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Prevalence and antimicrobial resistance profiles of *Campylobacter* species in South Africa: A "One Health" approach using systematic review and meta-analysis

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Highlights

- Animals had highest pooled prevalence estimate (PPE) of *Campylobacter* infection.
- Majority of *Campylobacter* prevalence studies were conducted in animals.
- Highest antibiotic resistance PPE by *Campylobacter* isolates is against clindamycin.
- Combined multi-drug resistance PPE of *Campylobacter* isolates is 35.3%.

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Abstract

Objectives: This study investigated the prevalence and antibiotic resistance (AR) profiles of *Campylobacter* spp. isolated from animals, humans and the environment in South Africa based on available published data.

Methods: Original articles published from January 1, 1990, to January 1, 2021, were searched from PubMed, ScienceDirect, Google Scholar, Africa Index Medicus, Scopus, and African

Journal Online databases. Data were analysed with Comprehensive Meta-Analysis (version 3.0).

Results: After screening, articles on animals (n=25), human (n=7), environment (n=3), animals/environment (n=2), and n=1 study from both animals, human and environment, were included in this review. The pooled prevalence estimates (PPE) were 28.8%, 16.4% 28.4% in animals, humans and the environment respectively. The *C. jejuni* and *C. coli* species were commonly isolated from humans, animals, and the environment in South Africa. The AR profiles were screened from 2032 *Campylobacter* spp. with highest PPE of AR observed against clindamycin (76.9%) and clarithromycin (76.5%). *Campylobacter* isolates tested with the disk diffusion assay and minimum inhibitory concentration methods recorded overall AR prevalence of 35.3% and 37.1% respectively, whilst Multi-Drug Resistance PPE was 35.3%.

Conclusion: Regular surveillance of *Campylobacter* spp. prevalence and its AMR strains is recommended, as well as formulation of a “One Health" approach for better management and control of *Campylobacter* spp. infection in South Africa.

Keywords

Campylobacter species, antimicrobial resistance, One Health, Meta-analysis, South Africa

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Introduction

Campylobacter is a zoonotic pathogen that causes campylobacteriosis with *C. jejuni* and *C. coli* being the commonly isolated species (Karikari et al., 2017). They infect animals such as chickens, cattle, sheep, pigs, birds, reptiles, and crustaceans (Hlashwayo et al., 2021), and cats and dogs (Begum et al., 2015; Koziel et al., 2014; Thépault et al., 2020; Karama et al., 2019). Most of these animals are natural reservoirs for *Campylobacter* spp. (Paintsil et al., 2022), and offer a significant risk to humans, as the bacteria is shed in livestock waste and

water sources (Oporto et al., 2007; Gahamanyi et al., 2020). Since campylobacteriosis outbreaks are infrequent and triggered by cross-contamination, it is difficult to identify the origins of contamination (Facciolà et al., 2017; Lee et al., 2017). *Campylobacter jejuni* and *C. coli* have been associated with human disease (Sheppard and Maiden, 2015; Igwaran and Okoh, 2019).

Findings from a recently published systematic review and meta-analysis found *C. jejuni* was the most prevalent species in sub–Saharan Africa (Hlashwayo et al., 2021). These findings are in coherence with another systematic review conducted in West Africa in 2022 (Paintsil et al., 2022), whereby *C. jejuni* was the most recorded species in terms of prevalence compared to *C. coli* with 52% and 30% respectively. *Campylobacter jejuni* is the most frequently detected *Campylobacter* spp. in food and the most common species linked to human campylobacteriosis (Christidis et al., 2016).

Campylobacteriosis is best managed using antibiotics such as erythromycin, amoxicillin, azithromycin, clarithromycin, tetracycline, and ciprofloxacin (Gahamanyi et al., 2020 Szczepanska et al., 2017; Shobo et al., 2016; Ramatla et al., 2022). Antibiotic resistance (AR) by *Campylobacter* spp. associated with animal sources has been widely reported globally (Karikari et al., 2017) including sub-Saharan Africa (Paintsil et al., 2022; Gahamanyi et al., 2020). An exception to this has been observed in immune-deficient or immune-suppressed people, where campylobacteriosis does not require antimicrobial therapy, except in severe cases as this disease is normally a self-limiting (Thakur et al., 2010; Guévremontet al., 2006; Gahamanyi et al., 2020).

Understanding the epidemiology of *Campylobacter* in animals, humans, and environment in South Africa is critical in the control of infections associated with the pathogen (Nannan et al., 2012; Thobela, 2017). An estimated 3.552 million children under the age of five years die in Africa every year, with diarrhoea (11%) being the leading cause of mortality (Mason et al.,

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2013). Few systematic review studies have focused on *Campylobacter* spp. prevalence and AR in Africa and those that have been conducted have focused on *Campylobacter* in human and food animals including their products (Thomas et al., 2020; Paintsil et al., 2022; Hlashwayo et al., 2021; Hlashwayo et al., 2020; Diriba et al., 2021). However, there is no comprehensive data available to estimate the prevalence of *Campylobacter* spp. in South Africa. The available study reports that are either limited to a single province (Sithole et al., 2021; Pillay et al., 2020) or to a specific *Campylobacter* species (Mileng et al. 2021). The main aim of this study was to perform a systematic review and meta-analysis in order to provide a comprehensive prevalence of *Campylobacter* spp. in South Africa, AR profiles in animals, humans, and environment based on available published data in South Africa.

Materials and methods

Study design

The systematic review protocol was developed and registered with the international prospective register of systematic reviews (PROSPERO CRD42022316070). The study was conducted using the recommended methodology for systematic reviews as outlined by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2021) which have been confirmed on a checklist (Supplementary Table S1). Journal articles published between 1990 and 2021 that reported on *Campylobacter* in animals, humans, and the environment (vegetables, water, and soil).

Search strategy

Studies were searched in five electronic databases, PubMed (https://pubmed.ncbi.nlm.nih.gov/, from 11/11/2021 to 12/11/2021); ScienceDirect (https://www.sciencedirect.com/ from 11/11/2021 to 12/11/2021); Google Scholar

(https://scholar.google.com/ from 25/11/2021 to 06/12/2021); Africa Index Medicus (https://indexmedicus.afro.who.int/, 12/01/2022), Scopus (https://www.scopus.com/, 12/01/2022 to 13/01/2022), and African Journal Online (https://www.ajol.info/index.php/ajol/, 12/01/2022). The following keywords were used to search for articles: *Campylobacter* species OR *Campylobacter jejuni* OR *Campylobacter coli* OR antibiotic OR antimicrobial resistance OR drug resistance OR bacterial resistance OR human OR water OR soil OR vegetable OR animal AND South Africa. Subsequently, the titles, abstracts and full article identified and downloaded. The last search was run on 29th of January 2022.

