistant to the antimicrobials. (b) Heterogeneity index. (c) Egger's regression test of Funnel plot asymmetry. CI: confidence interval; NA: not available due to study limitations.

mastitis-causing bacteria, there were enough studies only for *S. aureus*.

Enterobacteriaceae

The number of studies that analyzed the AMR of isolates depended on the antimicrobial agent considered. At least ten studies were available for streptomycin, gentamicin, amikacin, cefotaxime, enrofloxacin, nalidixic acid, ciprofloxacin, amoxicillin with clavulanic acid, ampicillin, and tetracycline. The pooled estimate of the prevalence of *Enterobacteriaceae* bacteria resistant to each of these antimicrobials is shown in Table 1. The highest prevalence of AMR was observed for tetracycline, followed by ampicillin, streptomycin and nalidixic acid. The lowest prevalence was observed for gentamicin and amikacin. Between-study heterogeneity was substantial for most antimicrobials. Funnel plots estimating publication bias are shown in Suppl. Fig. S1. According to the Egger's regression test, most antimicrobials could be affected by publication bias related to small studies, except for ampicillin, tetracycline, nalidixic acid and MDR (Table 1).

The AMR pattern of streptomycin, ampicillin and tetracycline was associated with the animal species from which they were isolated ($p < 0.01$) (Table 2). *Enterobacteriaceae* isolates from swine (followed by chicken) showed the highest prevalence of resistance to the three antimicrobials, with pooled estimates ranging from 0.40 [95% CI = 0.22; 0.63] for streptomycin to 0.64 [95% CI = 0.39; 0.83] for tetracycline. On the contrary, isolates from beef-cattle showed the lowest prevalence of resistance to the same antimicrobials, with pooled estimates ranging from 0.07 [95% CI = 0.01; 0.42] for streptomycin to 0.10 [95% CI = 0.04; 0.21] for tetracycline.

The AMR pattern of *Enterobacteriaceae* to streptomycin, cefotaxime, nalidixic acid, ampicillin and tetracycline was associated with the animal production system from which they were isolated ($p < 0.05$) (Table 2). Isolates coming from intensive production showed higher prevalence of resistance to each antimicrobial than isolates from extensive production. In intensive production, pooled estimates for these antimicrobials ranged from 0.066 [95% CI = 0.002; 0.663] for cefotaxime to 0.67 [95% CI = 0.438; 0.844] for tetracycline. In extensive animal production, pooled estimates for these antimicrobials ranged from 0.023 [95% CI = 0.004; 0.109] for cefotaxime to 0.17 [95% CI = 0.094; 0.282] for tetracycline.

Prevalence of AMR to amoxicillin with clavulanic acid was the only one associated with the bacteria within *Enterobacteriaceae* ($p < 0.05$) (Table 2). In this case, isolates from the genus *Salmonella* had a higher pooled estimate of AMR than *E. coli*, i.e., 0.27 and 0.04 respectively.

MDR in *Enterobacteriaceae* was associated with both the animal species ($p < 0.01$) and the animal production system ($p < 0.001$) (Fig. 4). Within each subgroup analysis, swine (followed by chicken) and intensive production showed the highest prevalence of MDR with respective pooled estimates of 0.47 [0.29; 0.66] and 0.62 [0.34; 0.83]. Dairy (followed by beef-cattle) and extensive production showed the lowest prevalence of MDR with respective pooled estimates of 0.056 [0.003; 0.524] and 0.107 [0.043; 0.240]. Results on dairy production should be considered with caution because there is only one study included.

Staphylococcus aureus

At least six studies were available with results on the prevalence of resistance to penicillin and erythromycin.

Table 2 Subgroup meta-analyses for *Enterobacteriaceae* from food-producing animals, by stratification variable.

Antimicrobial	Subgroup		N° studies	Pooled estimate	95% CI	Q	I ²	Q _s	p-value _s
Streptomycin	Animal	Swine	8	0.4045	[0.2161; 0.6260]	44.39	84.2%	12.17	0.0068
		Chicken	5	0.2770	[0.1232; 0.5110]	11.05	63.8%		
		Cattle	3	0.0659	[0.0069; 0.4191]	2.00	0.0%		
		Dairy	1	0.1667	[0.0299; 0.5651]	0.00	-		
	System	Nd	4	0.4197	[0.1618; 0.7304]	32.17	90.7%	8.40	0.0150
		Intensive	6	0.3393	[0.1737; 0.5565]	20.97	76.2%		
		Extensive	7	0.1139	[0.0392; 0.2883]	15.25	60.7%		
	Bacteria	<i>E. coli</i>	10	0.2990	[0.1452; 0.5185]	70.05	87.2%	0.88	0.3494
		<i>Salmonella</i>	7	0.2008	[0.0872; 0.3980]	11.05	45.7%		
Gentamicin	Animal	Swine	10	0.0999	[0.0314; 0.2755]	35.42	74.6%	1.08	0.5833
		Chicken	5	0.0427	[0.0049; 0.2860]	17.05	76.5%		
		Cattle	2	0.0420	[0.0000; 1.0000]	1.90	47.5%		
	System	Nd	4	0.0224	[0.0012; 0.3041]	13.21	77.3%	4.31	0.1157
		Intensive	8	0.1429	[0.0428; 0.3833]	26.55	73.6%		
		Extensive	5	0.0480	[0.0124; 0.1685]	2.68	0.0%		
	Bacteria	<i>E. coli</i>	6	0.0594	[0.0136; 0.2246]	17.80	71.9%	0.22	0.6423
		<i>Salmonella</i>	11	0.0850	[0.0248; 0.2531]	36.40	72.5%		
Amikacin	Animal	Swine	6	0.0322	[0.0054; 0.1698]	8.72	42.7%	3.14	0.2084
		Chicken	2	0.2002	[0.0000; 1.0000]	5.24	80.9%		
		Cattle	2	0.1085	[0.0018; 0.8913]	0.19	0.0%		
	System	Nd	2	0.0199	[0.0000; 0.9999]	1.94	48.5%	1.70	0.4266
		Intensive	5	0.0942	[0.0065; 0.6236]	19.65	79.6%		
		Extensive	3	0.0771	[0.0092; 0.4287]	0.93	0.0%		
	Bacteria	<i>E. coli</i>	5	0.0700	[0.0092; 0.3792]	32.89	87.8%	0.04	0.8326
		<i>Salmonella</i>	5	0.0553	[0.0046; 0.4271]	8.13	50.8%		
Cefotaxime	Animal	Swine	7	0.0157	[0.0052; 0.0463]	3.93	0.0%	1.37	0.5043
		Chicken	3	0.2071	[0.0000; 0.9999]	23.12	91.4%		
		Cattle	1	0.0109	[0.0001; 0.5725]	0.00	-		
	System	Nd	2	0.0062	[0.0009; 0.0392]	0.02	0.0%	13.14	0.0014
		Intensive	6	0.0659	[0.0025; 0.6632]	35.84	86.0%		
		Extensive	3	0.0227	[0.0044; 0.1094]	0.44	0.0%		
	Bacteria	<i>E. coli</i>	5	0.0101	[0.0078; 0.0131]	0.09	0.0%	2.96	0.0854
		<i>Salmonella</i>	6	0.0841	[0.0035; 0.7070]	33.64	85.1%		
Enrofloxacin	Animal	Swine	8	0.1148	[0.0312; 0.3431]	34.09	79.5%	0.56	0.9061
		Chicken	1	0.0385	[0.0008; 0.6604]	0.00	-		
		Cattle	1	0.0652	[0.0038; 0.5614]	0.00	-		
		Dairy	1	0.0556	[0.0021; 0.6243]	0.00	-		
	System	Nd	2	0.0507	[0.0000; 1.0000]	5.20	80.8%	1.87	0.3931
		Intensive	3	0.2197	[0.0060; 0.9296]	13.12	84.8%		
		Extensive	6	0.0707	[0.0238; 0.1919]	7.07	29.3%		
	Bacteria	<i>E. coli</i>	5	0.1041	[0.0283; 0.3166]	7.39	45.9%	0.02	0.8762
		<i>Salmonella</i>	6	0.0917	[0.0145; 0.4086]	28.24	82.3%		
Nalidixic acid	Animal	Swine	10	0.2883	[0.1414; 0.4992]	45.66	80.3%	4.52	0.1043
		Chicken	4	0.2006	[0.0013; 0.9800]	32.67	90.8%		
		Cattle	2	0.0947	[0.0002; 0.9830]	0.38	0.0%		
	System	Nd	4	0.0584	[0.0018; 0.6837]	37.00	91.9%	21.67	<0.0001
		Intensive	8	0.4846	[0.3034; 0.6698]	35.85	80.5%		
		Extensive	4	0.1204	[0.0516; 0.2559]	1.74	0.0%		
	Bacteria	<i>E. coli</i>	6	0.2253	[0.0414; 0.6622]	45.68	89.1%	0.02	0.8858
		<i>Salmonella</i>	10	0.2501	[0.0797; 0.5622]	61.57	85.4%		
Ciprofloxacin	Animal	Swine	8	0.0970	[0.0275; 0.2899]	21.44	67.4%	0.38	0.8264

