

Research Article

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The prevalence of coagulase-negative staphylococcus associated with bovine mastitis in China and its antimicrobial resistance rate: a meta-analysis

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Abstract

To contribute to the treatment decision and optimize coagulase-negative staphylococcus (CNS) control programs, we conducted a meta-analysis to investigate the epidemiology and antimicrobial resistance rates of coagulase-negative staphylococcus associated with bovine mastitis in China. Three databases (PubMed, Google scholar and China National Knowledge Infrastructure database) were utilized to obtain relevant publications. A total of 18 publications were included in our research, and 3 of them included antimicrobial resistant (AMR) test. The pooled prevalence of coagulase-negative staphylococcus was 17.28%. Subgroup analysis revealed that the prevalence was higher in South China than in North China, was higher in 2011–2020 than in 2000–2010 and was higher in clinical bovine mastitis cases than in subclinical cases. The pooled AMR were most resistant to β -lactams, followed by tetracyclines, quinolones, nitrofurans, lincosamides, sulfonamides, amphenicol and aminoglycosides. The pooled AMR rate of coagulase-negative staphylococcus was lower in 2011–2020 than in 2000–2010. Although the prevalence of CNS showed an increasing trend over 20 years, the AMR rate showed a decreasing trend, and the clinical type of mastitis was the most frequent and the prevalence was highest in South China. Finally, CNS was most resistant to β -lactams amongst the eight groups of antimicrobial agents.

Research on the pathogenicity of staphylococcus has mainly focused on coagulase-positive staphylococci, and coagulase-negative staphylococci (CNS) have received less attention. However, as the clinical detection rate for CNS increases, this is changing. CNS are potentially zoonotic opportunistic pathogens that can cause a variety of human and animal infections (Mahato *et al.*, 2017). In animals CNS are particularly associated with infections of the udder, especially subclinical mastitis, to the point where CNS have become a major pathogenic bacteria of bovine mastitis in countries or regions including China. CNS mammary infections are often persistent (Reyher *et al.*, 2011; Becker *et al.*, 2014; De Visscher *et al.*, 2016; Sztachanska *et al.*, 2016) exhibiting increased somatic cell count (SCC) in milk and consequential decrease in milk quality, resulting in serious economic losses. The most frequently reported CNS species in numerous studies of bovine mastitis are *Staphylococcus simulans*, *Staphylococcus epidermidis*, *Staphylococcus chromogenes* and *Staphylococcus heemolyticus*, *Staphylococcus chromogenes* has been isolated most commonly and appears to be present in all herds (Piessens *et al.*, 2011; Supré *et al.*, 2011; Mørk *et al.*, 2012; Bexiga *et al.*, 2014).

Clinical cases caused by CNS are usually treated with antibiotics. However, the irrational use of antibiotics can lead to the development of antibiotic resistance and potentially multiple antimicrobial resistance, which brings great difficulty to the treatment of bovine mastitis. Clinically, CNS have high resistance to β -lactam antibiotics, which may be caused by long-term use of β -lactam antibiotics. Strains carrying the resistant gene *Blaz* can produce β -lactamase (Murphy *et al.*, 2008). The 'National action plan to combat animal resources antimicrobial resistance (2017–2020)' (Ministry of Agriculture and Rural Affairs of the People's Republic of China, 2017) is one of the national protocols for standardizing veterinary medication, along with strict biosecurity, sterile standards and the prudent use of antimicrobials to reduce the transmission of antimicrobial-resistant pathogens. There are examples of good practice, for example, colistin is an antibiotic agent of last resort for some human infections, and Wang *et al.* (2020) reported that the policy of decreased use of colistin in agriculture had a significant effect on the reduction of colistin resistance in animals and humans in China.

Investigation of the prevalence and antimicrobial resistance (AMR) profiles of CNS can contribute to treatment decision and optimization of CNS control programs (Kaczorek *et al.*, 2017). Numerous publications focused on the AMR of other major bovine mastitis pathogens in China, including *Staphylococcus* spp. (Gao *et al.*, 2012; Ali *et al.*, 2017), and

we now propose that meta-analysis can overcome the insufficiently understood spatial and temporal distribution of CNS.

Material and methods

Literature search

The search protocol is shown diagrammatically in online Supplementary Fig. S1. A comprehensive and systematic literature search was conducted by two independent reviewers during November 2021, utilizing the PubMed (<http://www.pubmed.gov>) Google scholar (<https://scholar.google.com>) and China National Knowledge Infrastructure (CNKI) databases (<https://www.cnki.net/>) to identify the literature focusing on CNS mastitis in cows. The subject heading 'bovine mastitis AND pathogens' was used to find all trials on this topic written in the English or Chinese language. The time was set from 2000 to 2021 to assure the timeliness of the subsequent meta-analytic investigation and to examine how the prevalence of mastitis and antimicrobial resistance rates have changed over the last 20 years. In China, the climate varies greatly from north to south, with north China dry and cold and south China hot and humid, so the whole analysis is divided into north and south China.