Inclusion criteria

Studies included in the meta-analysis were based on the following: (1) journal articles published in English language, (2) studies conducted in South Africa, (3) studies that included author names, publication year, location, total number of isolates, total samples collected, and conditions, (4) studies that reported the proportion of animals, humans and water collected from the environment harbouring *Campylobacter* spp. as well as their AR profiles within South Africa, (5) the availability of the full texts, (6) as well as studies conducted within the period spanning the year 1990 to the year 2021. The studies that were eligible had the following characteristics: articles focusing on the prevalence of *Campylobacter* spp. isolated from various animals including cattle, chickens, goats, sheep, ostriches, dogs, turkey, seabirds and pigs, as well as from the environment such as water, slurry and litter in South Africa.

Exclusion criteria

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Studies were excluded if they were: (1) not published in English, (2) reviews and experimental studies, (3) book chapters were also excluded, (4) studies with no clearly defined number of samples screened, (5) no number of isolates, (6) studies not conducted in South Africa, (7) articles not published between 1990 and 2021.

Data quality control measures

Two authors independently used the Joanna Briggs Institute (JBI) Critical Appraisal Tools Checklist 2017 review guideline (Buccheri and Sharifi, 2017) for prevalence studies to verify the methodological soundness of the research articles chosen for quantitative synthesis. The inclusion of studies was based on the assessment criteria score of 5 or above (Supplementary Table S2).

Data extraction and data collection

Full versions of potentially relevant articles were obtained to determine eligibility. The data from each paper was compiled independently and placed into a spreadsheet, including author names, publication year, location, total number of isolates, and total samples collected was entered into a spreadsheet (Microsoft Excel® 2013). Text, tables, and figures were used to extract the data. The meta-analysis only included journal articles that dealt with antimicrobial resistance of *Campylobacter* spp. in South Africa.

Meta-Analysis

Only journal papers specific to *Campylobacter* spp. were included in the meta-analysis. Comprehensive Meta-Analysis (CMA) Version 3.0 program (https://www.meta-analysis.com/) was used to conduct the meta-analysis. To estimate the pooled prevalence for subgroup analysis, the random-effects model was used and the corresponding 95%

confidence interval (CI) was calculated. The pooled prevalence estimates (PPE) is arrived at by using the inverse of the sampling variance and a constant variable across the population effects to weigh each study. Higgin's I^2 (inverse variance) and Cochran's Q method were used to assess Cochran's heterogeneity (Q) within studies as well as percentage variation in prevalence. Values close to 0% indicate no heterogeneity, low, moderate, or high heterogeneity were defined as I^2 values of ≤25%, 50%, or ≥75%, respectively (Monyama et al., 2022). Heterogeneity with a *p*-value less than 0.05 ($P< 0.05$) was considered statistically significant. Subgroup analysis was carried out on the study's outcome based on province, diagnostic methods, study year, and *Campylobacter* species. Subgroup analyses with less than 3 studies were not included in meta-analysis Lastly, if the number of positive *Campylobacter* spp. reported exceeded the sample size, a prevalence rate of 100% was recorded.

Publication bias

An inverted funnel plot was used to ascertain publication bias using the visual eye test, as well as Egger's and Begg's bias indicator tests (Venâncio et al., 2022; Light et al., 1994). The influence of publishing and selection bias was tested using the Begg-Mazumdar bias indicator test (Egger et al., 1997). A funnel plot often displays effect sizes plotted against their standard errors or precisions (the inverse of standard errors). This allowed us to generate the best estimate of the unbiased pooled effect size by producing a funnel plot that included both the observed studies and the imputed studies required to determine the lack of bias.

Results

Search results

The search process yielded a total of 4 473 studies. A total of 2 552 studies were recorded after duplicates were removed and 2489 after study titles and abstracts were reviewed. Sixty-

three full text articles were assessed for eligibility resulting in further exclusion of 25 studies for reasons such as repeated data, not investigating *Campylobacter*, and unclear results presentation (Figure 1). Meta-analysis was based on a total of 38 articles which reported the prevalence of *Campylobacter* spp., while AR was reported in 17 of the 38 studies (Figure 1). The quality assessment score from the Joanna Briggs Institute (JBI) critical appraisal ranges from 1 to 9. The lowest score was found only on 55.6% (5/9) studies (Supplementary Table S2).

Characteristics of eligible studies

The number of samples per study ranged from 10 to 2400, and all studies were published between 1990 and 2021. Limpopo (*n* = 7) was observed to have the highest number of studies followed by KwaZulu-Natal (*n* = 6), North West (*n* = 5), Gauteng (*n* = 2), Eastern Cape (*n* = 4), and Western Cape (*n* = 2) being the least (Figure 2). Furthermore, one study was conducted in both Eastern Cape and KwaZulu-Natal provinces and another one in both Western Cape and Gauteng provinces. Ten studies were conducted across all the provinces. The prevalence of *Campylobacter* spp. ranged from 23.6% to 41.8% across the country. *Campylobacter jejuni* was reported in twenty-seven (*n* = 27) studies with 1694/9957 (17%) isolates, while *C. coli* was identified in twenty-four (*n* = 24) studies with 817/7297 (11%) isolates. The other *Campylobacter* spp. were detected from 17 studies with 938/8044 (12%) isolates. Disk diffusion assay and minimal inhibitory concentration were the most commonly used methods for evaluating antibiotic-resistant *Campylobacter* species. *Campylobacter* spp. were isolates from water, human and animal faecal samples, sheath washes and animal products including milk and meat from chicken, turkey, beef, and pork.

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Pooling and heterogeneity of overall prevalence of *Campylobacter* species. in animals, human and the environment

Pooled prevalence estimates (PPE) of *Campylobacter* spp. in animals, human, and the environment as well as summary of the subgroup analysis are shown in Table 2. A total of 137666 samples were reportedly screened, and only 10809 were confirmed as *Campylobacter* spp. Of 10809 isolates, only 2609 *Campylobacter* spp. were identified in animals from 25 studies, with a PPE of 28.8% (95% CI: 19.1 – 40.9) (Figure 3). Seven studies were included in the meta-analysis for human isolates, with a PPE of 16.4% (95% CI: 11.8 – 16.4) (Figure 3). The PPE for isolates from the environment was 28.4% (95% CI: 11.9– 53.9) from three studies (Figure 3).

Prevalence by diagnostic methods

Six diagnostic techniques were used to identify *Campylobacter* spp. (Figure 4). The highest PPE was observed on studies using the traditional culture and isolation technique with 45.6% (95% CI: 13.9 – 81.3) from five studies, followed by conventional PCR with 32.1% (95% CI: 21.0 – 45.6) from twenty-four studies, and lastly by qPCR with 15.6% (95% CI: 8.9 – 26.1) from four studies (Table 2). Due to low number of eligible studies that utilized the API and *Campylobacter* kit, the data was not computed.