Table 2 (Continued)

Antimicrobial	Subgroup	N° studies	Pooled estimate	95% CI	Q	I ²	Q _s	p-value _s
Amoxicillin/clav. acid	System	Chicken	2	0.0765	[0.0002; 0.9735]	0.47	0.0%	5.15 0.0763
		Cattle	2	0.0415	[0.0000; 1.0000]	1.90	47.5%	
		Nd	1	0.0053	[0.0002; 0.1041]	0.00	-	
		Intensive	7	0.1325	[0.0497; 0.3085]	16.03	62.6%	
		Extensive	4	0.0557	[0.0085; 0.2896]	2.45	0.0%	
	Bacteria	<i>E. coli</i>	4	0.0576	[0.0116; 0.2416]	4.29	30.0%	1.06 0.3043
		<i>Salmonella</i>	8	0.1186	[0.0341; 0.3391]	16.53	57.6%	
	Animal	Swine	8	0.0810	[0.0198; 0.2781]	19.22	63.6%	1.53 0.6764
		Chicken	2	0.2412	[0.0000; 1.0000]	14.18	92.9%	
		Cattle	3	0.0267	[0.0004; 0.6288]	2.49	19.6%	
		Dairy	1	0.0263	[0.0003; 0.6893]	0.00	-	
		Nd	1	0.0071	[0.0001; 0.3312]	0.00	-	
Ampicillin	System	Intensive	8	0.1328	[0.0243; 0.4845]	43.55	83.9%	2.84 0.2412
		Extensive	5	0.0395	[0.0076; 0.1802]	4.74	15.6%	
		<i>E. coli</i>	9	0.0357	[0.0109; 0.1105]	19.25	58.4%	
		<i>Salmonella</i>	5	0.2669	[0.0308; 0.8067]	23.81	83.2%	
	Animal	Swine	11	0.4345	[0.2438; 0.6469]	45.60	78.1%	21.35 <0.0001
		Chicken	4	0.3771	[0.0385; 0.9015]	16.12	81.4%	
		Cattle	3	0.0672	[0.0149; 0.2550]	0.75	0.0%	
		Dairy	1	0.1111	[0.0099; 0.6105]	0.00	-	
		Nd	3	0.3900	[0.0253; 0.9404]	46.04	95.7%	
Tetracycline	System	Intensive	9	0.5050	[0.2636; 0.7441]	38.58	79.3%	13.24 0.0013
		Extensive	7	0.1134	[0.0482; 0.2440]	11.91	49.6%	
		<i>E. coli</i>	10	0.2545	[0.1110; 0.4828]	86.32	89.6%	
		<i>Salmonella</i>	9	0.4399	[0.1787; 0.7392]	42.43	81.1%	
	Animal	Swine	11	0.6362	[0.3896; 0.8274]	66.13	84.9%	36.32 <0.0001
		Chicken	5	0.4180	[0.1095; 0.8076]	22.18	82.0%	
		Cattle	3	0.0993	[0.0445; 0.2071]	0.21	0.0%	
		Dairy	1	0.3333	[0.0365; 0.8685]	0.00	-	
		Nd	3	0.6887	[0.0624; 0.9866]	26.24	92.4%	
Multidrug resistance	System	Intensive	9	0.6721	[0.4376; 0.8438]	38.91	79.4%	24.93 <0.0001
		Extensive	8	0.1680	[0.0940; 0.2819]	10.56	33.7%	
		<i>E. coli</i>	10	0.5430	[0.2348; 0.8215]	119.37	92.5%	
		<i>Salmonella</i>	10	0.3880	[0.2049; 0.6093]	26.92	66.6%	
	Animal	Swine	11	0.4733	[0.2909; 0.6631]	66.54	85.0%	12.57 0.0057
		Chicken	4	0.3840	[0.0194; 0.9516]	13.36	77.5%	
		Cattle	2	0.0682	[0.0000; 0.9979]	0.75	0.0%	
		Dairy	1	0.0556	[0.0031; 0.5235]	0.00	-	
		Nd	4	0.3671	[0.1530; 0.6507]	26.77	88.8%	
	System	Intensive	8	0.6191	[0.3439; 0.8345]	29.69	76.4%	19.82 <0.0001
		Extensive	6	0.1066	[0.0432; 0.2399]	6.05	17.4%	
		<i>E. coli</i>	7	0.2916	[0.1025; 0.5974]	37.5	84.0%	
		<i>Salmonella</i>	11	0.4415	[0.1935; 0.7225]	77.27	87.1%	
	Bacteria	<i>E. coli</i>	7	0.2916	[0.1025; 0.5974]	37.5	84.0%	0.76 0.3838
		<i>Salmonella</i>	11	0.4415	[0.1935; 0.7225]	77.27	87.1%	

(s) Cochran's Q equivalent and test of between-study heterogeneity for subgroups. CI, confidence interval. Significant associations among stratification variables (Animal, System, Bacteria) and AMR are indicated in bold letters.