Inclusion and exclusion criteria

The study was conducted by two reviewers independently in accordance with PRISMA reporting standards (Page *et al.*, 2021) and specific exclusion criteria were defined to exclude review articles, articles not meeting the inclusion criteria due to wrong indexation ('off topic') or out of the considered time period (earlier than 2000), small sample size (less than three samples), undeclared bacterial identification method, samples containing non-mastitis diseases, undeclared sample size or number of bacterial isolates. Retrieval and management of references was performed with Excel.

Statistical analysis

Data were extracted from individual studies using a predesigned form obtaining data on the author, year, province, the number of samples, the number of CNS isolates, mastitis type (clinical and subclinical mastitis criterion: Laboratory handbook on bovine mastitis. National Mastitis Council), bacterial identification method, the number of antibiotic-resistant isolates and laboratory procedures. The same two reviewers independently, and in duplicate, assessed the methodological quality of each individual study based on prespecified study quality indicators adapted from the Downs and Black checklist. Meta-analysis result graphs are forest graph and funnel graph. Forest graph is the classic graph in meta-analysis result and consists of two parts: graph and data list. The data list part contains information on each original study as well as sample size, number of outcome events and effect values. The arrangement of the original studies should generally follow a certain order, such as the age of publication or the weight of contribution. The effect values are usually mean differences, OR, RR or HR, and confidence intervals are to be provided. Funnel plots are used to explore possible publication bias. The abscissa (*x*-axis) lists effect values (taken as natural logarithms), such as log values of OR, RR, etc. whilst the ordinate (*y*-axis) gives the standard error (SE) of effect values as dots where each dot is of a consistent size and represents a study. There should

be at least 10 studies with appropriate dot size. The funnel consists of three lines, where the vertical line represents the position of the combined effect values on the *x*-axis and the two diagonal lines represent the 95% CI.

The numbers of CNS, antimicrobial-resistant isolates and mastitis milk samples within individual studies were calculated for their proportion. Resistance was considered a dichotomous outcome, as classified by individual primary studies. Isolates with intermediate susceptibility were classified as susceptible.

Meta-analyses were performed separately for CNS prevalence and their AMR rates. Meta-analysis was performed using the 'meta' and 'metafor' package in R (Version 4.0.5) and only conducted if four or more studies were considered, because between-study variance cannot be estimated accurately when it is less than this number and may result in biased pooled estimates after the meta-analysis.

We pooled the prevalence of CNS using random effects models. Subgroup meta-analyses were conducted for isolate time, isolate regions and mastitis type to illustrate the heterogeneity between included studies. For the AMR studies, we pooled analyses within eight groups with higher frequency of clinical use: β -lactams, quinolones, tetracyclines, nitrofurans, lincosamides, sulfonamides, amphenicol and aminoglycosides. Publication bias test was performed using the 'Egger' test, and the funnel plot was created.

Results

Inclusion of publications

A total of 34, 86 and 136 articles were obtained from PubMed, Google scholar, and CNKI, respectively. Of these, 24 duplicate publications were excluded. A further 141 publications were excluded because their results did not contain CNS, 11 articles were beyond the considered period (before 2000) and 3 articles were excluded as being reviews. A total of 7 publications were excluded because they did not declare the sample size or the number of bacterial isolates, 14 articles did not declare sampling region and 38 articles did not declare the grade of mastitis. In total, therefore, 18 full text publications were included in our research, 3 of which included the AMR test (online Supplementary Table S1 1).

Prevalence of CNS

The pooled prevalence of CNS was 17.28% (95% confidence interval (CI): 11.44%–25.24%). An evident heterogeneity was observed ($I^2 = 95\%$, $\tau^2 = 0.947$, $P < 0.01$). Therefore, subgroup analysis was conducted to explore the sources of heterogeneity (Fig. 1).

Subgroup analysis

We divided the research articles into subgroups based on the research period (2000–2010 *vs.* 2010–2020), sample sites (North China *vs.* South China) and mastitis grade (clinical mastitis *vs.* subclinical mastitis). Data are shown in Fig. 1. The pooled prevalence of CNS values by period were 13.15 and 22.42% (2000–2010 *vs.* 2010–2020), by grade they were 18.94 and 13.45% (clinical *vs.* subclinical) and by region were 19.58 and 15.57% (North China *vs.* South China).

