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Review

A meta-analytic perspective on *Arcobacter* spp. antibiotic resistance

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ABSTRACT

Objectives: Over the years, an increased prevalence of resistant strains of *Arcobacter* has been observed, which may be due to *Arcobacter* exposure to antibiotics used both in animal production and human medicine. A systematic review was performed with the objective of summarising the results of the rates of antimicrobial resistance of *Arcobacter* isolates.
Methods: The systematic review was performed according to PRISMA (Preferred Reported Items for Systematic Reviews and Meta-Analysis) recommendations, followed by meta-analysis.
Results: It was observed that the resistance rate ranged between 69.3–99.2% for penicillins and 30.5–97.4% for cephalosporins. The overall percentage of resistance to fluoroquinolones ranged from 4.3% to 14.0%, with the highest resistance percentage observed for levofloxacin. Resistance rates ranged between 10.7–39.8% for macrolides, 1.8–12.9% for aminoglycosides and 0.8–7.1% for tetracyclines.
Conclusions: These results show that *Arcobacter* spp. present resistance to various antibiotics commonly used and advocate further studies of the associated resistance mechanisms.
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Contents

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1. Introduction

The *Arcobacter* genus belongs to the family *Campylobacteraceae*, which comprises two other genera, namely *Campylobacter* and *Sulfurospirillum*. The *Arcobacter* genus shows an unusually varied range of habitats, being found in various hosts and environments including diseased and healthy animals, humans, environmental and water samples, foods and food-processing facilities [1]. Over the years this genus became a large and heterogeneous group of bacteria, currently comprising 28 recognised species [2–7]. Among these, *Arcobacter butzleri*, *Arcobacter cryaerophilus* and *Arcobacter skirrowii* are recognised human and animal pathogens and have been associated with enteritis and bacteraemia in humans, and more frequently with abortion, mastitis or diarrhoea in animals [3]. These species are considered foodborne pathogens, for which the consumption of *Arcobacter*-contaminated food or water has been considered the most probable mode of transmission [1]. *Arcobacter butzleri* has been described as the most prevalent species and the one more frequently linked with diarrhoeal disease, being the fourth species most frequently detected in diarrhoeal samples among *Campylobacter*-like organisms [8–10]. However, lack of surveillance may prevent a correct estimation of the number of cases of diarrhoea associated with *Arcobacter* spp. infection. Its relevance as a human pathogen is underlined by the resistance to antimicrobials, the presence of several putative virulence genes, along with its adherence, invasion, intracellular survival abilities and induction of pro-inflammatory cytokine secretion in intestinal epithelial cells [11,12]. Despite most often being self-limiting, *Arcobacter* enteritis severity or prolongation of symptoms could support the use of antibiotic treatment [1]. Regarding case studies reporting *Arcobacter* intestinal infection, treatments have included the use of quinolones, tetracyclines, macrolides or even β-lactam antibiotics combined with β-lactamase inhibitors [13]. Nonetheless, a variable magnitude of resistance rates to fluoroquinolones, macrolides, chloramphenicol, aminoglycosides, penicillins, tetracyclines and other classes of antibiotics has been reported for *Arcobacter* strains of environmental, animal and human origin [12]. When considering that macrolides and fluoroquinolones are the drugs of choice for *Campylobacter* treatment [14], the low resistance rate to fluoroquinolones reported by Vandenberg et al. in 2006 led the authors to suggest that these could be used for treating severe *Arcobacter* enteritis [15]. However, some studies have reported high levels of resistance to fluoroquinolones or macrolides [12], thus suggesting that acquired resistance might compromise the treatment of illnesses caused by this microorganism. The high prevalence of antimicrobial resistance may be due to *Arcobacter* spp. exposure to antibiotics used both in animal production and human medicine [16].

Considering this context, the main goal of this work was to perform a systematic review followed by meta-analysis in order to quantitatively summarise the overall prevalence of antimicrobial resistance among *Arcobacter* spp. isolates.

2. Materials and methods

2.1. Search and selection of studies

The ISI Web of Science, Scopus, PubMed and SciELO databases were searched using the terms 'resistance' AND '*Arcobacter*' for articles published or placed online on or before 15 November 2017. The search was performed without restrictions, with the subsequent analysis limited to articles published in English, Spanish and Portuguese. Following the PRISMA (Preferred Reported Items for Systematic Reviews and Meta-Analyses) statement [17,18], titles and abstracts of the articles were initially screened by two authors, with a third researcher consulted in cases of disagreement. Full-text articles, excluding reviews, conference abstracts and book chapters, were retrieved. All articles reporting antimicrobial resistance of *Arcobacter* spp. were considered when presenting a resistance categorisation or the minimum inhibitory concentration (MIC) distribution, with no minimum number of samples or antibiotic tested being considered.

2.2. Data extraction and statistical analyses

The following data were extracted from all studies: first author's last name; year of publication; sampling period; country; *Arcobacter* species; sample size; origin of strains; antimicrobial resistance evaluation method; and status of resistance to antibiotics (Supplementary Table S1 in the online version at DOI: 10.1016/j.jgar.2018.12.018). Considering the PRISMA recommendations [17,18], two authors independently extracted the data, with discrepancies resolved by discussion within the research team.

Meta-analysis of the prevalence of antimicrobial-resistant *Arcobacter* spp. was performed using Comprehensive Meta-Analysis Software v.2.0 (https://www.meta-analysis.com/). Forest plots were generated to show the study-specific effect sizes, with the pooled estimate (PE) considered with a 95% confidence interval (CI), using the random-effects model [19]. The I^2 statistic was employed to measure heterogeneity among studies [20]. Values close to 0% indicate no heterogeneity, whilst values close to 25%, 50% and 75% correspond to low, moderate and high heterogeneity, respectively [20]. To evaluate the impact of publication bias, funnel plots were obtained plotting the logit event rate against the corresponding standard error [21,22], with the studies symmetrically distributed in the absence of publication bias. To avoid misinterpretation of the funnel plots, Egger's regression test was also employed [23]. Moreover, the Trim and Fill method, which uses an iterative procedure to remove studies that contain a small sample size, re-computing the effect size at each iteration until the funnel plot is symmetrical, was further applied, resulting in an unbiased estimate of the pooled effect size [24,25]. This approach provides an intuitive visual display since it generates funnel plots including both the observed studies (represented as blue circles) and the imputed studies (represented as red circles).

A sensitivity analysis was performed by removing each study at a time to evaluate the stability of the results. In addition, a subgroup analysis was performed considering the method of antimicrobial resistance evaluation, continent (Turkey was included in Asia), economy (classified according to the World Development Indicators database [26]), *Arcobacter* species and type of sample in order to further investigate the prevalence of antimicrobial resistance among *Arcobacter* spp. Forest plots of comparisons between the risk difference of resistant strains to each antimicrobial amongst the different methods, types of samples, *Arcobacter* species, continents and economies were obtained, and a *P*-value of <0.050 was considered statistically significant (favouring the antimicrobial resistance). Multidrug resistance was also subjected to meta-analysis, with the *Arcobacter* isolates classified as multidrug-resistant according to the standard definitions previously established [27]. Meta-regression analysis

for year of publication and the prevalence of *Arcobacter* isolates resistant to the antimicrobials was also performed.

3. Results

3.1. Selection of studies and study characteristics

For this systematic review, a total of 478 articles were screened, of which 41 were considered eligible for inclusion in the present meta-analysis. From these 41 studies, 1 was excluded due to the lack of MIC values or classification of the strains as resistant or susceptible (Fig. 1). The 40 remaining articles presented data from 19 countries, mentioning a total of 89 antibiotics, of which only 15 were selected for further evaluation.