Prevalence by study provinces

The highest prevalence of *Campylobacter* spp. was reported in the Eastern Cape province (97.2%; 95% CI: 67.7 – 99.8, 4 studies), followed by KwaZulu-Natal provinces (72.9%; 95% CI: 62.6 – 81.2, 6 studies), Limpopo (27.1%; 95% CI: 18.9 – 37.2, 6 studies), North West with (15.1%; 95% CI: 3.6 – 45.5, 5 studies), and all provinces (11.3%; 95% CI: 7.5 – 16.6, 6 studies) (Table 2).

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Prevalence by years of study

Studies conducted between 2010 and 2021 yielded a high PPE of 38.6% (95% CI: 27.2 – 51.4), from 29 studies with 3583 isolates, followed by eight studies conducted during 2000 – 2010 with a pooled prevalence estimate of 20.0% (95% CI: 13.4− 29.0) from 453 isolates (Table 2). There was only one study published between 1990 to 2000 (Lastovica, 1996).

Prevalence by *Campylobacter* species

Campylobacter spp. was screened for 11057 isolates, of which 1694 were *C. jejuni*, 817 *C. coli* and 938 were *Campylobacter* species. The overall PPE for *C. jejuni* was 61.4% based on twenty-seven studies (95% CI: 50.1 – 71.5). The *C. coli* had a PPE of 24.3% (95% CI: 18.6 – 31.1) based on twenty-four studies (Table 2). While other *Campylobacter* spp. had 54.1% (95% CI: 35.8 – 71.4) based on twenty-eight articles. For uncharacterized *Campylobacter* spp., a PPE of 54.1% was documented.

Prevalence of antibiotic resistance in *Campylobacter* species

Out of 20 studies subjected to meta-analysis for antibiotic resistance, only 14 used DDA with a PPE of 40.8% (95% CI: 22.3 – 62.3). Minimum inhibitory concentration (MIC) was employed in 6 studies with a PPE of 37.1% (95% CI: 17.4 – 42.4). The heterogeneity estimates of the different AR profile of *Campylobacter* spp. isolated from animals, human and the environment is shown in Table 2.

Prevalence based on antibiotic resistance profile

The *Campylobacter* spp. antibiotic resistance (AR) profiles were screened from 2032 *Campylobacter* spp. obtained from 17 studies and the results are summarized in Table 3. A

total of ten (n = 10) studies classified as multidrug resistance (MDR), which is defined as resistance to more than two drugs with a PPE of 35.3%. The PPE of clindamycin was 76.9%, followed by clarithromycin 76.5%, doxycycline 67.1%, ampicillin 60.4%, tetracycline 56.3%, erythromycin 49.6%, ciprofloxacin 38.5%, nalidixic acid 35.8%, chloramphenicol 33.3%, imipenem 30.0%, and gentamicin 27.7% (Table 3).

Other antibiotic resistance patterns included the following: penicillin 2 (12.5%), levofloxacin 2 (12.5%), florfenicol 2 (12.5%), vancomycin 2 (12.5%), metronidazole 1 (6.3%), ceftiofur 1 (6.3%), fosfomycin 1 (6.3%), enrofloxacin 1 (6.3%), tylosin 1 (6.3%), lincomycin 1 (6.3%), methicillin 1 (6.3%), ceftriaxone 1 (6.3%), azithromycin 1 (6.3%), sulfamethoxazole-trimethoprim 1 (6.3%), amoxicillin/clavulanic acid 1 (6.3%) and norfloxacin 1 (6.3%).

Publication bias

The Begg and Mazumdar rank correlation test demonstrated no significant publishing bias for practically all parameters except for one antibiotic (Clindamycin), where both asymmetry of the funnel plots and *P*-value 0.043 indicated considerable bias (Figure 5).

Discussion

This systematic review and meta-analysis produced an overall PPE of 32.0% for *Campylobacter* spp. from 38 analysed studies in South Africa. This finding is consistent with other systematic reviews that reported that there are few *Campylobacter* research studies in Africa (Thomas et al., 2020; Paintsil et al., 2022; Hlashwayo et al., 2021; Hlashwayo et al., 2020). The results obtained from this study revealed the PPE of 28.8%, 16.4% and 28.4% of *Campylobacter* spp. in animals, humans, and the environment respectively. These findings highlight the primary public health risk connected with the presence of *Campylobacter* spp. in the animal food supply chain, as well as the environment, which may eventually harm

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humans. The estimated pooled prevalence differed between the nine provinces that reported *Campylobacter* species in human, animal, and the environment across South Africa.

In this study, we observed a significant increase of the studies on *Campylobacter* spp. conducted from 1990 to 2021. The increased number of funds for research might be the possible reasons for this change. Furthermore, this could be due to new and improved detection methods becoming available in recent years (Paintsil et al., 2022).

Studies from various provinces were included in this systematic review and meta-analysis and most of these studies (76.3%) were carried out between 2010 and 2021, followed by period of the years 2000 to 2010 with 21%, and lastly 1990 to 2000 with 2.6% of the studies that screened a total of 1137852 samples. The Mpumalanga, Northern Cape, and the Free State provinces were not included in the data sets due to the absence of published data on the prevalence of *Campylobacter* spp. These could be due to lack of resources for research studies, a lack of funding, or the fact that campylobacteriosis is a neglected disease in those provinces as they are resource-poor areas.

The *C. jejuni* and *C. coli* PPE from this study is 61.4% % and 24.3% respectively. This is comparatively higher to similarly reported PPE from reviews conducted in sub-Saharan Africa with 8.3% and 9.9% on gastrointestinal pathogens and humans respectively (Fletcher et al., 2011; Hlashwayo et al., 2021). The disparity could be due to differences in *Campylobacter* isolates, the study population's makeup, or the microbiological diagnostic methods employed.

The most sensitive diagnostic techniques are the molecular-based methods, and this meta-analysis used prevalence data from studies that also used these methods to detect *Campylobacter* spp. Most of the studies (32.1%) in this review used PCR to confirm *Campylobacter* spp. in animals, humans, and the environment on 10442 samples. A

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systematic review on *Campylobacter* spp. in West Africa reported closely similar results (34%) that are consistent with current data (Paintsil et al., 2022). However, our *Campylobacter* spp. PPE results are higher than those reported from systematic review conducted in Africa as continent (Hlashwayo et al., 2021) and the country Ethiopia (Diriba et al., 2021), with prevalence of 10% and 9.9% respectively. Since *Campylobacter* spp. can become unviable during transport and processing, the culture-based method can have some limitations (Hlashwayo et al., 2021). Environmental stress during sample transportation and processing can make some *Campylobacter* spp. viable but not culturable on media (Lv et al., 2020; Paintsil et al., 2022). Hence, some studies make use of culture-based method together with molecular techniques, such as PCR, due to its high sensitivity (Ramatla et al., 2021; Monyama et al., 2022).