The pooled estimates of the prevalence of *S. aureus* resistant to each of these antimicrobials is shown in Table 1. The highest prevalence of AMR was observed for penicillin. Between-study heterogeneity was substantial for both antimicrobials. Funnel plots estimating publication bias showed some degree of asymmetry (Suppl. Fig. S2).

Discussion

Within the antimicrobials authorized by SENASA for their use in animals, 85% are shared with human medicine or belong to groups classified by the WHO as critically important antimicrobials for humans (SENASA Resolution 559/2011)⁹⁷. Given that the use of antimicrobials in animals increases AMR in

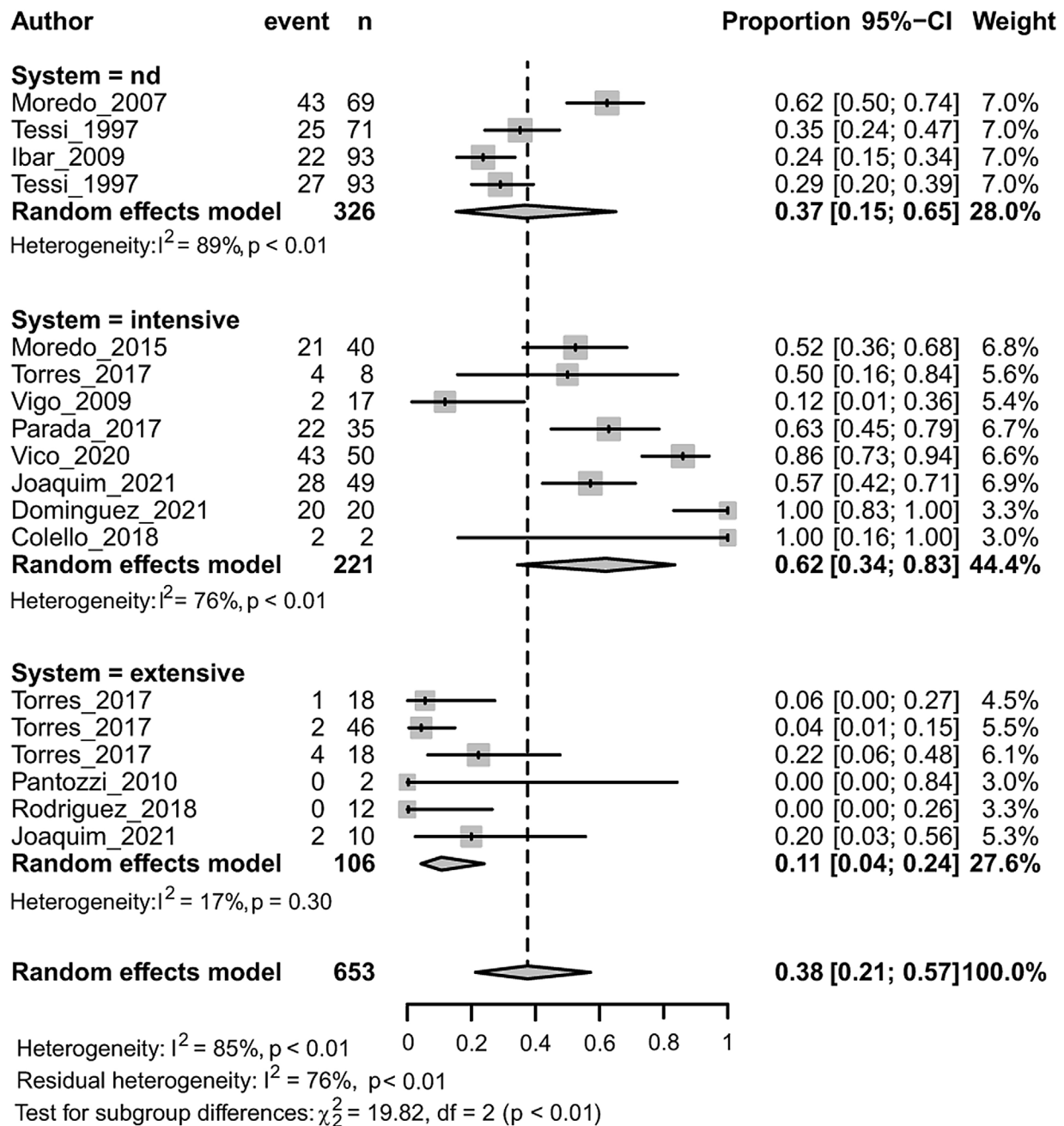


Figure 4 Forest plot of prevalence of multidrug resistance in *Enterobacteriaceae* from food-producing animals.

humans³⁷, there is enough justification to manage their use, fate and AMR surveillance in food-producing animals and the open environment. The study of AMR in animal production in Argentina, as in many other countries, is not yet completely coordinated nor harmonized and there are still important gaps. The type of samples and antimicrobials tested differed widely among authors. However, most authors agreed with the methods and guidelines followed to interpret AMR. The CLSI guidelines were the ones preferred in Argentina, together with the EUCAST guidelines, which are both the most popular worldwide⁴³.

Meta-analyses are a powerful tool to quantitatively summarize available data and assess possible sources of

heterogeneity, such as animal species or production systems³⁵. Further studies are needed, particularly for *Campylobacter* spp. and *Enterococcus* spp., because not enough data is yet available to perform meta-analyses. The same situation occurs for some classes of antimicrobials classified as critically important for human medicine by the 5th report from the WHO, including polymyxins and glycopeptides.

In this study, the AMR profiles from the qualitative synthesis could be divided into two main categories: AMR developed to antimicrobials authorized for veterinary use (SENASA Resolution 559/2011) and AMR developed to antimicrobials used exclusively for human medicine⁹⁷.

The first category includes the combination of amoxicillin and clavulanic acid, ampicillin, ceftiofur, doxycycline, enrofloxacin, erythromycin, fosfomicin, gentamicin, kanamycin, neomycin, penicillin, rifampicin, spiramycin, streptomycin, tetracycline, tilmicosin and tylosin. The second category includes amikacin, aztreonam, cefepime, cefotaxime, ciprofloxacin, colistin (since 2019 banned for animal use), nalidixic acid and polymyxin B. Although all of them are critically important antimicrobials, the second category is the most alarming in terms of public health.

According to the WHO ranking, the following are 'high-priority critically important antimicrobials': quinolones, 3rd-generation cephalosporins or higher, macrolides and ketolides, glycopeptides and polymyxins⁹⁷. In the following paragraphs some results of these antimicrobials from the qualitative synthesis and meta-analyses performed, will be discussed.

Quinolones

Quinolones are one of the only therapies available to treat severe *Salmonella* spp. and *E. coli* infections in humans⁹⁷. In this study, the reports included in the qualitative synthesis showed prevalence of resistance to quinolones ranging from extremely high in *Campylobacter* spp. from both swine⁶⁵, and chicken^{62,98}, in *E. coli* from chicken¹⁹ and diarrheic beef-cattle calves⁷⁹, and very high in *Salmonella* spp. isolated from swine⁶⁶ and chicken²⁰. These results are similar to those from countries where the use of fluoroquinolones is approved in food-producing animals, such as *E. coli* isolated from chickens in China⁹⁹ and reports from the EU²¹. When the pooled prevalence of AMR to quinolones was estimated for *Enterobacteriaceae*, the levels found were low, moderate, and high for ciprofloxacin, enrofloxacin and nalidixic acid, respectively. In Australia, a country where fluoroquinolones are preserved, complete susceptibility to ciprofloxacin was reported in commensal *E. coli* and *Salmonella* spp. isolated from meat chickens¹.