For this meta-analysis on the prevalence of antimicrobial resistance among *Arcobacter* spp., all antibiotics with more than one study were considered. The maximum number of studies associated with an antibiotic was 30, which also corresponded to the highest number of isolates evaluated ($n = 1819$). Regarding the subgroup analysis, meta-regression and comparisons, only 15 antibiotics were selected for evaluation. This selection was performed considering the recommended antibiotics for treatment of *Arcobacter* spp. infections and also those usually reported as used for treatment in case studies [12]. Considering these conditions, macrolides, fluoroquinolones, aminoglycosides, tetracyclines, cephalosporins and β-lactams were included. Among these antibiotics, those mentioned in less than five studies were removed from the evaluation. Overall, the resistance classification of each article was used, with the exception of three studies where the resistance breakpoints from Clinical and Laboratory Standards (CLSI) document M100-S26 [28], used for *Entreobacteriaceae*, *Staphylococcus* spp. and non-*Entreobacteriaceae*, were applied.

3.2. Meta-analysis

The primary objective of this meta-analysis was to evaluate the extent of *Arcobacter* spp. resistance to antibiotics. The collective prevalence of resistant *Arcobacter* isolates is presented in Supplementary Table S2 in the online version at DOI: 10.1016/j.jgar.2018.12.018. The publication year of the included papers ranged from 1998 to 2018, encompassing *Arcobacter* spp. isolates collected from 1994 to 2017. First, the prevalence of resistant *Arcobacter* spp. was evaluated for 45 antibiotics, and when considering the grouping of antibiotics by classes, penicillins and cephalosporins were among those presenting overall a higher resistance rate. The percentage of resistant isolates ranged from 69.3–99.2% for penicillins and 30.5–97.4% for cephalosporins. However, when the assessment was performed for a penicillin in combination with other drug, in some cases the resistance prevalence decreased. The resistance rate for amoxicillin had a PE of 0.748 (95% CI 0.558–0.875), but when combined either with clavulanic acid or gentamicin the PE was significantly reduced ($P < 0.001$) [amoxicillin/clavulanic acid, PE = 0.366 (95% CI 0.253–0.496); amoxicillin/gentamicin, PE = 0.230 (95% CI 0.142–0.352)].

The overall prevalence of resistance to fluoroquinolones ranged from 0.043–0.140, with the highest resistance rate observed for levofloxacin (PE = 0.140, 95% CI 0.048–0.342) and the lowest for norfloxacin (PE = 0.043, 95% CI 0.000–0.823), both second-generation fluoroquinolones. When taking a general overview for quinolones, this value increased, with nalidixic acid presenting the highest prevalence of resistance (PE = 0.539, 95% CI 0.398–0.674).

Regarding macrolides, erythromycin, azithromycin and spiramycin were all evaluated in the studies included, showing resistance rates of 10.7%, 39.8% and 26.5%, respectively. Resistance rates ranged from 1.8–12.9% for tetracyclines and 0.8–7.1% for

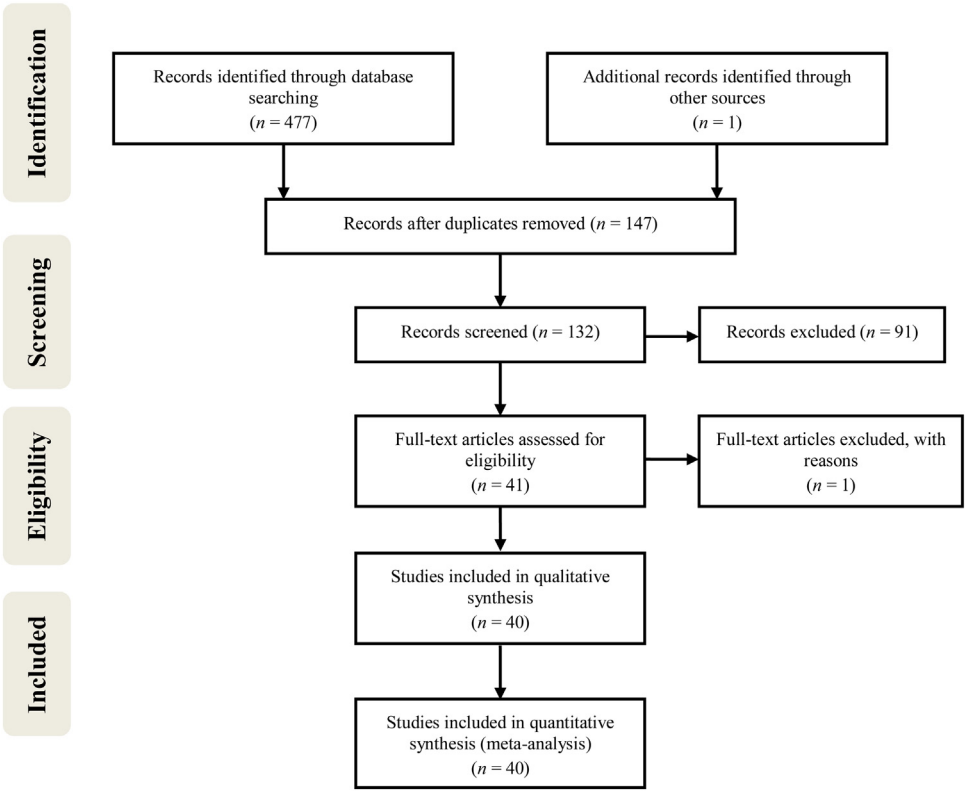

Fig. 1. Flow diagram of database search, study selection and articles included in the meta-analysis.

aminoglycosides. Overall, among the antibiotics considered, *Arcobacter* spp. presented the lowest rate of resistance to aminoglycosides. Imipenem and nitrofurantoin also showed low resistance rates, with PEs of 0.090 (95% CI 0.000–0.986) and 0.019 (95% CI 0.003–0.121), respectively. However, considering the CI of imipenem and the low number of studies that tested these molecules, this result should be taken with caution.

Regarding the heterogeneity results, the I^2 statistic demonstrated that high heterogeneity ($I^2 > 75\%$) was found for most of the antibiotics considered. Nevertheless, for cloxacillin, amikacin, nitrofurantoin, oxytetracycline, oxacillin, cefazolin and tobramycin, no heterogeneity ($I^2 = 0\%$) was found among the results, which is probably due to the reduced number of studies that included these molecules.

3.3. Subgroup analysis, comparisons and meta-regression

Multiple subgroup analyses were performed considering the antibiotic resistance prevalence according to *Arcobacter* species, continent of origin of the isolates, type of economy of the countries, type of sample from where the strains were isolated and the methodology used for evaluating antimicrobial resistance. Furthermore, comparisons between resistance to each antibiotic according the type of samples, *Arcobacter* species, methodology, continents and economies were also undertaken.