Antimicrobial-resistant (AR) bacteria are a global issue that affects every country worldwide. The AR is a source of concern since it increases the likelihood of treatment failure (Kebede et al., 2017). Development of antimicrobial resistance may be due to misuse in both human disease treatment and in animal husbandry (Kashoma et al., 2015; Hlashwayo et al., 2020). In certain instances, farmers disregard the withdrawal period and recommended dosages, and this leads to antibiotic resistance (Olabode et al., 2017). Additionally, pathogens with resistance can be directly transferred to humans from animals and animal products (Noreen et al., 2020).

We observed a significant increase in *Campylobacter* spp. AR prevalence (29.6% to 63.1%) from 1990 to 2021. Antimicrobials are widely used in animal farming for growth promotion and as prophylaxis, which could explain the rising trend (Mengistu et al., 2020; Paintsil et al., 2022). This could also be due to new and improved detection methods (Paintsil et al., 2022), awareness of campylobacteriosis and the availability of resources to conduct research.

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The meta-analyses showed that the PPE of AR by *Campylobacter* species was higher against clindamycin (76.8%). Resistance against clindamycin is of public concern because it has been reported to possess good *in vitro* activity against *C. jejuni* and is used to treat *Campylobacter* spp. infections in humans (Varela et al., 2007). The AR against clarithromycin had second highest PPE, however, it is not commonly used to treat *Campylobacter* infections because its maximum inhibitory concentration (MIC_{90}s) is 2-fold higher than of the erythromycin (Gibreel, and Taylor, 2006). Macrolides/lincosamides (clindamycin and erythromycin) are infrequently used to treat respiratory disease and mastitis in dairy cattle (Englen et al., 2007).

An aminoglycoside like gentamicin can also be used to treat serious systemic infections (Skirrow, and Blaser, 2000; Gibreel, and Taylor, 2006). The AR by *Campylobacter* spp. PPE against gentamicin was low (27.7%) in this study. This is lower than what was observed in previous studies conducted in Ghana, Japan, Brazil; 47%, 33%, 30% respectively (Karikari et al., 2017; Koga et al., 2017; de Moura et al., 2013), however, is higher than the values reported in Malaysia (4%), and Egypt (0%) (Tang et al., 2016; Abd El-Baky et al., 2014). The differences could also be explained by the countries differing drug administration policies. For treating *Campylobacter* gastroenteritis, erythromycin is the preferred antibiotic, but ciprofloxacin and tetracycline are alternative drugs (Gibreel, and Taylor, 2006; Hlashwayo et al., 2021). Our review shows that AR PPE against erythromycin is 49.6% among the antibiotics tested. The overuse of erythromycin due to its low risk of side effects could explain the observed high resistance in humans (Paintsil et al., 2022). It is possible that ciprofloxacin-resistant isolates originated in humans, where this antibiotic is routinely used (Kashoma et al., 2015). In this study, the proportion of the public health implication of multidrug resistance (MDR) isolates were observed from ten studies.

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Food safety, zoonotic disease control, laboratory services, neglected tropical diseases, environmental health, and antimicrobial resistance are among the areas of work where a "One Health" approach is particularly relevant, according to the World Health Organization (WHO) (Ramatla et al., 2022). Campylobacteriosis is most often caused by the consumption of contaminated animals and food products of animal origin such as cattle, pigs, ostriches, poultry, and sheep (Chlebicz and Śliżewska, 2018; Del Collo et al., 2017), vegetables are also a frequent vector of transmission. It can also be acquired through direct contact with infected pets, including cats and dogs at home environment (Shane, 2000). Shellfish have also been shown to contain *Campylobacter* bacteria according to the World Health Organization (WHO) (https://www.who.int/news-room/fact-sheets/detail/campylobacter). This review reported the presence of *Campylobacter* spp. in both human, animals and as well as environment samples suggesting that the pathogen may be circulating indefinitely.

Limitations

There are few limitations to our systematic review and meta-analysis: (a) The search strategy was limited to articles published in English meaning that there may have been articles published in other languages that were overlooked. (b) Because the number of studies from some provinces was limited, the findings may not be the true representative of the rest of the country. (c) In comparison to other provinces, some had more research reports than other. d) There were few studies available on environmental samples, limiting comparisons of the prevalence and resistance profile. (e) Due to the inconsistent data reported within each study, it was not possible to compare resistance patterns by species.

5. Conclusions

The results obtained in this study revealed that the *C. jejuni* and *C. coli* are commonly isolated from humans, animals, and environment in South Africa. In some provinces, such as

Free State, Mpumalanga and Northern Cape, there are significant gaps in surveillance and a lack of published studies on the prevalence of *Campylobacter* species. These findings revealed a significant incidence of *Campylobacter* spp. in animals, as opposed to humans and the environment. This is an indication of the primary public health threat posed by the presence of *Campylobacter* spp. via animal production chain, which can later impact the human population. To the best of our knowledge, this is the first comprehensive study assessing AR of *Campylobacter* spp. among humans, animals, and the environment in South Africa. For the prevention and control of *Campylobacter* spp. and its AR in South Africa, regular surveillance of AR strains and early detection of these isolates using phenotypic and genotypic laboratory approaches is recommended. Furthermore, the human and animal health as well as environmental sectors need to formulate singular and deliberate "One Health" approach for management and control of *Campylobacter* spp. in South Africa.

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Disclosures

The authors have no conflict of interests.

Ethical approval

Approval was not required.

Authors' contributions

TR, MP, TEO, KEL, and OT conceived and designed the study. TR performed the literature review and extraction of data. TR, MCM and MT analysed and interpreted the data, created figures and tables, and drafted the manuscript. OT, KEL and CB offered mentorship and guidance on antimicrobial resistance. RN, and MBNM offered veterinary expertise. All authors read, commented, and approved the final manuscript.