Moreover, in human medicine, the Latin American Network for Antimicrobial Resistance Surveillance reported 70.4% ciprofloxacin-resistant *Campylobacter* spp. in Argentina⁴⁶, representing a serious threat to public health. On the contrary, ciprofloxacin-resistant *Campylobacter* spp. is rare or low in countries where the use of fluoroquinolones has never been approved in food-producing animals⁹⁰.

In Argentina, ciprofloxacin is exclusively used for human medicine; however, animal administration of enrofloxacin can lead to similar concentrations of plasmatic enrofloxacin and ciprofloxacin^{4,15,29}. Enrofloxacin was not on the list of approved growth promoters submitted to the OIE in 2013 and 2014, therefore the extremely high levels of resistance observed could be related to misuse. Concordantly, residual levels of enrofloxacin considered toxic for human consumption were recently found in dehydrated eggs from Argentina⁸⁵.

Cephalosporins

In Argentina, the main cephalosporins available for veterinary use are ceftiofur and cefquinome (SENASA Resolution 559/2011). In the qualitative synthesis of this study, data

on resistance to ceftiofur come from *E. coli*^{3,19,89} and *Salmonella* spp.^{42,92}. Prevalence of resistance in swine is in between what has been reported in US (very low) and China (moderate)^{26,99}, or higher^{3,24}. For *E. coli* from cattle, susceptibility to cefotaxime was complete in animals at local slaughterhouses, while high prevalence of cefotaxime-resistance has been associated with diarrheic beef and dairy calves in Argentina and grazing beef cattle in the USA (Florida)^{65,89}. When the pooled prevalence of AMR to cefotaxime was estimated for *Enterobacteriaceae*, the levels found were low. Therefore, local resistance to 3rd generation cephalosporins seems to be related to animals with clinical symptoms.

Finally, the extremely high prevalence of resistance to cephalosporins reported for colistin-resistant *E. coli* from chicken could be a result of co-selection due to the administration of colistin as growth promoter⁴¹.

Macrolides

In this study, up to an extremely high prevalence of macrolide resistance was observed in swine and chicken, including *Salmonella* spp. from family-farming chicken. Resistance to macrolides in *Enterococcus* spp.⁶⁵ from swine and chicken was higher than that reported in the USA. However, resistance to erythromycin in US beef cattle was moderate while in this study susceptibility was complete²⁶. The pooled prevalence of erythromycin resistance in *S. aureus* from dairy cattle estimated in this study (0.125) was higher than the worldwide one (0.085) estimated by Molineri et al.⁵⁴.

In Argentina, tylosin is administered as a growth promoter (Luna F., personal communication, 2022, SENASA). This use is most likely contributing to the selection of macrolide-resistant bacteria¹⁰. Moreover, another non-therapeutic use of macrolides is as metaphylactics in calves entering feedlots to prevent bovine respiratory disease²⁵. Therefore, it would be of great importance to know the levels of resistance in this type of production system.

Tetracyclines

As Argentina still has endemic *Brucella* spp. infections, the recommendation is to continue considering tetracyclines as critically important antimicrobials⁹⁷. Despite this recommendation, chlortetracycline and oxytetracycline are administered as growth promoters in food-producing animals (Luna F., personal communication, 2022, SENASA). In the qualitative synthesis, resistance to tetracycline increases over time until reaching extremely high levels of resistance in *E. coli*, *Enterococcus* spp. and *Campylobacter* spp. (except bacteria from beef and dairy cattle). Similar results were also reported in the USA, China and the EU^{21,26,99}.

As described in some global meta-analyses^{75,76}, in our study, tetracycline was the antimicrobial with the highest pooled prevalence of AMR in *Enterobacteriaceae* from Argentina. Particularly in intensive production, AMR was similar to the pooled prevalence reported for *Salmonella* spp. from swine in China (0.68, 95% CI: 0.59, 0.77)⁷⁶.

Extremely high levels of resistance to tetracyclines do not only represent loss of the effectiveness of these antimicrobials, but it has also been suggested that tetracycline-resistant *E. coli* is more likely to be resistant to other antimicrobials⁷⁴.

Polymyxins

In Argentina, colistin was the only polymyxin authorized in animals and was extensively used as a growth promoter. Resistance to colistin can occur by chromosomal mutations and by acquisition of plasmid-carrying determinants, mainly *mcr-1*. Quiroga et al. (2019) have reviewed the outburst of this resistance gene in Latin America and the risk of the rapid dissemination of *mcr-1* has alerted actors worldwide⁷⁰.

In Argentina, the alarming results reported by independent researchers and the national surveillance program, have led to new regulations. In line with the WHO and OIE recommendations and to preserve the efficacy of colistin, on January 2019 SENASA banned the production, distribution, import, use and possession of veterinary products containing colistin (RESOL-2019-22-APN-PRES#SENASA).

To date, there is not enough available information about this group of antimicrobials to perform meta-analyses, which will be necessary to estimate the effect of the intervention applied in the country. Of special importance is the methodology followed to test AMR to colistin, given that disk-diffusion is considered unreliable because colistin diffuses poorly into agar, resulting in smaller inhibition zones⁴⁷.

Glycopeptides

Glycopeptides were never authorized for their use in Argentine animal production. Concordantly, vancomycin-resistant *Enterococcus* spp.⁶⁵ was neither isolated from swine, chicken nor beef cattle, until recently. Since 2018, information about glycopeptide resistance has been reported for swine and chicken^{14,91}. Resistance to this antimicrobial is common in countries where avoparcin was used as feed additive²². Similarly, as occurs with colistin, there are not enough data available on this group to perform meta-analyses.

AMR, animal species and animal production systems

Industrialization of agriculture has been accompanied by important benefits and risks to human, animal, and environmental health. In many developing countries, the change occurred at such a high speed that caused social impacts with increased risk of marginalization of small-holder farmers³³. When analyzing the transitions in food animal production from the One Health approach, Silbergeld et al. (2019) states that the use of antimicrobial drugs in food animal production is the innovation that has most profoundly and dangerously transformed human health at the global level. In concordance, the author calls for an end to the use of antimicrobials for non-therapeutic purposes

and the cruelties of confinement⁷⁸. In our study, a reduced number of the articles included compared AMR among different animal species⁶⁵ or production systems^{42,62,89}. However, through meta-analyses of proportions followed by subgroup analyses, it was possible to test the association between AMR and the variables 'animal species' and 'animal production systems'³⁵, as previously applied in global meta-analyses^{77,84}. Patterns of AMR to streptomycin, ampicillin, tetracycline and MDR were associated with the animal species, while patterns of AMR to streptomycin, cefotaxime, nalidixic acid, ampicillin, tetracycline and MDR were associated with the animal production system from which they were isolated (Table 2 and Fig. 4). Greater prevalence of resistance was associated with swine (followed by chicken), and with intensive production. On the contrary, beef (or dairy) cattle and, extensive production, showed the lowest prevalence of resistance and resistance to a lesser number of antimicrobials.