3.3.1. Arcobacter species

Table 1 summarises the analysis regarding the prevalence of antibiotic resistance according to *Arcobacter* species. *Arcobacter* isolates were only included when identified to species level, and the species were only included if they were evaluated in more than one study. *Arcobacter butzleri* was the species with the highest resistance rate for ampicillin, amoxicillin/clavulanic acid (AMC), cefalotin, azithromycin and levofloxacin. In contrast, *A. butzleri* was the most susceptible species to erythromycin, gentamicin, tetracycline, streptomycin, enrofloxacin and doxycycline. The resistance rate was significantly higher than that observed for *A. cryaerophilus* for AMC ($P = 0.034$), ampicillin ($P < 0.001$), cefalotin ($P < 0.001$) and azithromycin ($P < 0.001$) (Fig. 2A). Compared with *A. skirrowii*, the resistance rate was higher for ampicillin ($P < 0.001$), cefotaxime ($P < 0.001$), cefalotin ($P < 0.001$) and levofloxacin ($P = 0.006$) (Fig. 2B). Regarding *A. skirrowii*, this species appears to be more susceptible to penicillins and cephalosporins but more resistant to macrolides and tetracyclines compared with *A. butzleri* and *A. cryaerophilus* (Fig. 2B,C). However, when considering the overall difference between the selected antibiotics, this difference was not significant. It is important to notice that azithromycin presented a different tendency than erythromycin, the other macrolide under investigation.

3.3.2. Continent and country economy classification

A subgroup analysis evaluating the antibiotic resistance across continents was performed, followed by a comparison among them (except for Africa, since it was only mentioned in one study), and distributing countries according to their economy level.

When considering the overall resistance rate, the highest prevalence of resistance to fluoroquinolones was observed in America, which contrasted with the lowest resistance rate observed for erythromycin and tetracycline (Table 2). Regarding cephalosporins, Asia was the continent with the highest prevalence of resistance, with PEs ranging from 0.865–0.943. In Europe, cefoperazone (89.6%) and amoxicillin (89.1%) were the antibiotics for which the highest rates of resistance were observed, in contrast to what was observed for gentamicin (3.4%) (Table 2). Comparing the resistance of *Arcobacter* isolates among continents, a higher prevalence of resistance to amoxicillin, AMC, cefotaxime, cefalotin, ciprofloxacin, azithromycin and doxycycline ($P < 0.001$) was observed in Europe compared with Asia (Fig. 3A). In general, a significant resistance rate was found in America ($P = 0.034$) compared with Europe, with focus on resistance to erythromycin, tetracycline, levofloxacin and azithromycin ($P < 0.001$) (Fig. 3B). When Asia and America were compared, resistance to ciprofloxacin, erythromycin and tetracycline were significantly higher in America than in Asia ($P < 0.001$) (Fig. 3C). Finally, grouping countries by level of economic development (Fig. 3D), it is observed that developing economies presented significantly higher resistance rates compared with developed economies ($P < 0.001$).

3.3.3. Origin of the isolates

A subgroup analysis considering the origin of the isolates was performed (Table 3), splitting the isolates as coming from the environment (water sources), food-related origin (animal food-origin including meat or faeces, vegetables and samples from food-processing plants) and humans. Overall, environmental isolates were less resistant to erythromycin, ciprofloxacin, tetracycline, gentamicin and streptomycin, whilst *Arcobacter* spp. isolated from food were more susceptible to AMC, cefalotin, cefoperazone, azithromycin, ampicillin and amoxicillin (Table 3). No statistical difference was observed comparing environmental with human

Table 1
Subgroup analysis comparing the prevalence of antimicrobial resistance, measured by pooled estimate (PE), according to *Arcobacter* species.

Antimicrobial agent	*A. butzleri*		*A. cryaerophilus*		*A. skirrowii*	
	PE	95% CI	PE	95% CI	PE	95% CI
Erythromycin	0.096	0.048–0.183	0.127	0.054–0.266	0.255	0.067–0.620
Ciprofloxacin	0.093	0.054–0.155	0.112	0.052–0.224	0.070	0.008–0.407
Gentamicin	0.027	0.014–0.051	0.051	0.021–0.118	0.070	0.009–0.390
Ampicillin	0.717	0.607–0.805	0.545	0.359–0.719	0.497	0.213–0.783
Tetracycline	0.060	0.021–0.162	0.180	0.050–0.476	0.478	0.079–0.907
AMC	0.384	0.258–0.527	0.271	0.141–0.457	0.271	0.092–0.579
Streptomycin	0.034	0.010–0.114	0.140	0.036–0.420	0.187	0.047–0.517
Enrofloxacin	0.087	0.047–0.155	0.150	0.070–0.292	0.230	0.084–0.492
Cefotaxime	0.863	0.566–0.968	0.886	0.423–0.988	0.237	0.017–0.849
Cefalotin	0.956	0.879–0.984	0.510	0.250–0.766	0.239	0.055–0.627
Cefoperazone	0.945	0.866–0.979	0.956	0.844–0.989	0.901	0.706–0.972
Azithromycin	0.576	0.172–0.899	0.159	0.026–0.572	0.167	0.002–0.953
Levofloxacin	0.162	0.059–0.372	0.096	0.020–0.353	0.040	0.003–0.353
Doxycycline	0.125	0.038–0.340	0.133	0.034–0.401	0.369	0.061–0.842
Amoxicillin	0.625	0.356–0.834	0.613	0.227–0.895	0.638	0.215–0.919

CI, confidence interval; AMC, amoxicillin/clavulanic acid.

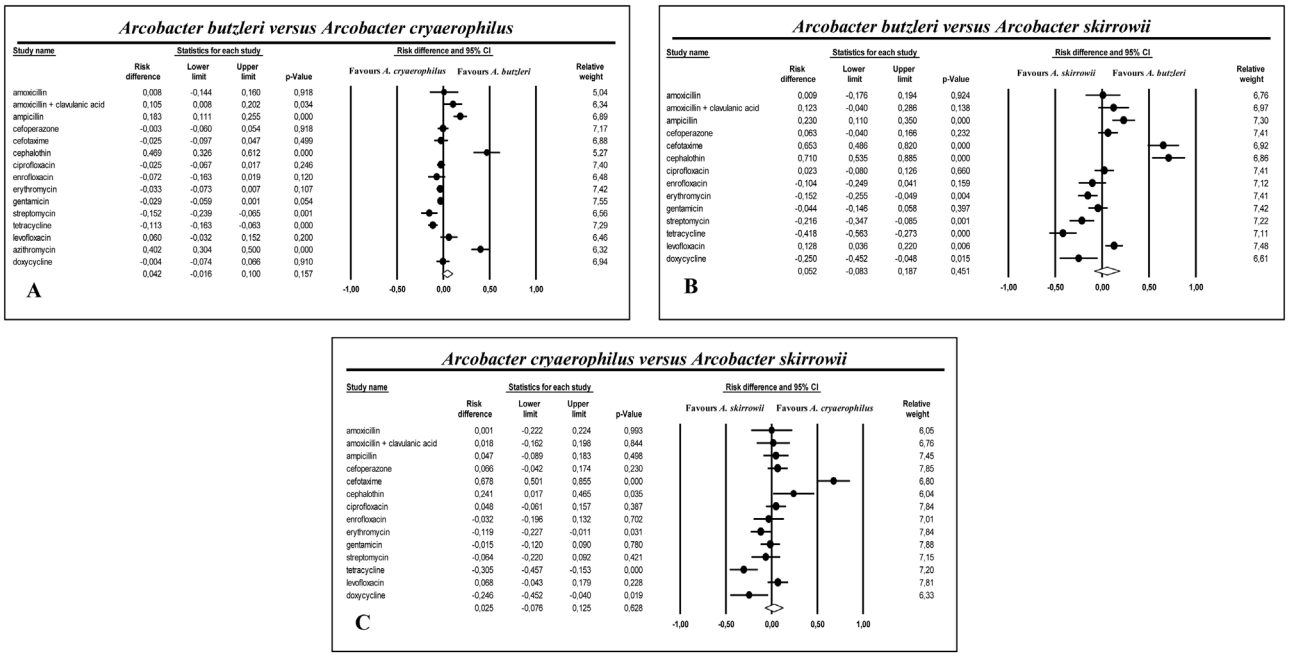

Fig. 2. Forest plots of comparisons between the risk difference of *Arcobacter* spp. isolates resistant to each antimicrobial.