Declaration of interests

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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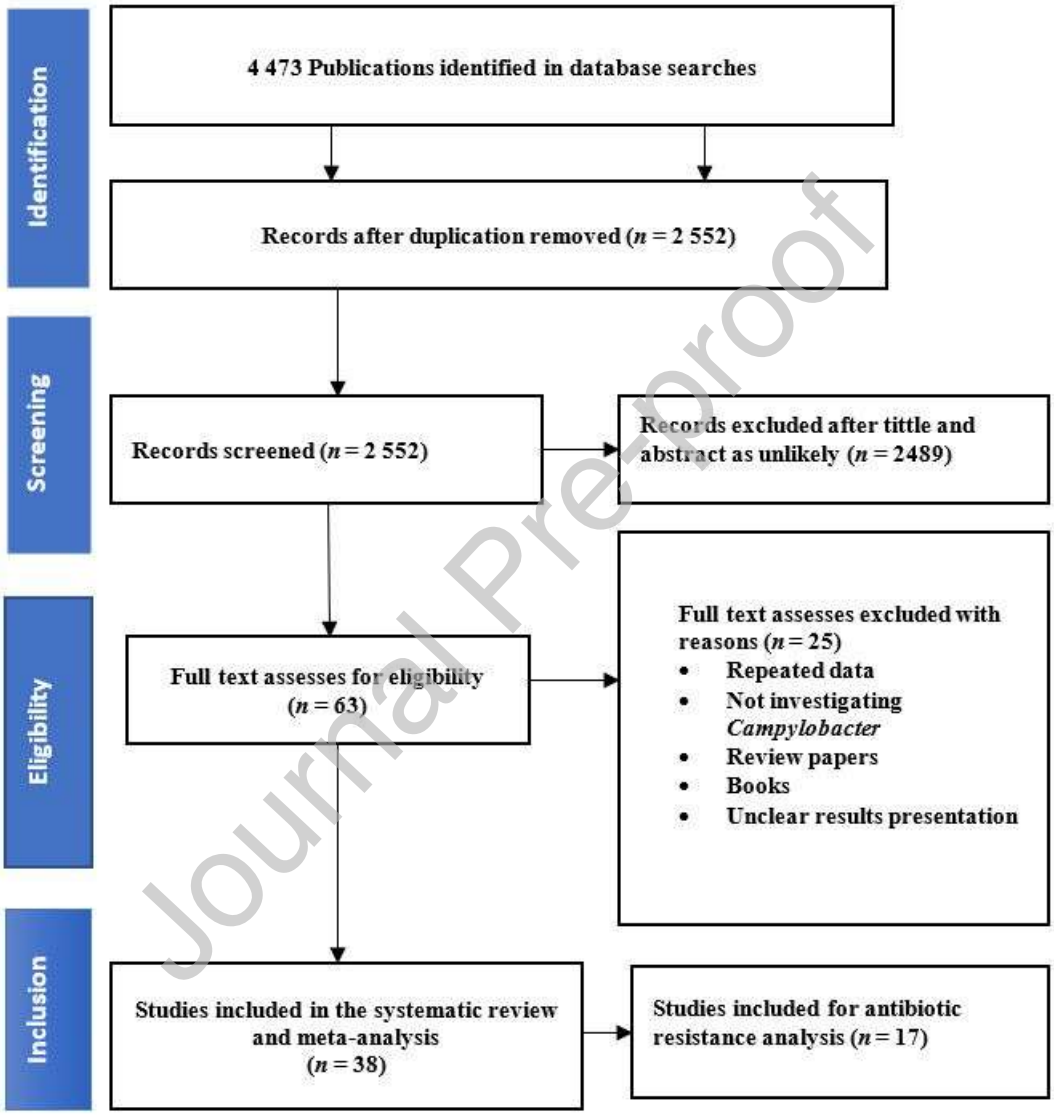

Figure 1. PRISMA flowchart for systematic review and meta-analysis of *Campylobacter* species in South Africa from 1990 to 2021.

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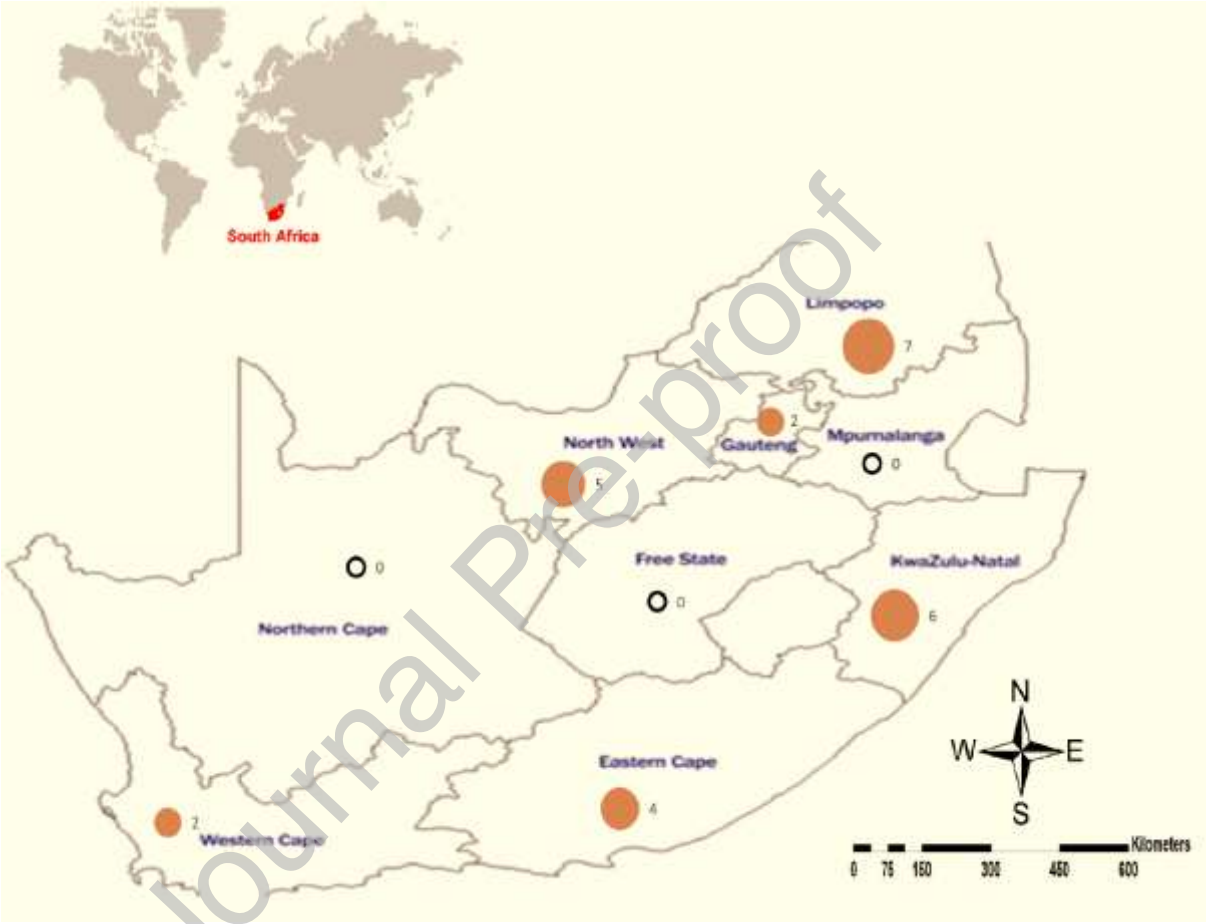

Figure 2. Map showing the number of published studies on *Campylobacter* spp. per province. Black circle shows that there were no studies conducted.

