ORIGINAL ARTICLE

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

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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

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Introduction

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

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. 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 protein. 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 health.

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

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. Given the dry pipeline for new antimicrobials, we must expertly manage the drugs that are currently available. 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 approach.

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 Argentina, 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 yearly, 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), 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. (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 level, 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 analyzed. Isolates with intermediate
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} and {dmetar} 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 estimates.

The binary parameter 'proportion' (with 95% confidence intervals) was the one selected to measure effect size. 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} 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 tau$^2$ in the subgroups. 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 metabias²⁵. 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 Rios (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 swine⁶, 8, 12, 13, 14, 18, 19, 24, 39, 42, 45, 56-59, 65-66, 89, 91-93, followed by dairy⁶, 7, 12, 16, 17, 21, 32, 36, 44, 52, 55, 58, 67, 68, 71, 73, 79-83, 89, chicken⁶, 8, 12, 18, 19, 24, 39, 42, 45, 56-59, 65-66, 89, 91-93, and beef cattle⁶, 12, 44, 52, 65, 79, 83 (Fig. 2B). Among mastitis-causing bacteria, all isolates belonged to genera Staphylococcus⁶, 1, 3, 11, 32, 55, 68, 71, 73, 80-83 and Streptococcus⁶, 36, while E. coli was the most frequently studied food-transmitted bacteria⁶, 8, 12, 18, 19, 24, 44, 45, 52, 56-59, 63, 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 microdilution⁶, 18, 19, 35, 37, which was particularly needed to test susceptibility to colistin. Conversely, the E-test was used as a complement, but never as an only option⁶, 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 colistin⁶⁸, 69.

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 jejuni⁶⁸; group ‘Enterococcus’ only included Enterococcus spp.⁴, 14, 65, 91; group ‘E. coli’ included E. coliⁱ, 18, 24, 25, 56, 58, 59, 65, 79, 86, 89; Shiga-toxin-producing E. coli¹², 44, 52, enterotoxigenic E. coli³⁷, colistin-resistant E. coli¹⁹ and integron positive E. coli¹², 45; group ‘Salmonella’ included Salmonella spp.¹³, 65, 72, 86, 92, 93, Salmonella enterica⁶⁶, 67, Salmonella enterica subspecies enterica³⁹ and Salmonella Heidelberg¹, 2, 10; and group ‘dairy’ included E. coli⁷⁹, 89, Shiga-toxin-producing E. coli¹², 44, enterotoxigenic E. coli⁶⁷, integron positive E. coli¹² and, mastitis-causing bacteria Staphylococcus aureus¹¹, 55, 68, 73, 80, 81, 83, coagulase-negative staphylococci³², 71, 80, 82, 83, coagulase-positive staphylococci¹¹, Streptococcus spp.¹⁶ and Streptococcus agalactiae⁶⁶.

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 ansamycins⁵⁵, 67 (S. aureus and E. coli) and glycolcyclines⁴ (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 four⁶, 65, 98 in chicken, with no reports from beef cattle (Fig. 3 and Suppl. table* 52).

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%),
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 ampicillin. 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 antimicrobial. 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 ampicillin (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, chicken, and beef cattle (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: ceftaxime; DOX: doxycycline; ENR: enrofloxacin; ERY: erythromycin; FOX: fosfomycin; GEN: gentamicin; IMI: 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: tilmicosin; TLS: tylosin; TYC: 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, others assessed *E. coli* isolated from swine with diarrhea, or diarrheic piglets and healthy pigs, enterotoxigenic *E. coli* and integron positive *E. coli* or Shiga-toxin producing *E. coli*. 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 until 2019; Faccone et al. (2019) reported extremely high levels of AMR to cefotaxime and high levels of AMR to colistin, when isolating *E. coli* using plates containing cefotaxime, colistin or both. Moreover, at least one study reported very high resistance to enrofloxacin and ciprofloxacin. In swine with diarrhea, extremely high prevalence of AMR to erythromycin, tilmicosin and tylosin was found.