Table 2
Subgroup analysis comparing the prevalence of antimicrobial-resistant *Arcobacter* spp., measured by pooled estimate (PE), considering the continent and economy.

Antimicrobial agent	Continent								Economy			
	America		Asia		Europe		Africa		Developed		Developing	
	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI
Erythromycin	0.031	0.005–0.165	0.125	0.046–0.299	0.133	0.054–0.292	N/A	N/A	0.101	0.041–0.230	0.110	0.041–0.263
Ciprofloxacin	0.124	0.042–0.313	0.051	0.020–0.128	0.114	0.059–0.208	0.100	0.007–0.629	0.109	0.060–0.190	0.072	0.032–0.152
Gentamicin	0.024	0.005–0.107	0.019	0.004–0.074	0.034	0.013–0.089	0.150	0.006–0.833	0.030	0.011–0.076	0.029	0.010–0.078
Ampicillin	0.631	0.385–0.824	0.742	0.582–0.855	0.706	0.546–0.827	N/A	N/A	0.600	0.430–0.750	0.791	0.662–0.880
Tetracycline	0.009	0.000–0.173	0.072	0.016–0.269	0.075	0.017–0.279	N/A	N/A	0.048	0.011–0.182	0.072	0.017–0.263
AMC	N/A	N/A	0.378	0.227–0.558	0.255	0.122–0.459	0.850	0.419–0.978	0.299	0.164–0.481	0.457	0.261–0.667
Streptomycin	N/A	N/A	0.038	0.008–0.158	0.055	0.004–0.442	0.800	0.117–0.992	0.028	0.003–0.209	0.114	0.027–0.371
Enrofloxacin	N/A	N/A	0.088	0.037–0.194	0.070	0.010–0.364	N/A	N/A	0.070	0.010–0.364	0.088	0.037–0.194
Cefotaxime	N/A	N/A	0.865	0.281–0.991	0.768	0.375–0.948	N/A	N/A	0.768	0.375–0.948	0.865	0.281–0.991
Cefalotin	N/A	N/A	0.931	0.746–0.984	0.730	0.093–0.986	N/A	N/A	0.773	0.373–0.951	0.939	0.789–0.984
Cefoperazone	N/A	N/A	0.943	0.885–0.973	0.896	0.846–0.931	N/A	N/A	0.896	0.846–0.931	0.943	0.885–0.973
Azithromycin	0.695	0.038–0.993	0.590	0.073–0.963	0.095	0.004–0.710	N/A	N/A	0.253	0.031–0.784	0.590	0.084–0.958
Levofloxacin	0.348	0.043–0.863	N/A	N/A	0.096	0.021–0.349	N/A	N/A	0.096	0.021–0.349	0.348	0.043–0.863
Doxycycline	N/A	N/A	0.343	0.064–0.799	0.063	0.014–0.245	N/A	N/A	0.063	0.014–0.245	0.343	0.064–0.799
Amoxicillin	N/A	N/A	0.638	0.389–0.830	0.891	0.563–0.981	0.900	0.459–0.990	0.891	0.558–0.981	0.695	0.468–0.855

CI, confidence interval; N/A, not available; AMC, amoxicillin/clavulanic acid.

isolates, except for erythromycin ($P < 0.001$) (Fig. 4A); food isolates were in general more susceptible to ampicillin ($P = 0.029$ and $P < 0.001$ for comparison with environmental and human isolates, respectively) (Fig. 4B,C). Moreover, food isolates were more resistant to erythromycin compared with environmental isolates ($P = 0.001$) and also to AMC ($P = 0.015$) and to azithromycin ($P < 0.001$) compared with human isolates (Fig. 4B,C). Overall, 638 isolates from 13 studies were evaluated for multidrug resistance (Supplementary Table S2 in the online version at DOI: 10.1016/j.jgar.2018.12.018). It was found that 68.9% (95% CI 45.2–85.6%) of the isolates presented resistance to at least one antibiotic of three or more different classes. The prevalence of multidrug resistance ranged from 0.222 in environmental isolates to 0.902 in human isolates (Table 3).

3.3.4. Antimicrobial susceptibility testing method

Different testing methodologies may have had an impact on the observed differences in resistance rates, therefore a subgroup analysis was performed comparing the prevalence of antimicrobial-resistant *Arcobacter* spp. considering that fact (Table 4). In general, cefoperazone was the antibiotic that showed the highest resistance rate determined by the agar plate dilution method (92.1%), broth microdilution (88.9%) and disk diffusion assay (94.3%). Moreover, with the agar plate dilution method the highest percentage of *Arcobacter* resistant isolates was found for tetracycline (90.5%) and cefotaxime (92.9%). Furthermore, comparisons between the different methodologies were also performed (Fig. 5), except for the Sensititre™ semiautomated method since only one

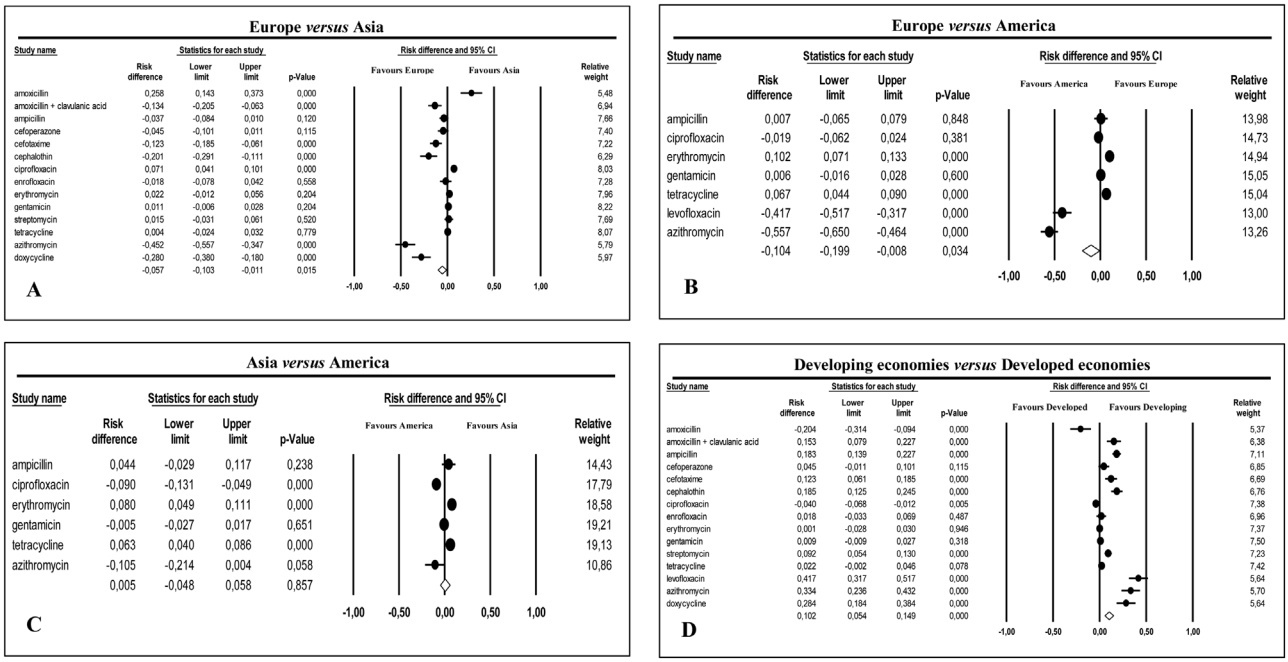

Fig. 3. Forest plots of comparisons between the risk difference of *Arcobacter* spp. isolates resistant to each antimicrobial among continents (A–C) and economies (D).