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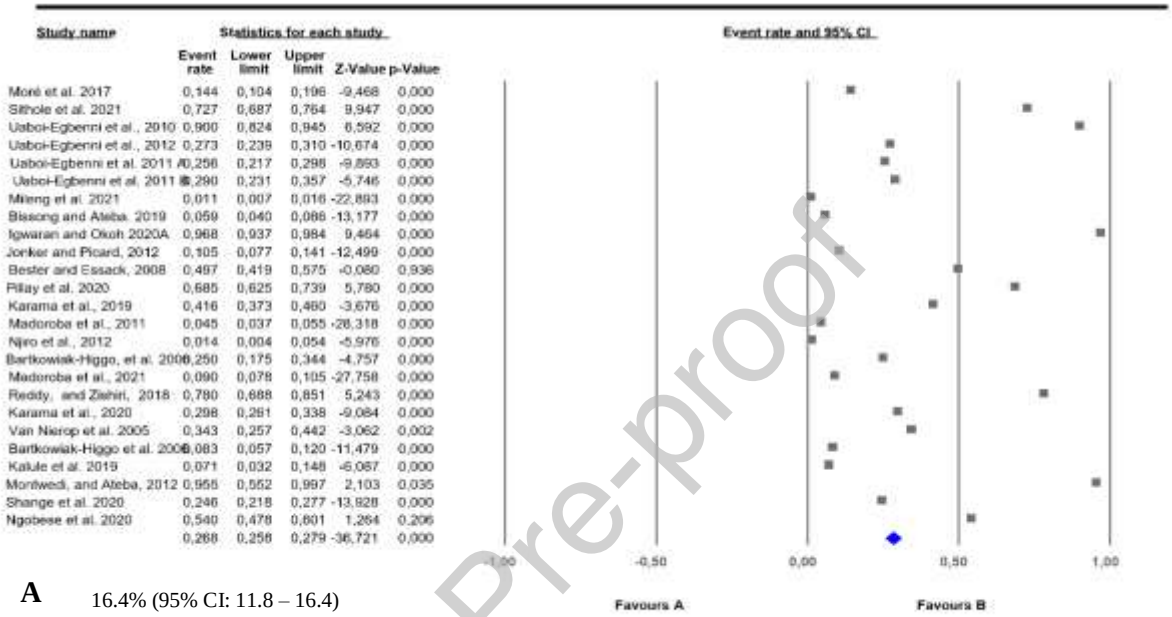
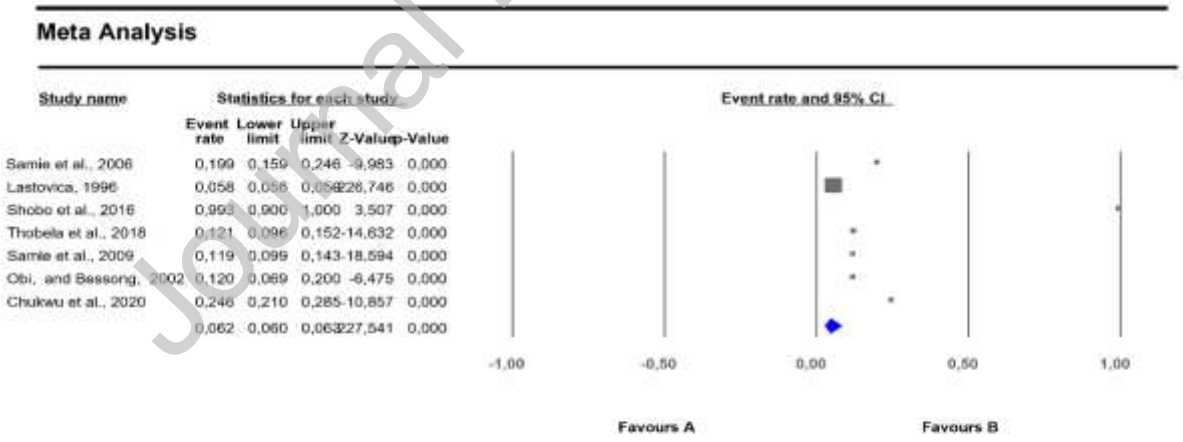


A 16.4% (95% CI: 11.8 – 16.4)



B 28.8% (95% CI: 19.1 – 40.9)

Analysis

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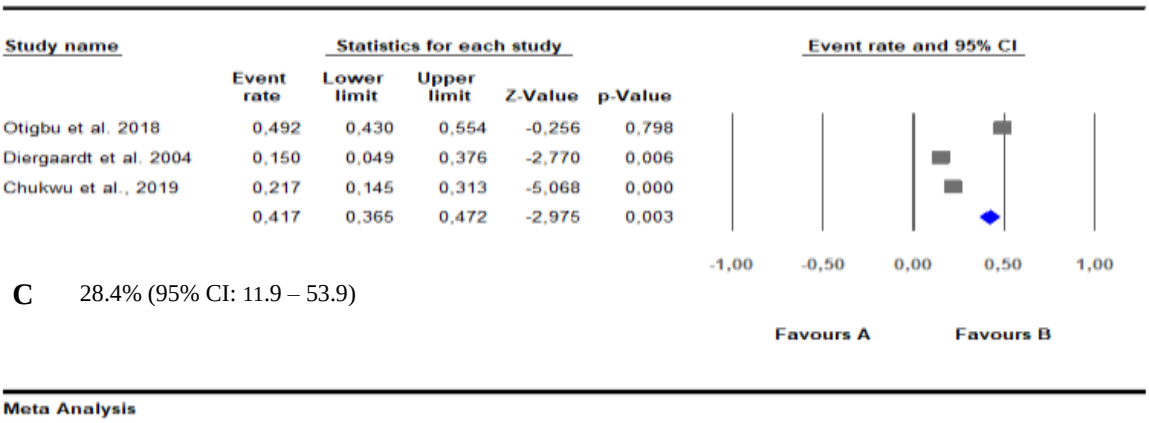

Figure 3. Forest plot showing the pooled prevalence of *Campylobacter* spp. in A) humans, B) animals and C) the environment from South Africa. The squares show the individual point estimate. The diamond at the base indicates the pooled estimates from the total studies. Favour A = positive effect while B= negative effect.