Food-producing animals are not only vehicles of AMR transmission but also endpoints in the dissemination, selection, and spread of antimicrobial-resistant bacteria and AMR genes⁸⁷. Among the studies included in this review, authors reported the presence of a variety of resistance-encoding genes and cassettes including, *aac(6')-le-aph(2')-la*¹⁴, *aadA1*⁴⁴, *aadA5*⁶⁷, *aphA3*³⁶, *bla_{CTX-M-1/15}*²⁴, *bla_{CTX-M-2}*^{19,24}, *bla_{CTX-M-8/25}*²⁴, *bla_{CTX-M-9/14}*^{19,24}, *bla_{CMY}*^{19,24}, *bla_{PER-2}*²⁴, *bla_{TEM}*⁴⁴, *bla_Z*⁵⁵, *dhfrA17*⁶⁷, *drfA1*⁴⁴, *ermB*³⁶, *ermC*⁵⁵, *floR*⁴⁴, *lnu(B)*³⁶, *mcr-1*^{18,19,24}, *mecA*⁸⁰, *oqxAB*¹⁹, *qepA*¹⁹, *qnrA*¹⁹, *qnrB*¹⁹, *qnrD*¹⁹, *qnrS*¹⁹, *strA*, *strB*, *sul1*, *sul2*, *tet(A)*, *tet(B)*⁴⁴, *tet(M)*³⁶, *tet(O)*³⁶, *vanA*¹⁴. Therefore, a seemingly beneficial practice that would be the redirection of livestock manure to soils to close the cycles of nutrients and the organic matter now represents an ideal scenario for the dissemination of these contaminants. Thus, manure is a very difficult waste to dispose of, which in many cases leads to its accumulation in small areas with subsequent contamination of soil, air and ground water.

Due to the expansion and globalization of food and animal trade, international tourism and host movements, AMR can easily surpass local, national and continental borders, making AMR a worldwide problem⁵¹. In the EU and North America surveillance data are available and research networks are active; however, these are still largely lacking in low and middle income countries⁹⁴. Moreover, it has been stated that AMR is aggravated in developing countries due to the gross abuse in the use of antimicrobials, including non-human uses⁵. In between, there are those countries, with a long history of extensive systems, such as Argentina, which in the last decades have started to shift gradually to intensive, industrialized, or confined systems, and to increase chicken and swine production. Limited interventions in one country, continent and for instance, in the developing world, could compromise the efficacy and endanger the AMR containment policies implemented in other parts of the world²⁸.

Answering to the need for global surveillance programs, the OIE encourages the application of national surveillance programs, whose results are being integrated in global reports⁶⁴. This approach will provide guidance for antimicrobial use and tools to detect and contain the development and spread of AMR worldwide.

Conclusions

The data presented in this study gives documented evidence that support the hypothesis that AMR to common food-transmitted bacteria is reaching alarming levels in our country. This situation was especially observed in animal production systems related to confined-intensive breeding relying on the habitual use of antimicrobials as is mostly the case for swine and chicken production in Argentina. In addition, we identified that there are still important local gaps of information regarding beef-cattle from feedlot, as well as *Campylobacter* spp. and *Enterococcus* spp. All these findings emphasize the urgent need for National coordination. Restrictive measures for non-therapeutic and/or massive uses of highest priority antimicrobials should be applied to maintain the efficacy of these chemical agents, to preserve human and animal health as well as to ensure food safety and food security.

Funding

This work was supported by UBACYT [20020190200419BA] and LOMASCyT [FCA-91 Res. N° 857/2018], Argentina. The funding sources were not involved in, the study design, the collection, analysis and interpretation of data, the writing of the report, nor the decision to submit the article for publication.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ram.2022.07.001](https://doi.org/10.1016/j.ram.2022.07.001).

References

- Abraham S, O'Dea M, Sahibzada S, Hewson K, Pavic A, Veltman T, Abraham R, Harris T, Trott DJ, Jordan D. *Escherichia coli* and *Salmonella* spp. isolated from Australian meat chickens remain susceptible to critically important antimicrobial agents. PLOS ONE. 2019;14.
- Aidara-Kane A, Angulo FJ, Conly J, Minato Y, Silbergeld EK, McEwen SA, Collignon PJ, Balkhy H, Collignon P, Friedman C, Hollis A, Kariuki S, Kwak HS, McEwen S, Moulin G, Ngandjio A, Rollin B, Rossi F, Wallinga D. World Health Organization (WHO) guidelines on use of medically important antimicrobials in food-producing animals. Antimicrob Resist Infect Control. 2018;7:1–8.
- Alustiza FB, Bessone G, Conde MB, Marini S, Zielinski G, Bessone F. Genes de virulencia y susceptibilidad antibiótica de cepas de *Escherichia coli* aisladas de cerdos con diarreas – Engormix. In: VIII Cong. de Producción Porcina del Mercosur – XIII Cong. Nacional de Producción Porcina – XIX Jornadas de Actualización Porcina; 2017.
- Anadón A, Martínez-Larrañaga MR, Díaz MJ, Fernández-Cruz ML, Martínez MA, Frejo MT, Martínez M, Iturbe J, Tafur M. Pharmacokinetic variables and tissue residues of enrofloxacin and ciprofloxacin in healthy pigs. Am J Vet Res. 1999;60:1377–82.
- Ayukekibong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrob Resist Infect Control. 2017;6:47.
- Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153–60.
- Baptiste KE, Kyvsgaard NC. Do antimicrobial mass medications work? A systematic review and meta-analysis of randomised clinical trials investigating antimicrobial prophylaxis or metaphylaxis against naturally occurring bovine respiratory disease. Pathog Dis. 2017;75:83.
- Bessone FA, Bessone G, Marini S, Conde MB, Alustiza FE, Zielinski G. Presence and characterization of *Escherichia coli* virulence genes isolated from diseased pigs in the central region of Argentina. Vet World. 2017;10:939.
- Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, Teillant A, Laxminarayan R. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci U S A. 2015;112:5649–54.
- Boerlin P, Wissing A, Aarestrup FM, Frey J, Nicolet J. Antimicrobial growth promoter ban and resistance to macrolides and vancomycin in enterococci from pigs. J Clin Microbiol. 2001;39:4193–5.
- Calvinho LF, Toselli FG, Weimann WR, Canavesio VR, Neder VE, Iguzquiza IA. Antimicrobial sensitivity of coagulase-positive staphylococcal strains isolated from bovine mastitis in the central dairy catchment area of Argentina. Rev Argent Microbiol. 2002;34:171–5.
- Colello R, Krüger A, Di Conza J, Rossen JWA, Friedrich AW, Gutkind G, Etcheverría AI, Padola NL. Antimicrobial resistance in Class 1 integron-positive shiga toxin-producing *Escherichia coli* isolated from cattle, pigs, food and farm environment. Microorganisms. 2018;6:99.
- Colello R, Ruiz MJ, Padín VM, Rogé AD, Leotta G, Padola NL, Etcheverría AI. Detection and characterization of *Salmonella* serotypes in the production chain of two pig farms in Buenos Aires Province, Argentina. Front Microbiol. 2018;9:1370.
- Delpech G, Sparo MD, Baldaccini MB, Ceci M, Leonardo GA. High level resistance to gentamicin and vancomycin in enterococci isolated from poultry in Argentina. PARIPEX – Indian J Res. 2019;7:434–6.
- Delsol AA, Woodward MJ, Roe JM. Effect of a 5 day enrofloxacin treatment on *Salmonella enterica* serotype Typhimurium DT104 in the pig. J Antimicrob Chemother. 2004;53:396–8.
- Denamiel G, Llorente P, Carabella M, Rebuelto M, Gentilini E. Anti-microbial susceptibility of *Streptococcus* spp. isolated from Bovine Mastitis in Argentina. J Vet Med Ser B Infect Dis Vet Public Health. 2005;52:125–8.
- Ding Y, Saw WY, Tan LWL, Moong DKN, Nagarajan N, Teo YY, Seedorf H. Extended-spectrum β -lactamase-producing and mcr-1-positive *Escherichia coli* from the gut microbiota of healthy Singaporeans. Appl Environ Microbiol. 2021;87:1–13.
- Dominguez JE, Figueroa Espinosa RA, Redondo LM, Cejas D, Gutkind GO, Chacana PA, Di Conza JA, Fernández-Miyakawa ME. Plasmid-mediated colistin resistance in *Escherichia coli* recovered from healthy poultry. Rev Argent Microbiol. 2017;49:297–8.
- Dominguez JE, Redondo LM, Figueroa Espinosa RA, Cejas D, Gutkind GO, Chacana PA, Di Conza JA, Fernández Miyakawa ME. Simultaneous carriage of mcr-1 and other antimicrobial resistance determinants in *Escherichia coli* From poultry. Front Microbiol. 2018;9:1679.
- Dominguez JE, Viñas MR, Herrera M, Moroni M, Gutkind GO, Mercado EC, Di Conza JA, Chacana PA. Molecular characterization and antimicrobial resistance profiles of *Salmonella* Heidelberg isolates from poultry. Zoonoses Public Health. 2021;68:309–15.