Table 3
Subgroup analysis comparing the prevalence of antimicrobial-resistant *Arcobacter* spp., measured by pooled estimate (PE), according to sample type.

Antimicrobial agent	Environment		Food		Human	
	PE	95% CI	PE	95% CI	PE	95% CI
Multidrug-resistant	0.222	0.103–0.414	0.669	0.384–0.868	0.902	0.678–0.976
Erythromycin	0.019	0.001–0.270	0.091	0.043–0.183	0.147	0.104–0.371
Ciprofloxacin	0.075	0.009–0.420	0.107	0.059–0.187	0.084	0.031–0.187
Gentamicin	0.028	0.002–0.281	0.036	0.017–0.075	0.027	0.007–0.098
Ampicillin	0.796	0.431–0.953	0.664	0.540–0.769	0.777	0.526–0.916
Tetracycline	0.027	0.001–0.525	0.062	0.017–0.200	0.046	0.007–0.235
AMC	0.413	0.171–0.706	0.438	0.299–0.588	0.279	0.110–0.548
Streptomycin	0.018	0.001–0.400	0.054	0.011–0.234	0.049	0.001–0.655
Enrofloxacin	0.148	0.014–0.628	0.070	0.026–0.179	0.204	0.031–0.678
Cefotaxime	0.981	0.473–1.000	0.872	0.611–0.967	N/A	N/A
Cefalotin	0.938	0.649–0.992	0.888	0.734–0.958	0.286	0.023–0.870
Cefoperazone	N/A	N/A	0.947	0.848–0.983	0.875	0.214–0.994
Azithromycin	N/A	N/A	0.675	0.359–0.885	0.143	0.022–0.552
Levofloxacin	N/A	N/A	0.185	0.057–0.460	N/A	N/A
Doxycycline	0.037	0.000–0.760	0.010	0.013–0.491	0.092	0.011–0.489
Amoxicillin	N/A	N/A	0.772	0.505–0.919	0.667	0.056–0.985

CI, confidence interval; N/A, not available; AMC, amoxicillin/clavulanic acid.

study evaluated the susceptibility of *Arcobacter* isolates using this method. Overall, comparing the microdilution method and disk diffusion assay, the isolates studied by the disk diffusion were significantly more resistant ($P < 0.001$) to amoxicillin, cefotaxime and erythromycin. Comparing the agar plate dilution and disk diffusion methods, the antibiotics that presented significantly higher resistance rates ($P < 0.001$) were cefotaxime, ciprofloxacin and tetracycline when evaluated by the agar plate dilution method.

3.3.5. Meta-regression analysis

Analysis of the evolution of resistance over the years was performed using a meta-regression analysis considering the year of publication (Table 5). Since the year considered for the meta-regression was the year of publication and not the year of the sampling, this may skew the results. A tendency of increased prevalence of *Arcobacter* spp. resistant to ciprofloxacin, gentamicin and tetracycline over the years was observed (slope positive; $P < 0.001$); however, an inverse behaviour was found for erythromycin, cefotaxime and azithromycin (slope negative; $P < 0.001$). No significant tendency was verified for the other nine antibiotics included in the subgroup analysis.

3.4. Publication bias and sensitivity analysis

Funnel plots were obtained for the 15 antimicrobials with the objective of analysing publication bias (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.jgar.2018.12.018). It was observed that for erythromycin, ciprofloxacin, gentamicin, tetracycline, AMC, streptomycin, enrofloxacin, azithromycin and levofloxacin, there were more studies on the left part of the corresponding funnel plots, and so using the Trim and Fill adjustment various studies were imputed to the right part of the plots to adjust the funnel plots for the absence of publication

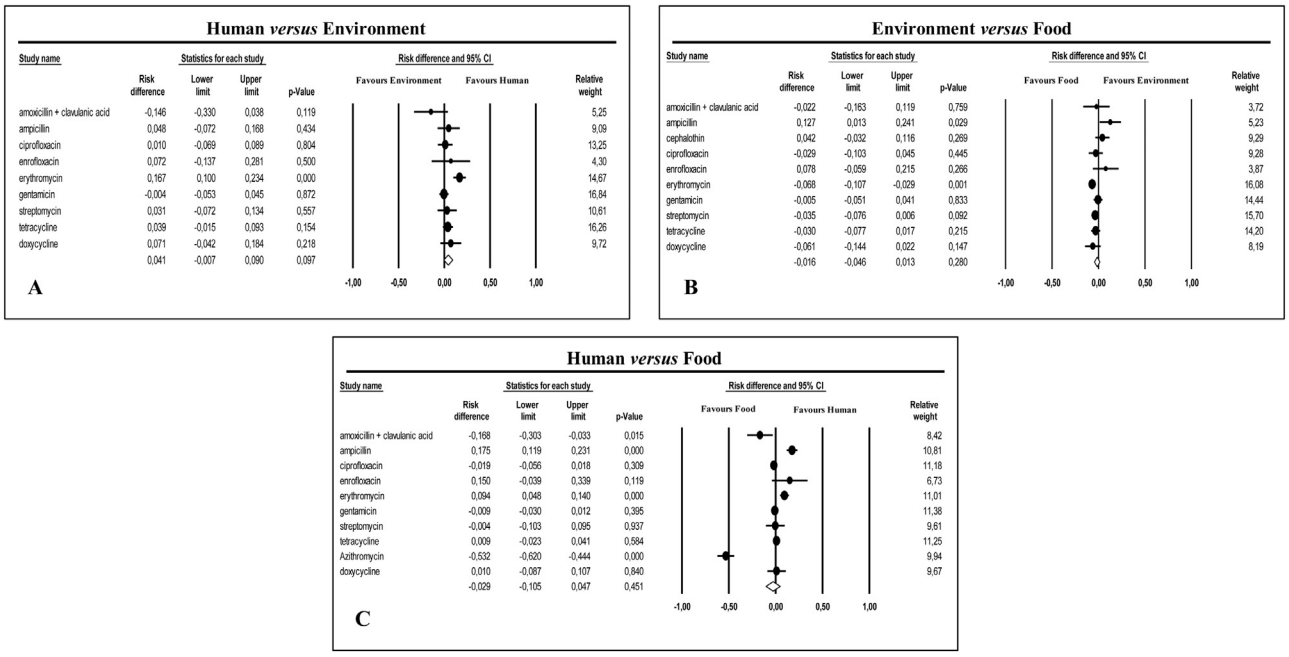

Fig. 4. Forest plots of comparisons between the risk difference of *Arcobacter* spp. isolates resistant to each antimicrobial among different sample types.

Table 4
Subgroup analysis comparing the prevalence of antimicrobial-resistant *Arcobacter* spp., measured by pooled estimate (PE), considering the method of antimicrobial susceptibility testing.