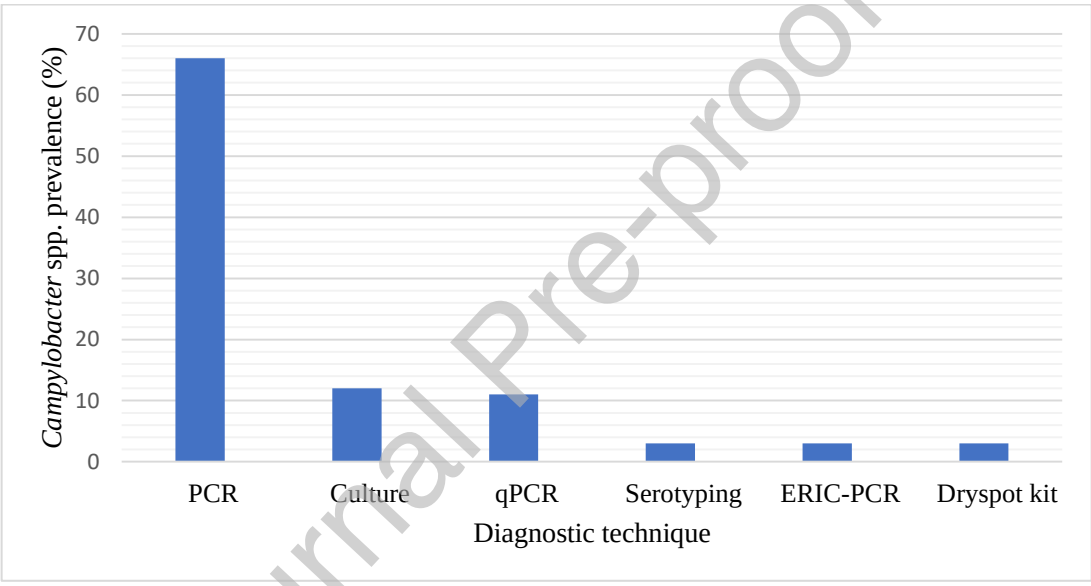

Figure 4. The pooled prevalence of *Campylobacter* spp. using different diagnostic techniques.

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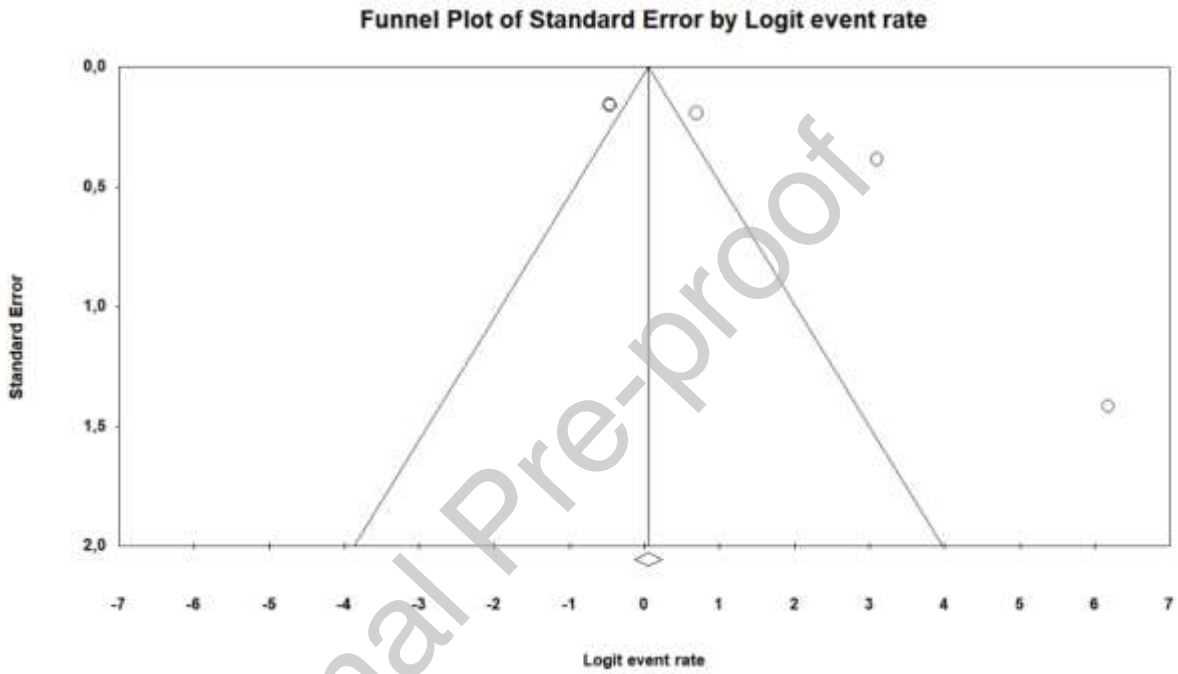

Figure 5: Funnel plot with 95% confidence limits of the pooled prevalence of the studies conducted on clindamycin.

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Table 1. Overview of *Campylobacter* species studies in animals, humans and the environment published from 1990 to 2021 in South Africa.

ID	Study (Citation)	Province	Diagnostic Method	Sample size	Isolates	Type of samples	Sampled host/site
1	Moré et al., 2017	Western Cape	PCR	229	33	Swabs	Seabirds

2	Sithole et al., 2021**	KwaZulu-Natal	PCR	520	378	Faecal, litter, and slurry	Pigs
3	Uaboi-Egbenni et al., 2010**	Limpopo	PCR	100	90	Faecal	Sheep
4	Uaboi-Egbenni et al., 2012*	Limpopo	Dryspot *Campylobacter* test kit	600	164	Faecal	Chickens and cattle
5	Uaboi-Egbenni et al., 2011 A	Limpopo	PCR	450	115	Faecal	Pigs
6	Uaboi-Egbenni et al., 2011 B**	Limpopo	PCR	200	58	Faecal	Goats
7	Mileng et al., 2021**	South Africa	PCR	2400	26	Faecal	Chicken
8	Bissong and Ateba, 2019	South Africa	PCR	408	24	Cloacal	Chicken
9	Igwaran and Okoh, 2020A**	South Africa	PCR	248	240	Raw meat	Chicken, turkey, beef, and pork
10	Jonker and Picard, 2012**	Western Cape and Gauteng	Culture	362	38	Colons	Chicken and pigs
11	Bester and Essack, 2008*	KwaZulu-Natal	Culture	155	77	Meat	Chicken
12	Bester and Essack, 2012	KwaZulu-Natal	Culture and Biochemical	363	293	Caecal	Chicken
13	Pillay et al., 2020**	KwaZulu-Natal	PCR	257	176	Litter, faecal and water	Chickens
14	Karama et al., 2019	Gauteng	PCR	481	200	Faecal swab	Dogs
15	Madoroba et al., 2011	South Africa	PCR	1999	90	Sheath washes and sheath scrapings	Cattle
16	Njiro et al., 2012	Gauteng	PCR	143	2	Sheath wash	Cattle
17	Bartkowiak-Higgo et al., 2006	South Africa	PCR	100	25	Liver, and intestine	Chicken
18	Madoroba et al., 2021	South Africa	qPCR	1758	159	Meat and meat products	Bovine, ovine, caprine, poultry, and game meat
19	Reddy and Zishiri, 2017	KwaZulu-Natal	PCR	100	78	Faecal	Chicken
20	Igwaran and Okoh, 2020B	Eastern Cape	ERIC-PCR	376	376	Milk, water, and meat	Cattle and water
21	Igwaran and Okoh, 2020C**	Eastern Cape	PCR	128	128	Water and milk	Cattle and water
2	Karama et	Gauteng	PCR	537	16	Faecal swab	Cattle and calves