21. EFSA. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014. *EFSA J.* 2016;14.
22. EFSA. Biological hazards data | European Food Safety Authority, <https://www.efsa.europa.eu/en/data/biological-hazards-data>.
23. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629–34.
24. Faccione D, Moredo FA, Giacoboni GI, Albornoz E, Alarcón L, Nieves VF, Corso A. Multidrug-resistant *Escherichia coli* harbouring mcr-1 and blaCTX-M genes isolated from swine in Argentina. *J Glob Antimicrob Resist.* 2019;18:160–2.
25. Fazio LE, Landoni MF. Comparación de la eficacia de oxite-traciclina y tilmicosina en el tratamiento metafláctico de la enfermedad respiratoria bovina en animales de feedlot. *Analecta Vet.* 2010;30:35–40.
26. FDA-NARMS. 2012_2013 integrated report on antimicrobial resistance from food-producing animals; 2015.
27. Founou LL, Founou RC, Essack SY. Antimicrobial resistance in the farm-to-plate continuum: more than a food safety issue. *Futur Sci OA.* 2021;7:FSO692.
28. Founou LL, Founou RC, Essack SY. Antibiotic resistance in the food chain: a developing country-perspective. *Front Microbiol.* 2016;7:1881.
29. Garcia MA, Solans C, Calvo A, Hernandez E, Rey R, Bregante MA, Puig M. Determination of enrofloxacin and its primary metabolite, ciprofloxacin, in pig tissues. Application to residue studies. *Biomed Chromatogr.* 2005;19:27–31.
30. Gaynes R. The discovery of penicillin – new insights after more than 75 years of clinical use. *Emerg Infect Dis.* 2017;23:849–53.
31. Gentilini E, Denamiel G, Llorente P, Godaly S, Rebuelto M, DeGregorio O. Antimicrobial susceptibility of *Staphylococcus aureus* isolated from Bovine Mastitis in Argentina. *J Dairy Sci.* 2000;83:1224–7.
32. Gentilini E, Denamiel G, Betancor A, Rebuelto M, Rodriguez Fermepin M, De Torrest RA. Antimicrobial susceptibility of coagulase-negative staphylococci isolated from Bovine Mastitis in Argentina. *J Dairy Sci.* 2002;85:1913–7.
33. Gilbert M, Conchedda G, Van Boeckel TP, Cinardi G, Linard C, Nicolas G, Thanapongtharm W, D'Aiotti L, Wint W, Newman SH, Robinson TP. Income disparities and the global distribution of intensively farmed chicken and pigs. *PLOS ONE.* 2015;10:e0133381.
34. González Pereyra V, Pol M, Pastorino F, Herrero A. Quantification of antimicrobial usage in dairy cows and preweaned calves in Argentina. *Prev Vet Med.* 2015;122:273–9.
35. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing meta-analysis with R: a hands-on guide: doing meta-analysis with R; 2021, <http://dx.doi.org/10.1201/9781003107347> [Epub ahead of print].
36. Hernandez L, Bottini E, Cadona J, Cacciato C, Monteavaro C, Bustamante A, Sanso A. Multidrug resistance and molecular characterization of *Streptococcus agalactiae* isolates from dairy cattle with Mastitis. *Front Cell Infect Microbiol.* 2021;11:647324.
37. Hoelzer K, Wong N, Thomas J, Talkington K, Jungman E, Coukell A. Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence? *BMC Vet Res.* 2017;13:211.
38. Hu S, Lv Z, Xiang Q, Wang Y, Shen J, Ke Y. Dietary factors of blaNDM carriage in health community population: a cross-sectional study. *Int J Environ Res Public Health.* 2021;18:5959.
39. Ibar MP, Vigo G, Piñeyro P, Caffer MI, Quiroga P, Perfumo C, Centron D, Giacoboni G. Serovars of *Salmonella enterica* subspecies enterica and its antimicrobial resistance in slaughterhouse pigs. *Rev Argent Microbiol.* 2009;41:156–62.
40. INDEC. Instituto Nacional de Estadística y Censos de la República Argentina, <https://www.indec.gob.ar/indec/web/Nivel3-Tema-3-2>.
41. Jayol A, Nordmann P, Desroches M, Decusser J-W, Poirel L. Acquisition of broad-spectrum cephalosporin resistance leading to colistin resistance in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother.* 2016;60:3199–201.
42. Joaquim P, Herrera M, Dupuis A, Chacana P. Virulence genes and antimicrobial susceptibility in *Salmonella enterica* serotypes isolated from swine production in Argentina. *Rev Argent Microbiol.* 2021;53:233–9.
43. Kassim A, Omuse G, Premji Z, Revathi G. Comparison of Clinical Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing guidelines for the interpretation of antibiotic susceptibility at a University Teaching Hospital in Nairobi, Kenya: a cross-sectional study. *Ann Clin Microbiol Antimicrob.* 2016;15:21.
44. Krüger A, Lucchesi PMA, Mariel Sanso A, Etcheverría AI, Bustamante AV, Burgán J, Fernández L, Fernández D, Leotta G, Friedrich AW, Padola NL, Rossen JWA. Genetic characterization of Shiga toxin-producing *Escherichia coli* O26:H11 strains isolated from animal, food, and clinical samples. *Front Cell Infect Microbiol.* 2015;5:74.
45. de la Torre E, Colello R, Fernández D, Etcheverría A, Di Conza J, Gutkind GO, Tapia MO, Dieguez SN, Soraci AL, Padola NL. Multidrug resistance in *Escherichia coli* carrying integrons isolated from a pig farm with moderate antibiotic use. *J Gen Appl Microbiol.* 2015;61:270–3.
46. Latin American Network for Surveillance of Antimicrobial Resistance. ReLAVRA – OPS | antimicrobianos.com.ar, <http://antimicrobianos.com.ar/category/resistencia/relavra/>.
47. De Louvois J. Factors influencing the assay of antimicrobial drugs in clinical samples by the agar plate diffusion method. *J Antimicrob Chemother.* 1982;9:253–65.
48. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect.* 2012;18:268–81.
49. Maron D, Smith TJ, Nachman KE. Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. *Global Health.* 2013;9:48.
50. Mathias Harrer M, Cuijpers P, Furukawa T, Ebert DD. Companion R package for the guide “Doing Meta-Analysis in R”; 2021. <http://dmetar.protectlab.org/>
51. Memish ZA, Venkatesh S, Shibl AM. Impact of travel on international spread of antimicrobial resistance. *Int J Antimicrob Agents.* 2003;21:135–42.
52. Mercado EC, Giffre A, Rodriguez SM, Cataldi A, Irino K, Elizondo AM, Cipolla AL, Romano MI, Malena R, Mendez MA. Non-O157 Shiga toxin-producing *Escherichia coli* isolated from Diarrhoeic Calves in Argentina. *J Vet Med Ser B Infect Dis Vet Public Health.* 2004;51:82–8.
53. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
54. Molineri AI, Camussone C, Zbrun MV, Suárez Archilla G, Cristiani M, Neder V, Calvino L, Signorini M. Antimicrobial resistance of *Staphylococcus aureus* isolated from bovine mastitis: systematic review and meta-analysis. *Prev Vet Med.* 2021;188:105261.
55. Monistero V, Barberio A, Biscarini F, Cremonesi P, Castiglioni B, Graber HU, Bottini E, Ceballos-Marquez A, Kroemker V, Petzer IM, Pollera C, Santisteban C, Veiga Dos Santos M, Bronzo V, Piccinini R, Re G, Cocchi M, Moroni P. Different distribution of antimicrobial resistance genes and virulence profiles of *Staphylococcus aureus* strains isolated from clinical mastitis in six countries. *J Dairy Sci.* 2020;103:3431–46.