Antimicrobial agent	Agar plate dilution		Broth microdilution		Disk diffusion		Gradient strip diffusion		Sensititre™ semiautomated	
	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI
Erythromycin	0.070	0.011–0.350	0.023	0.001–0.365	0.161	0.065–0.347	0.084	0.022–0.278	0.034	0.001–0.564
Ciprofloxacin	0.166	0.041–0.482	0.187	0.024–0.679	0.071	0.032–0.150	0.089	0.031–0.231	0.082	0.009–0.462
Gentamicin	0.010	0.001–0.064	0.025	0.002–0.241	0.050	0.021–0.117	0.031	0.009–0.100	0.008	0.001–0.084
Ampicillin	0.636	0.377–0.835	0.764	0.433–0.932	0.747	0.615–0.845	0.629	0.414–0.803	N/A	N/A
Tetracycline	0.905	0.168–0.998	0.031	0.001–0.435	0.060	0.020–0.170	0.044	0.007–0.219	0.003	0.000–0.240
AMC	N/A	N/A	0.062	0.011–0.271	0.410	0.297–0.533	N/A	N/A	N/A	N/A
Streptomycin	N/A	N/A	N/A	N/A	0.058	0.014–0.210	0.222	0.005–0.939	N/A	N/A
Enrofloxacin	N/A	N/A	N/A	N/A	0.087	0.042–0.172	N/A	N/A	N/A	N/A
Cefotaxime	0.929	0.757–0.982	0.077	0.007–0.482	0.764	0.434–0.932	N/A	N/A	N/A	N/A
Cefalotin	N/A	N/A	N/A	N/A	0.888	0.742–0.956	N/A	N/A	N/A	N/A
Cefoperazone	0.921	0.844–0.962	0.889	0.784–0.946	0.943	0.856–0.979	N/A	N/A	N/A	N/A
Azithromycin	N/A	N/A	N/A	N/A	0.590	0.063–0.968	0.143	0.002–0.925	0.695	0.030–0.994
Levofloxacin	0.172	0.032–0.570	N/A	N/A	0.120	0.004–0.824	N/A	N/A	N/A	N/A
Doxycycline	0.016	0.000–0.352	0.071	0.001–0.853	0.187	0.033–0.611	0.238	0.012–0.890	N/A	N/A
Amoxicillin	N/A	N/A	0.891	0.558–0.981	0.695	0.468–0.855	N/A	N/A	N/A	N/A

CI, confidence interval; N/A, not available; AMC, amoxicillin/clavulanic acid.

bias. Contrariwise, for ampicillin, cefotaxime, cefalotin, cefoperazone and amoxicillin, the necessary imputed studies were added to the left part of the funnel plots, indicating that more studies were on the right. These observations indicate that the funnel plots are not symmetric because of the presence of publication bias, except for doxycycline for which it was possible to observe symmetrical funnel plots, with no need of additional imputed studies.

Besides visual examination of the funnel plots, Egger's regression test was also employed to analyse the potential impact of publication bias on the results of this meta-analysis. The results of this test (Supplementary Table S3 in the online version at DOI: 10.1016/j.jgar.2018.12.018) showed that for erythromycin, ciprofloxacin, gentamicin, tetracycline and streptomycin there is evidence to reject the null hypothesis ($P < 0.050$), indicating that there is asymmetry in the funnel plots. Consequently, apparent publication bias exists in the studies included in this meta-analysis.

Regarding the sensitivity analysis (results not shown), it was verified that in general the pooled effects of the prevalence of antimicrobial-resistant *Arcobacter* spp. did not change substantially if a single or a few studies were omitted, indicating that the results obtained are robust.

4. Discussion

This systematic review followed by meta-analysis assessed the prevalence of *Arcobacter* spp. resistant to various antibiotics, some of them used to treat severe infections caused by this bacterium. This analysis verified that penicillins and cephalosporins, which have been reported in a few studies as used to treat these infections [13], are among the classes of antibiotics with an overall higher resistance rate than macrolides, fluoroquinolones, aminoglycosides and tetracyclines, which are classes of antibiotics recommended by various authors for treating serious *Arcobacter* spp. infections [12]. Through the comparisons between the risk

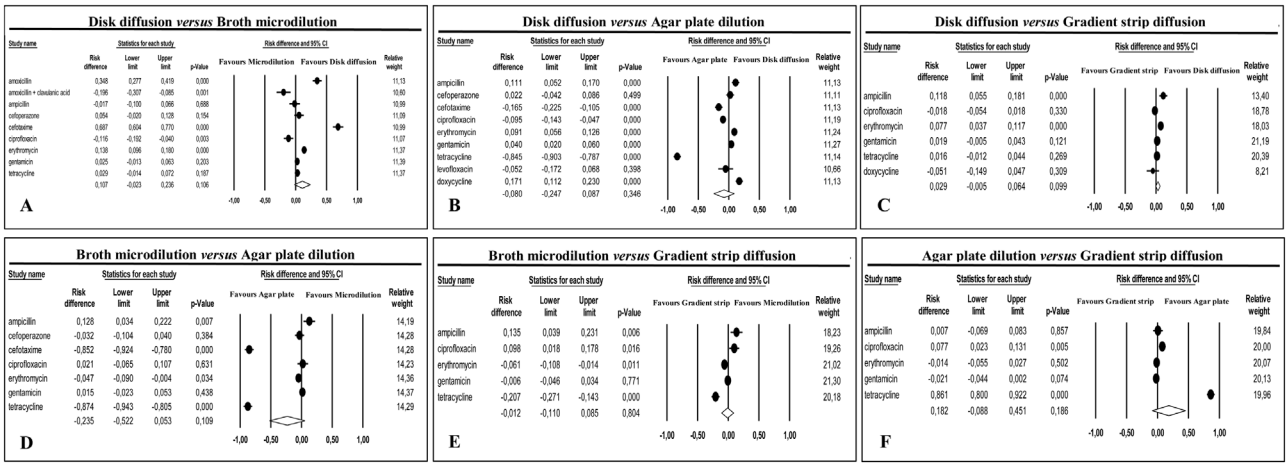

Fig. 5. Forest plots of comparisons between the risk difference of *Arcobacter* spp. isolates resistant to each antimicrobial according to the antimicrobial susceptibility testing method.

Table 5
Summary of random weighted meta-regression analysis with year of publication as independent variable and prevalence of *Arcobacter* isolates resistant to each antimicrobial (logit event rate) as outcome variable.

Antimicrobial agent	Intercept	Slope	*P*-value
Erythromycin	72.174	−0.036	<0.001
Ciprofloxacin	−160.584	0.079	<0.001
Gentamicin	−242.887	0.119	<0.001
Ampicillin	11.564	−0.005	>0.050
Tetracycline	−542.017	0.268	<0.001
Amoxicillin/clavulanic acid	29.577	−0.015	>0.050
Streptomycin	−294.506	0.146	>0.050
Enrofloxacin	30.725	−0.018	>0.050
Cefotaxime	144.922	−0.072	<0.001
Cefalotin	60.602	−0.029	>0.050
Cefoperazone	38.448	−0.018	>0.050
Azithromycin	413.663	−0.206	<0.001
Levofloxacin	−656.866	0.3248	>0.050
Doxycycline	−193.584	0.095	>0.050
Amoxicillin	−52.421	0.026	>0.050