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2	al., 2020**				0		
23	Van Nierop et al., 2005	Gauteng	PCR	99	34	Carcasses	Chicken
24	Karama et al., 2019	South Africa	PCR	481	200	Faecal	Dogs
25	Kalule et al., 2019	Western Cape	PCR	85	6	Meat	Chicken, beef, and pork
26	Montwedi and Ateba, 2012	North West	Culture and API	10	10	Meat	Chicken
27	Shange et al., 2020	South Africa	PCR	836	206	Cloacal swap	Ostriches
28	Otigbu et al., 2018**	Eastern Cape	PCR	244	120	Water	Water
29	Diergaardt et al., 2004	South Africa	PCR	20	3	Water	Water
30	Ngobese et al., 2020	Eastern Cape and KwaZulu-Natal	PCR	250	135	Faecal	Cattle, chickens, goats, sheep, and pigs
31	Samie et al., 2007A	Limpopo	PCR	322	64	Stool	Human
32	Lastovica, 1996	South Africa	Biotyping and Serotyping	121195	6999	Blood	Human
33	Shobo et al., 2016*	KwaZulu-Natal	PCR	72	72	Stool	Human
34	Thobela et al., 2018	South Africa	qPCR	512	62	Stool	Human
35	Obi and Bessong, 2002*	Limpopo	Culture and biochemical	100	12	Stool	Human
36	Chukwu et al., 2020*	North West	qPCR	505	124	Stool	Human
37	Samie et al., 2007B*	Limpopo	PCR	565	115	Stool	Human
38	Chukwu et al., 2019*	North West	qPCR	92	20	Water	Water

PCR = polymerase chain reaction, qPCR= real-time polymerase chain reaction, ERIC-PCR= Enterobacterial repetitive intergenic consensus- polymerase chain reaction, API= Application Programming Interface.

*= Antibiotic resistance (AR)

** = Multidrug resistance (MDR)

Table 2. The proportion of *Campylobacter* species isolated from humans, animals, and the environment, as well as the screening methods used with sample locations.

Risk factors	Number of studies	Pooled estimates			Measure of heterogeneity			Publication bias
		Sample size	Number of positive	I^2 % (95%CI)	Q Value	I^2	*Q-P*	Begg and Mazumdar rank *P*-value
Overall study								
Human	7	124094	7546	16.4% (11.8 – 16.4)	82.518	91.517	0.0001	0.45077
Environment	3	356	143	28.4 (53.9 – 11.9)	24.570	91.860	0.0001	0.13541
Animal	25	12627	2609	28.8 (19.1 – 40.9)	2237.834	98.928	0.0001	0.34567
Animal/ environment	2	504	504	–	–	–	–	–
Animal/human environment	1	85	6	–	–	–	–	–
Study year								
1990 – 2000	1	121195	6999	–	–	–	–	–
2000 – 2010	8	2484	453	20.0 (13.4– 29.0)	147.001	94.558	0.0001	0.50000
2010 – 2021	29	14173	3583	38.6 (27.2 – 51.4)	2657.496	98.946	0.081	0.35369
Diagnostic technique								
PCR	25	10864	2155	32.1 (21.1 – 45.6)	2559.912	98.938	0.003	0.17363
Culture	5	1366	490	46.5 (13.9 – 81.3)	317.388	98.740	0.833	0.40325
qPCR	4	2270	221	15.6 (8.9 – 26.1)	85.857	96.506	0.0001	0.14532
Serotyping	1	121195	6999	–	–	–	–	–
ERIC-PCR	1	376	376	–	–	–	–	–
Dryspot kit	1	600	164	–	–	–	–	–
Provinces								
KwaZulu-Natal	6	1467	1074	72.9 (62.6 – 81.2)	60.243	91.700	0.0001	0.5000
Gauteng	2	624	202	–				
Eastern Cape	4	996	863	97.2 (67.7 – 99.8)	124.482	97.590	0.013	0.50000
North West	4	3323	184	15.1 (3.6 –	267.15	98.503	0.028	0.50000

				45.5)	2			
Eastern Cape/KwaZulu-Natal	1	250	135	–	–	–	–	–
Western Cape/Gauteng	1	362	38	–	–	–	–	–
Limpopo	7	2337	716	27.1 (18.9 – 37.2)	180.540	96.123	0.0001	0.35526
Western Cape	2	314	39	–	–	–	–	–
All provinces	10	128707	7760	11.3 (7.5 – 16.6)	266.820	96.627	0.0001	0.39422
***Campylobacter* spp.**								
C. jejuni	27	9957	1694	61.4 (50.1 – 71.1)	732.510	96.314	0.0001	0.66710
C. coli	24	7297	817	24.3 (19.1 – 31.5)	330.832	93.048	0.0001	0.47539
Others	17	8044	938	54.1 (29.6 – 64.9)	478.441	96.656	0.0001	0.32954
Antibiotic resistance methods								
DDA	13	6157	1684	40.8 (22.3 – 62.3)	1188.341	99.158	0.403	0.62280
MIC	6	1154	302	37.1 (17.4 – 42.4)	106.712	95.315	0.0001	0.50000

PCR = polymerase chain reaction; qPCR= real-time polymerase chain reaction; ERIC-PCR= Enterobacterial repetitive intergenic consensus- polymerase chain reaction; DDA= disk diffusion assays; MIC= Minimal inhibitory concentration; I^2= inverse variance; *Q-p* = Cochran's; *CI*= confidence interval; Measure of heterogeneity= the weighted sum of squared differences between individual study effects and the pooled effect across studies.

Table 3. Pooled prevalence estimates and 95% CI of antibiotic resistance of *Campylobacter* spp. isolates from this study.

Antimicrobial agents	Number of studies	Number of isolates	% Prevalence (95%CI)	I^2 (95%CI)	*P*-value
Tetracycline	16	1092	48.3	(28.4 – 68.7)	0.500
Chloramphenicol	3	55	33.3	(15.8 – 57.1)	0.148
Ciprofloxacin	17	902	31.9	(18.8 – 48.8)	0.200
Clindamycin	5	605	76.8	(52.0 – 91.0)	0.043
Nalidixic acid	12	484	35.8	(28.1 – 44.3)	0.151
Ampicillin	13	1095	52.5	(33.9 – 70.4)	0.292
Clarithromycin	3	274	76.5	(50.2 – 91.4)	0.148
Erythromycin	18	1194	44.0	(27.8 – 61.6)	0.310

Gentamicin	14	568	22.7	(11.4 – 40.1)	0.151
Imipenem	4	206	30.0	(15.7 −49.8)	0.248
Doxycycline	5	497	67.1	(36.7 – 87.7)	0.312
MDR	10	688	35.3	(20.5 – 53.6)	0.124

MDR = multidrug-resistant

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