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 or not described. With respect to colistin, 49% of *E. coli* strains were resistant to this antimicrobial. Furthermore, colistin-resistant *E. coli* testing showed higher prevalence of resistance than *E. coli* to all antimicrobials except amikacin. Thus, extremely high prevalence of AMR was reported for streptomycin, cefotiofur, cefotaxime, cefepime, enrofloxacin, nalidixic acid, ampicillin and tetracycline. Finally, complete susceptibility to imipenem and meropenem was reported (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. Absence of AMR was reported for cefotiofur (Fig. 3). In *E. coli* and Shiga toxin-producing *E. coli*, resistance to cefotiofur, cefotaxime, cefepime, enrofloxacin, nalidixic acid, ampicillin and tetracycline. 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 cefotiofur. Results from healthy cows (see Section “**Enterobacteriaceae**”) contrast with those obtained when assessing *E. coli*, enterotoxigenic *E. coli*, and Shiga-toxin producing *E. coli* 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 assessed, 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, three in chicken, and one in beef cattle (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, while Joaquim et al. (2021) compared intensive production to backyard farms. Prevalence of AMR was rare to fosfomycin and polymyxins. The most recent study (2021) showed low resistance to 3rd and 4th generation cephalosporins, cefotiofur and cefepime, in intensive production. Extremely high AMR was reported for amoxicillin (Fig. 3 and Suppl. table S2).

In chicken, Tessi et al. (1997) and Rodriguez 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 derivatives. On the other hand, when assessing *Salmonella* Heidelberg from intensive production, very high prevalence of AMR was reported for cefotiofur and cefepime.

**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*. Other bacteria assessed were coagulase-negative staphylococci and *Streptococcus agalactiae*.

MDR was low or absent in *Staphylococcus* spp. isolated from dairy, with the highest value being 5.9% reported for coagulase-negative staphylococci. However, MDR was considerably higher in *S. agalactiae*, where 25% of the isolates were resistant to three or more antimicrobial classes.

**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.
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, enrofloxacín, nalidixic acid, ciprofloxacín, 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 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 0.096 [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.

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

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>No. of studies</th>
<th>No. of isolates</th>
<th>Pooled estimate</th>
<th>95% CI</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Cochran Q</th>
<th>Egger’s p-value&lt;sup&gt;c&lt;/sup&gt;</th>
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<td><strong>Enterobacteriaceae</strong></td>
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<tr>
<td>Streptomycin</td>
<td>17</td>
<td>646</td>
<td>0.2659</td>
<td>[0.1632; 0.4022]</td>
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<td>700</td>
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<td>77.6%</td>
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<td>688</td>
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<td>430</td>
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<td>[0.0380; 0.1944]</td>
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<tr>
<td>Amoxicillin/clav. acid</td>
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<td>445</td>
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<td>663</td>
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<td>633</td>
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<td>85.5%</td>
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</table>

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

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<th>Subgroup</th>
<th>N° studies</th>
<th>Pooled estimate</th>
<th>95% CI</th>
<th>Q</th>
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</table>
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). Given that the use of antimicrobials in animals increases AMR in the aquatic environment and contributes to the development of resistance in animal populations, it is crucial to implement strategies to mitigate this risk. These strategies may include the rational use of antimicrobials, the development of alternative treatments, and the implementation of surveillance programs to monitor the prevalence of AMR in animal populations.
B. Prack McCormick, M.P. Quiroga, V.E. Álvarez et al.

Article in press

<table>
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<tr>
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<tr>
<td><strong>Random effects model</strong></td>
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<td>0.37 [0.15; 0.65]</td>
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Heterogeneity: $I^2 = 89\%$, $p < 0.01$

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<tr>
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<tr>
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<tr>
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<td>49</td>
<td>0.57 [0.42; 0.71]</td>
<td>6.9%</td>
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Heterogeneity: $I^2 = 76\%$, $p < 0.01$

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Heterogeneity: $I^2 = 17\%$, $p = 0.30$

<table>
<thead>
<tr>
<th>Author</th>
<th>Event</th>
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<th>Proportion 95%--CI</th>
<th>Weight</th>
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<tbody>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>653</strong></td>
<td></td>
<td>0.38 [0.21; 0.57]</td>
<td>100.0%</td>
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</tbody>
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Heterogeneity: $I^2 = 85\%$, $p < 0.01$

Residual heterogeneity: $I^2 = 76\%$, $p < 0.01$

Test for subgroup differences: $\chi^2 = 19.82$, df = 2 ($p < 0.01$)

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

Humans\(^{37}\), 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 worldwide\(^{43}\).