difference of resistant strains to each antimicrobial, it was found that *A. butzleri* presented higher resistance rates for antibiotics belonging to the penicillin and cephalosporin classes than the other two species considered. The high resistance to penicillins may be associated with the presence of β-lactamases, supported by a decrease of the PE when amoxicillin was combined with clavulanic acid, a known β-lactamase inhibitor. Also, the presence of putative β-lactamases in *A. butzleri* has been described using whole-genome sequencing [29], which is further reinforced by the data found in the National Center for Biotechnology Information (NCBI) database. However, the functional role of these enzymes in penicillin and cephalosporin resistance still needs to be proven. The highest resistance observed for ampicillin in human isolates agrees with what was recently presented [30]. The use of cefoperazone in culture media frequently used for *Arcobacter* spp. isolation may potentially contribute to the level of resistance observed for this group of antibiotics. Nevertheless, among β-lactams, a low resistance rate to imipenem was observed in this meta-analysis, making carbapenems an option to treat *Arcobacter* infections as previously suggested [31]. Fluoroquinolones have been suggested as an alternative treatment for *A. butzleri* infections [15]; however the increased resistance observed for fluoroquinolones used in clinical settings over the years may pose a threat to this idea. The meta-regression analysis results points towards an increasing trend of resistance to ciprofloxacin and levofloxacin through time, despite the lack of statistical significance for levofloxacin. However, these results must be interpreted with caution given that the independent variable used for the meta-regression was the year of publication and not the sampling period. This behaviour may be associated with selective pressure caused by the widespread use of antibiotics, namely in animal husbandry. In *A. butzleri*, resistance to ciprofloxacin has been associated with a point mutation in DNA gyrase A, related to a threonine to isoleucine transition at position 85 [30,32–34]. This was the only mutation found in field isolates; however, an Asp89 → Tyr substitution was also associated with ciprofloxacin resistance in mutants generated in the laboratory [34]. Until now, no correlation has been established between the resistance to the other fluoroquinolones and a resistance mechanism.

Regarding the results obtained for macrolides, the species more resistant to erythromycin was *A. skirrowii.* In general, the resistance rate observed for *Arcobacter* spp. to erythromycin is closer to that described for *Campylobacter coli* than to *Campylobacter jejuni* [35]. The prevalence of resistance to azithromycin was higher than to erythromycin; in fact, azithromycin is known to induce a higher resistance than other macrolides as noted for *Helicobacter pylori* [36]. Acquisition of resistance to macrolides was described for several bacteria as being the result of an induction of point mutations in the peptidyl-encoding region in domain V of the 23S rRNA gene or in ribosomal proteins, hindering interaction of the macrolide with its target [37]. Other resistance mechanisms play a role, namely modification of cell permeability, efflux or inactivation of the drug, or even ribosomal methylation [37]. Behind the phenotypic resistance described for *Arcobacter* spp., no studies have proposed a mechanism of resistance to this class of antibiotics, knowledge of which could help to understand the differences observed among antibiotics of this class.

The low resistance rate found for gentamicin (2.8%) is in accordance with that reported for *C. jejuni* and *C. coli* isolated between 2007–2011 from retail meat in the USA and Europe [38,39]. An overall trend for a higher resistance rate to streptomycin than gentamicin was also observed, which is in accordance with what has been described for European isolates of *C. jejuni*/*coli* from broiler meat [39]. However, lower values of resistance to tetracycline were observed in this meta-analysis (5.9%) than those reported for *Campylobacter* food isolates in USA and for human and food isolates from European countries [38,39].

Regarding the source of isolation, there were no significant differences between the resistance rates to aminoglycosides and

tetracyclines. In general, the prevalence of tetracycline resistance was higher in Europe; however, no significant difference was observed for aminoglycosides. This means that tetracyclines and aminoglycosides may still be a choice for the treatment of severe infections by *Arcobacter* spp.

An overall significant difference in the prevalence of resistance to antibiotics was found when a comparison between the economical level of the countries was performed. The higher resistance rates found for developing countries may be associated with a less stringent control on antibiotic prescription and consumption in several sectors. However, the fact that only two countries (India and Nigeria) were lower-middle income according to the World Development Indicators database may skew the results.

The World Health Organization (WHO) has designated quinolones, third- and fourth-generation cephalosporins, and macrolides as groups of antibiotics clinically relevant to humans, pointing to the need to control their use in animals [40]. The observed trend in the decline of resistance prevalence to erythromycin, azithromycin and cefotaxime over the years may be related to the decreased use of these antibiotics in some European countries [41]. Indeed, the reduction of antibiotic use in farm animals was associated with a reduction in the prevalence of resistant bacteria in animals and humans [42].

In this analysis, a high prevalence of multidrug resistance was found, with an evidence of higher rates for humans than for food (all from animal origin) isolates. This difference may be linked to the number of isolates evaluated in each category ($n = 24$ for human isolates and $n = 587$ for food isolates), but also to the classes of antibiotics tested. Regarding environmental isolates, an overall lower prevalence of resistance and multidrug resistance was observed, which may be associated with the source of isolation. If water isolates were from faecally-contaminated water, a higher prevalence of antibiotic resistance would probably be observed. Indeed, Šilha et al. found that most multidrug-resistant strains were isolated from wastewater samples [43]. The levels of multidrug resistance in *Arcobacter* isolates are higher than those reported for *C. jejuni*/*coli* in Europe when considering strains from human and poultry origin [39], a trend that was previously observed by Son et al. [44].

The use of several types of methodologies for antimicrobial susceptibility testing may hamper the comparison between the results of different studies, which was also verified in the subgroup analysis when comparing the different methods. Another factor that strengthens this difficulty is the different conditions under which the assays were done. For example, assays were described as having different incubation conditions, such as different temperatures, atmospheres and periods. The lack of breakpoints established to classify the susceptibility of *Arcobacter* spp. and the different criteria applied for this evaluation in the included studies are also elements that can influence the resistance rates obtained.

The wide spread of antibiotic-resistant *Arcobacter* spp. through various environments may have a role in the dispersion of resistance. In fact, the association between the presence of resistance determinants among animals has been potentially linked with an increased antibiotic resistance in consumers [45].

The high resistance rate observed for *A. butzleri* also suggests that this species can act as a reservoir of genes contributing to antimicrobial resistance dissemination through the animal–human–environment interface, indirectly leading to the unsuccessful treatment of more severe infections [12]. This scenario of resistance transfer may occur in ecological niches where *Arcobacter* can be found, affecting other foodborne and waterborne pathogens.

Although this meta-analysis has a small number of studies included, it is the first work that systematised the resistance rates for *Arcobacter* spp. allowing to recognise some of the resistance trends associated with this emerging pathogen.

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Competing interests

None declared.

Ethical approval

Not required.