56. Moredo FA, Vigo GB, Cappuccio JA, Piñeyro P, Perfumo CJ, Giacoboni GI. Antimicrobial resistance of *Escherichia coli* isolated from pigs in Argentina. *Rev Argent Microbiol.* 2007;39:227–9.
57. Moredo FA, Piñeyro PE, Márquez GC, Sanz M, Colello R, Etcheverría A, Padola NL, Quiroga MA, Perfumo CJ, Galli L, Leotta GA. Enterotoxigenic *Escherichia coli* subclinical infection in pigs: bacteriological and genotypic characterization and antimicrobial resistance profiles. *Foodborne Pathog Dis.* 2015;12:704–11.
58. Moredo F, Colello R, Sanz ME, Cappuccio J, Carriquiriborde M, Etcheverría A, Perfumo CJ, Padola NL, Leotta GA. *Escherichia coli* con resistencia a múltiples antimicrobianos en granjas de producción porcina de la República Argentina. *Analecta Vet.* 2013;33:9–13.
59. Moredo F, Vigo GB, Sanz ME, Aguirre JI, Armocida A, Perfumo CJ. Caracterización enterotoxigénica y estudio de sensibilidad antimicrobiana in vitro de cepas de *Escherichia coli* aisladas de cerdos con cuadros clínicos de diarrea pre y posdestete. *Analecta Vet.* 1998;18:29–33.
60. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022;399:629–55.
61. Nobrega DB, Tang KL, Caffrey NP, De Buck J, Cork SC, Ronksley PE, Polachek AJ, Ganshorn H, Sharma N, Kastelic JP, Kellner JD, Ghali WA, Barkema HW. Prevalence of antimicrobial resistance genes and its association with restricted antimicrobial use in food-producing animals: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2021;76:561–75.
62. Notario R, Borda N, Gambandé T, Bermejo J, Ponessa A, Toledo V. Quinolone resistant *Campylobacter jejuni* strains isolated from humans and from poultry. *Medicina (B Aires).* 2011;71:331–5.
63. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations; 2016 [review on antimicrobial resistance].
64. OIE. Annual report on the use of antimicrobial agents in animals, http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/Survey_on_monitoring_antimicrobial_agents_Dec2016.pdf.
65. Pantozzi FL, Moredo FA, Vigo GB, Giacoboni GI. Antimicrobial resistance in indicator and zoonotic bacteria isolated from domestic animals in Argentina. *Rev Argent Microbiol.* 2010;42:49–52.
66. Parada J, Carranza A, Galas M. Resistencia a antimicrobianos de uso terapéutico en humanos en cepas de *Salmonella* Entérica aisladas de cerdos. - Engormix. In: VIII Cong. de Producción Porcina del Mercosur - XIII Cong. Nacional de Producción Porcina - XIX Jornadas de Actualización Porcina; 2017.
67. Pasayo RAG, Sanz ME, Padola NL, Moreira AR. Phenotypic and genotypic characterization of enterotoxigenic *Escherichia coli* isolated from diarrheic calves in Argentina. *Open Vet J.* 2019;9:65–73.
68. Pellegrino MS, Frola ID, Odierno LM, Bogni C. Bovine Mastitis: antimicrobial resistance of *Staphylococcus aureus* strains isolated from milk. *Revista Electronica de Veterinaria.* 2011;12:1–14.
69. Penders J, Stobberingh EE, Savelkoul PHM, Wolffs PFG. The human microbiome as a reservoir of antimicrobial resistance. *Front Microbiol.* 2013;4:87.
70. Quiroga C, Nastro M, Di Conza J. Current scenario of plasmid-mediated colistin resistance in Latin America. *Rev Argent Microbiol.* 2019;51:93–100.
71. Raspanti CG, Bonetto CC, Vissio C, Pellegrino MS, Reinoso EB, Dier SA, Bogni CI, Larriestra AJ, Odierno LM. Prevalence and antibiotic susceptibility of coagulase-negative *Staphylococcus* species from bovine subclinical mastitis in dairy herds in the central region of Argentina. *Rev Argent Microbiol.* 2016;48:50–6.
72. Rodríguez FI, Pascal DC, Pulido D, Osinalde JM, Caffer MI, Bueno DJ. Prevalence, antimicrobial resistance profile and comparison of selective plating media for the isolation of *Salmonella* in backyard chickens from Entre Ríos, Argentina. *Zoonoses Public Health.* 2018;65:e95–101.
73. Russi NB, Bantar C, Calvino LF. Antimicrobial susceptibility of *Staphylococcus aureus* causing bovine mastitis in Argentine dairy herds. *Rev Argent Microbiol.* 2008;40:116–9.
74. Sayah RS, Kaneene JB, Johnson Y, Miller R. Patterns of antimicrobial resistance observed in *Escherichia coli* isolates obtained from domestic- and wild-animal fecal samples, human septage, and surface water. *Appl Environ Microbiol.* 2005;71:1394–404.
75. Seni J, Moremi N, Matee M, van der Meer F, DeVinney R, Mshana SE, Pitout DJD. Preliminary insights into the occurrence of similar clones of extended-spectrum beta-lactamase-producing bacteria in humans, animals and the environment in Tanzania: a systematic review and meta-analysis between 2005 and 2016. *Zoonoses Public Health.* 2018;65:1–10.
76. Shen W, Chen H, Geng J, Wu RA, Wang X, Ding T. Prevalence, serovar distribution, and antibiotic resistance of *Salmonella* spp. isolated from pork in China: a systematic review and meta-analysis. *Int J Food Microbiol.* 2022;361:109473.
77. Signorini ML, Rossler E, Díaz David DC, Olivero CR, Romero-Scharpen A, Soto LP, Astesana DM, Berisvil AP, Zimmermann JA, Fusari ML, Frizzo LS, Zbrun MV. Antimicrobial resistance of thermotolerant *Campylobacter* species isolated from humans, food-producing animals, and products of animal origin: a worldwide meta-analysis. *Microb Drug Resist.* 2018;24:1174–90.
78. Silbergeld EK. One health and the agricultural transition in food animal production. *Glob Transit.* 2019;1:83–92.
79. Spetter MJ, Louge Uriarte EL, González Pasayo RA, Malena R, Moreira AR. Estudio retrospectivo de multiresistencia antimicrobiana en aislamientos de *Escherichia coli* de terneros con diarrea neonatal. *Rev Med Vet (B Aires).* 2015;96:4–9.
80. Srednik ME, Crespi E, Testorelli MF, Puigdevall T, Pereyra AMD, Rumi MV, Caggiano N, Gulone L, Mollerach M, Gentilini ER. First isolation of a methicillin-resistant *Staphylococcus aureus* from bovine mastitis in Argentina. *Vet Anim Sci.* 2018;7:100043.
81. Srednik ME, Usongo V, Lépine S, Janvier X, Archambault M, Gentilini ER. Characterisation of *Staphylococcus aureus* strains isolated from mastitis bovine milk in Argentina. *J Dairy Res.* 2018;85:57–63.
82. Srednik ME, Grieben MA, Bentancor A, Gentilini ER. Molecular identification of coagulase-negative staphylococci isolated from bovine mastitis and detection of β -lactam resistance. *J Infect Dev Ctries.* 2015;9:1022–7.
83. Srednik M, Archambault M, Jacques M, Gentilini E. Detection of a mecC-positive *Staphylococcus saprophyticus* from bovine mastitis in Argentina. *J Glob Antimicrob Resist.* 2017;10:261–3.
84. Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, Polachek AJ, Ganshorn H, Sharma N, Kellner JD, Ghali WA. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Health.* 2017;1:e316–27.
85. Teglia CM, Guíñez M, Culzoni MJ, Cerutti S. Determination of residual enrofloxacin in eggs due to long term administration to laying hens. Analysis of the consumer exposure assessment to egg derivatives. *Food Chem.* 2021;351:129279.
86. Tessi MA, Salsi MS, Caffer MI, Moguilevsky MA. Drug resistance of Enterobacteriaceae isolated from chicken carcasses. *J Food Prot.* 1997;60:1001–5.
87. Thanner S, Drissner D, Walsh F. Antimicrobial resistance in agriculture. *MBio.* 2016;7:e02227–2315.
88. Tilman D, Balzer C, Hill J, Befort BL. Global food demand and the sustainable intensification of agriculture. *Proc Natl Acad Sci U S A.* 2011;108:20260–4.