Meta-analyses are a powerful tool to quantitatively summarize available data and assess possible sources of heterogeneity, such as animal species or production systems\(^{39}\). 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 medicine\(^{37}\).
The first category includes the combination of amoxicillin and clavulanic acid, ampicillin, ceftiofur, doxycycline, enrofloxacin, erythromycin, fosfomycin, 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 'highest priority critically important antimicrobials': quinolones, 3rd-generation cephalosporins or higher, macrolides and ketolides, glycopeptides and polymyxins69. 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 chicken62,98, in *E. coli*. coli from chicken19 and diarrheic beef-cattle calves16, and very high in *Salmonella* spp. isolated from swine66 and chicken90. 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 China90 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 chickens8.

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 ciprofloxacin15,29. 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 Argentina25.

**Cephalosporins**

In Argentina, the main cephalosporins available for veterinary use are ceftiofur and ceftioquinome (SENASA Resolution 559/2011). In the qualitative synthesis of this study, data on resistance to ceftiofur come from *E. coli*18,92 and *Salmonella* spp.2,21. Prevalence of resistance in swine is in between what has been reported in US (very low) and China (moderate)21,99, or higher12,24. 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)65,99. 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.35 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 complete46. 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 bacteria15. 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, chlorotetracycline 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 EU1,34,99.

As described in some global meta-analyses75,76, 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)16.
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 antimicrobials\(^{44}\).

**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 outbreak of this resistance gene in Latin America and the risk of the rapid dissemination of \(mcr-1\) has alerted actors worldwide\(^{39}\).

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 zones\(^ {47}\).

**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 additive\(^ {22}\). 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 farmers\(^ {33}\). 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 confinement\(^ {78}\). In our study, a reduced number of the articles included compared AMR among different animal species\(^ {33,62,89}\) or production systems\(^ {12,62,89}\). 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’\(^ {39}\), 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 genes\(^ {67}\). Among the studies included in this review, authors reported the presence of a variety of resistance-encoding genes and cassettes including, \(aac(6)\)-\(le-aph(2)\)-Ia\(^ {44}\), \(aadA1\)\(^ {44}\), \(aadA5\)\(^ {38}\), \(aphA3\)\(^ {38}\), \(bla\_OXA-24\)\(^ {19,24}\), \(bla\_CTX-M-2\)\(^ {24}\), \(bla\_CTX-M-8/25\)\(^ {24}\), \(bla\_CMY-19,24\), \(bla\_PER-2\)\(^ {19}\), \(bla\_TEM-46\)\(^ {19}\), \(draF1\)\(^ {44}\), \(ermB\)\(^ {16}\), \(ermC\)\(^ {9}\), \(fioR\)\(^ {38}\), \(lnuB\)\(^ {38}\), \(mcr-118,19,24\), \(mel\)\(^ {20}\), \(qepA\)\(^ {19}\), \(qnrA\)\(^ {19}\), \(qnrB\)\(^ {19}\), \(qnrD\)\(^ {19}\), \(qnrS\)\(^ {19}\), \(strA\), \(strB\), \(sul\)\(_1\), \(sul\)\(_2\), \(tet(A)\), \(tet(B)\), \(tet(M)\), \(tet(O)\)\(^ {38}\), \(vanA\)\(^ {14}\). 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 problem\(^ {67}\). 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 countries\(^ {84}\). 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 uses\(^ {4}\). 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 world\(^ {67}\).

Answering to the need for global surveillance programs, the OIE encourages the application of national surveillance programs, whose results are being integrated in global reports\(^ {64}\). 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 *Enteroctococcus* 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.

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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.

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