References

[1] Collado L, Figueras MJ. Taxonomy, epidemiology, and clinical relevance of the genus *Arcobacter*. Clin Microbiol Rev 2011;24:174–92.
[2] Diéguez AL, Balboa S, Magnesen T, Romalde JL. *Arcobacter lekithochrous* sp. nov., isolated from a molluscan hatchery. Int J Syst Evol Microbiol 2017;67:1327–32.
[3] Ferreira S, Oleastro M, Domingues F. Arcobacter spp. in food chain—from culture to omics. In: Singh OV, editor. Foodborne pathogens and antibiotic resistance. Hoboken, NJ: John Wiley & Sons, Inc; 2017. p. 73–117.
[4] Figueras MJ, Pérez-Cataluña A, Salas-Massó N, Levican A, Collado L. '*Arcobacter porcinus*' sp. nov., a novel *Arcobacter* species uncovered by *Arcobacter thereius*. New Microbes New Infect 2017;15:104–6.
[5] Park S, Jung YT, Kim S, Yoon JH. *Arcobacter acticola* sp. nov., isolated from seawater on the East Sea in South Korea. J Microbiol 2016;54:655–9.
[6] Tanaka R, Cleenwerck I, Mizutani Y, Iehata S, Bossier P, Vandamme P. *Arcobacter haliotis* sp. nov., isolated from abalone species *Haliotis gigantea*. Int J Syst Evol Microbiol 2017;67:3050–6.
[7] Pérez-Cataluña A, Salas-Massó N, Figueras MJ. *Arcobacter canalis* sp. nov., isolated from a water canal contaminated with urban sewage. Int J Syst Evol Microbiol 2018;68:1258–64.
[8] Collado L, Gutiérrez M, González M, Fernández H. Assessment of the prevalence and diversity of emergent campylobacteria in human stool samples using a combination of traditional and molecular methods. Diagn Microbiol Infect Dis 2013;75:434–6.
[9] Ferreira S, Júlio C, Queiroz JA, Domingues FC, Oleastro M. Molecular diagnosis of *Arcobacter* and *Campylobacter* in diarrhoeal samples among Portuguese patients. Diagn Microbiol Infect Dis 2014;78:220–5.
[10] Vandenberg O, Dediste A, Houf K, Ibekwem S, Souayah H, Cadranel S, et al. *Arcobacter* species in humans. Emerg Infect Dis 2004;10:1863–7.
[11] Ferreira S, Queiroz JA, Oleastro M, Domingues FC. Genotypic and phenotypic features of *Arcobacter butzleri* pathogenicity. Microb Pathog 2014;76:19–25.
[12] Ferreira S, Queiroz JA, Oleastro M, Domingues FC. Insights in the pathogenesis and resistance of *Arcobacter*: a review. Crit Rev Microbiol 2016;42:364–83.
[13] Figueras MJ, Levican A, Pujol I, Ballester F, Quilez MJR, Gomez-Bertomeu F. A severe case of persistent diarrhoea associated with *Arcobacter cryaerophilus* but attributed to *Campylobacter* sp. and a review of the clinical incidence of *Arcobacter* spp. New Microbes New Infect 2014;2:31–7.
[14] Alfredson DA, Korolik V. Antibiotic resistance and resistance mechanisms in *Campylobacter jejuni* and *Campylobacter coli*. FEMS Microbiol Lett 2007;277:123–32.
[15] Vandenberg O, Houf K, Douat N, Vlaes L, Retore P, Butzler J-P, et al. Antimicrobial susceptibility of clinical isolates of non-*jejuni*/*coli*campylobacters and arcobacters from Belgium. J Antimicrob Chemother 2006;57:908–13.
[16] Rahimi E. Prevalence and antimicrobial resistance of *Arcobacter* species isolated from poultry meat in Iran. Br Poult Sci 2014;55:174–80.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–70.
[18] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1–9.

[19] Borenstein M, Hedges L, Higgins J. Introduction to meta-analysis. Chichester, UK: John Wiley & Sons; 2009.
[20] Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[21] Light RJ, Pillemer DB. Summing up: the science of reviewing research. Cambridge, MA: Harvard University Press; 1984.
[22] Light RJ, Singer JD, Willett JB. The visual presentation and interpretation of meta-analyses. In: Cooper M, Hedges LV, editors. The handbook of research synthesis. New York, NY: Russell Sage Foundation; 1994. p. 439–53.
[23] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[24] Duval S, Tweedie R. A non parametric 'trim and fill' method of accounting for publication bias in meta-analysis. J Am Stat Assoc 2000;95:89–98.
[25] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[26] The World Bank. World Development Indicators. https://data.worldbank.org/products/wdi. [Accessed 15 December 2017].
[27] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. 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.
[28] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-sixth edition. CLSI document M100-S26. Wayne, PA: CLSI; 2016.
[29] Miller WG, Parker CT, Rubenfield M, Mendz GL, Wösten MMSM, Ussery DW, et al. The complete genome sequence and analysis of the epsilonproteobacterium *Arcobacter butzleri*. PLoS One 2007;2:e1358.
[30] Van den Abeele AM, Vogelaers D, Vanlaere E, Houf K. Antimicrobial susceptibility testing of *Arcobacter butzleri* and *Arcobacter cryaerophilus* strains isolated from Belgian patients. J Antimicrob Chemother 2016;71:1241–4.
[31] Fera MT, Maugeri TL, Giannone M, Gugliandolo C, La Camera E, Blandino G, et al. *In vitro* susceptibility of *Arcobacter butzleri* and *Arcobacter cryaerophilus* to different antimicrobial agents. Int J Antimicrob Agents 2003;21:488–91.
[32] Abdelbaqi K, Ménard A, Prouzet-Mauleon V, Bringaud F, Lehours P, Mégraud F. Nucleotide sequence of the *gyrA* gene of *Arcobacter* species and characterization of human ciprofloxacin-resistant clinical isolates. FEMS Immunol Med Microbiol 2007;49:337–45.
[33] González A, Bayas Morejón IF, Ferrús MA. Isolation, molecular identification and quinolone-susceptibility testing of *Arcobacter* spp. isolated from fresh vegetables in Spain. Food Microbiol 2017;65:279–83.
[34] Ferreira S, Correia DR, Oleastro M, Domingues FC. *Arcobacter butzleri* ciprofloxacin resistance: point mutations in DNA gyrase A and role on fitness cost. Microb Drug Resist 2018;24:915–22, doi:http://dx.doi.org/10.1089/mdr.2017.0295.
[35] Bolinger H, Kathariou S. The current state of macrolide resistance in *Campylobacter* spp.: trends and impacts of resistance mechanisms. Appl Environ Microbiol 2017;83: e00416-17.
[36] Miendje Deyi VY, Bontems P, Vanderpas J, De Koster E, Ntounda R, Van Den Borre C, et al. Multicenter survey of routine determinations of resistance of *Helicobacter pylori* to antimicrobials over the last 20 years (1990 to 2009) in Belgium. J Clin Microbiol 2011;49:2200–9.
[37] Fyfe C, Grossman TH, Kerstein K, Sutcliffe J. Resistance to macrolide antibiotics in public health pathogens. Cold Spring Harb Perspect Med 2016;6:1–38.
[38] US Food and Drug Administration (FDA). National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): 2012 executive report. FDA; 2013.
[39] European Food Safety Authority. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2015. EFSA J 2017, doi:http://dx.doi.org/10.2903/j.efsa.2017.4694.
[40] Collignon PC, Conly JM, Andremont A, McEwen SA, Aidara-Kane A. World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies to control antimicrobial resistance from food animal production. Clin Infect Dis 2016;63:1087–93.
[41] Garcia-Migura L, Hendriksen RS, Fraile L, Aarestrup FM. Antimicrobial resistance of zoonotic and commensal bacteria in Europe: the missing link between consumption and resistance in veterinary medicine. Vet Microbiol 2014;170:1–9.
[42] Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, et al. 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.
[43] Šilha D, Pejchalová M, Šilhová L. Susceptibility to 18 drugs and multidrug resistance of *Arcobacter* isolates from different sources within the Czech Republic. J Glob Antimicrob Resist 2017;9:74–7.
[44] Son I, Englen MD, Berrang ME, Fedorka-Cray PJ, Harrison MA. Antimicrobial resistance of *Arcobacter* and *Campylobacter* from broiler carcasses. Int J Antimicrob Agents 2007;29:451–5.
[45] Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. Clin Microbiol Rev 2011;24:718–33.