89. Torres Luque A, Gonzalez Moreno C, Pasteris SE, Orden JA, de la Fuente R, Otero MC. Antimicrobial resistant *Escherichia coli* in the reproductive tract microbiota of cows and sows. *Comp Immunol Microbiol Infect Dis*. 2017;55:13–9.
90. Unicomb L, Ferguson J, Riley TV, Collignon P. Fluoroquinolone resistance in *Campylobacter* absent from isolates, Australia. *Emerg Infect Dis*. 2003;9:1482–3.
91. Vallejo M, Gil MS, Parada RB, Marguet ER. Resistencia a metales pesados y antimicrobianos en cepas de enterococos aisladas de cerdos del Valle Inferior del Río Chubut - Argentina. *Revista Colombiana de Ciencia Animal - RECIA*. 2020;12:e763.
92. Vico JP, Lorenzutti AM, Zogbi AP, Aleu G, Sánchez IC, Caffer MI, Rosmini MR, Mainar-Jaime RC. Prevalence, associated risk factors, and antimicrobial resistance profiles of non-typhoidal *Salmonella* in large scale swine production in Córdoba, Argentina. *Res Vet Sci*. 2020;130:161–9.
93. Vigo GB, Cappuccio JA, Piñeyro PE, Salve A, Machuca MA, Quiroga MA, Moredo F, Giacoboni G, Cancer JL, Caffer IG, Binsztein N, Pichel M, Perfumo CJ. *Salmonella enterica* sub-clinical infection: bacteriological, serological pulsed-field gel electrophoresis, and antimicrobial resistance profiles – longitudinal study in a three-site farrow-to-finish farm. *Foodborne Pathog Dis*. 2009;6:965–72.
94. Wertheim HFL, Schultsz C. Antibiotics in low- and middle-income countries. *Ned Tijdschr Geneesk*. 2014;158:A8049.
95. World Health Organization. WHO | FAO/OIE/WHO Tripartite Collaboration on AMR, https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/.
96. World Health Organization. Antibiotic resistance, key facts, <https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance>.
97. World Health Organization. Critically important antimicrobials for human medicine: ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use; 2016.
98. Zbrun MV, Olivero C, Romero-Scharpen A, Rossler E, Soto LP, Astesana DM, Blajman JE, Berisvil A, Signorini ML, Frizzo LS. Antimicrobial resistance in thermotolerant *Campylobacter* isolated from different stages of the poultry meat supply chain in Argentina. *Food Control*. 2015;57:136–41.
99. Zhang P, Shen Z, Zhang C, Song L, Wang B, Shang J, Yue X, Qu Z, Li X, Wu L, Zheng Y, Aditya A, Wang Y, Xu S, Wu C. Surveillance of antimicrobial resistance among *Escherichia coli* from chicken and swine, China, 2008–2015. *Vet Microbiol*. 2017;203:49–55.