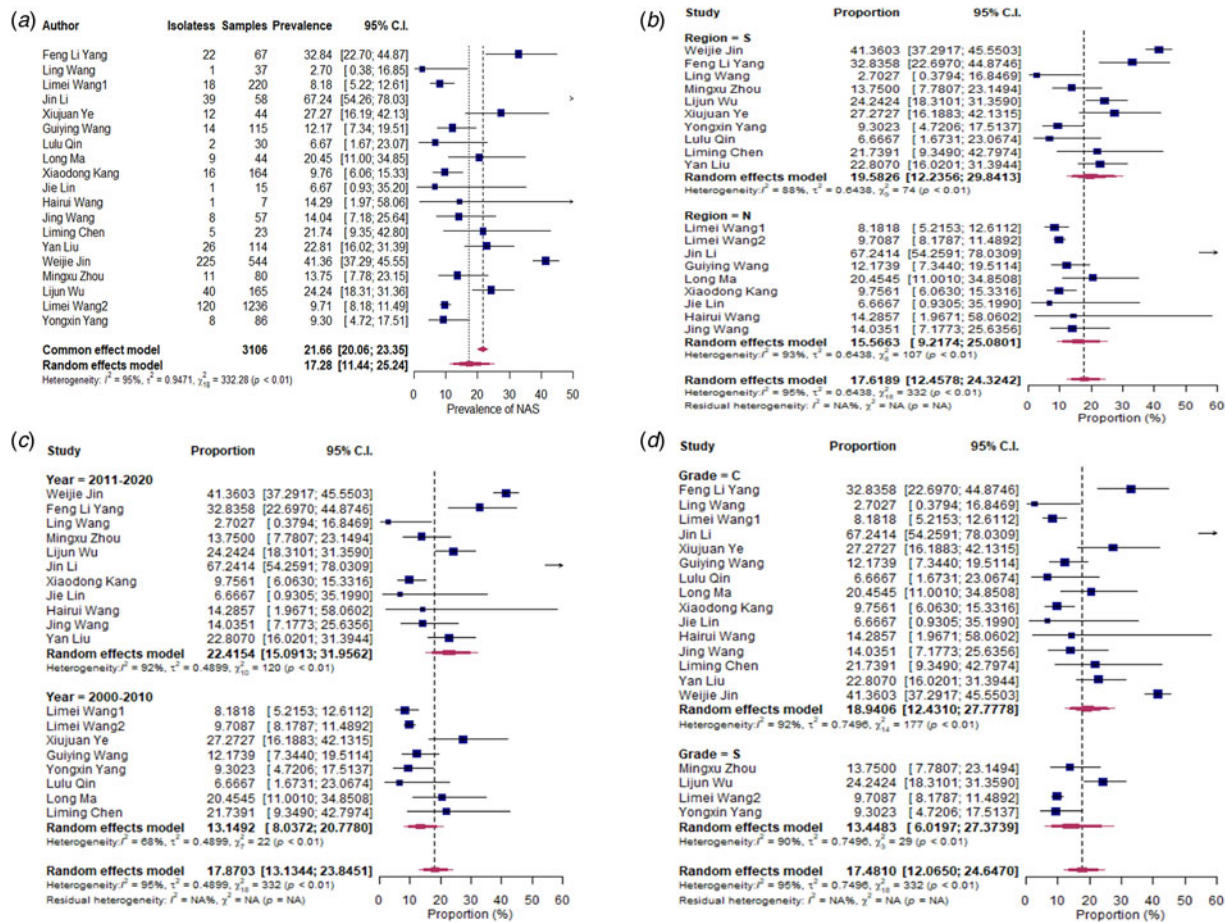


Figure 1. a: Forest plot of CNS prevalence in 3105 milk samples. b: Forest plot of CNS prevalence in north and south China. c: Forest plot of CNS prevalence in the period of 2000–2010 and 2010–2020. d: Forest plot of CNS prevalence of CNS isolated in clinical mastitis and subclinical mastitis cases.

Publication bias of the prevalence of CNS

The funnel plot (Fig. 3) exhibited an even distribution of the studies around the mean effect size, which suggested that the publication bias was invident.

Antimicrobial resistance rate of CNS

The pooled AMR rate revealed that CNS were most resistant to β -lactams (32.22%, 95% CI: 24.43%–41.14%), followed by tetracyclines (20.67%, 95% CI: 14.63%–28.39%), quinolones (15.78%, 95% CI: 10.69%–22.69%), nitrofurans (13.37%, 95% CI: 8.84%–19.72%), lincosamides (13.02%, 95% CI: 8.61%–19.22%), sulfonamides (11.41%, 95% CI: 7.37%–17.25%), amphenicol (9.52%, 95% CI: 5.93%–14.94%) and aminoglycosides (5.75%, 95% CI: 0.62%–37.22%) (Fig. 2). Subgroup analysis indicated that the AMR rate of CNS decreased from 2000–2010 (26.26%, 95% CI: 7.78%–60.07%) to 2011–2020 (16.92%, 95% CI: 14.88%–19.17%) (Fig. 2).

Publication bias of the AMR rate of CNS

The funnel plot (Fig. 3) exhibited an even distribution of the studies around the mean effect size, which suggested negligible publication bias.

Discussion

The bacteria most often isolated from subclinical mastitis is staphylococcus (Ceciliani *et al.*, 2021; Francisco *et al.*, 2021). Staphylococcus is divided into two major categories, coagulase positive (*coagulase-positive staphylococci*, CPS) and coagulase-negative (CNS). CNS are important pathogens of bovine mastitis in most herds, and the infection rate has been increasing in recent years. Understanding the prevalence and AMR profiling of bovine mastitis CNS may contribute to therapeutic interventions and preventive strategies.

In our study, the overall prevalence of CNS was 17.28% and was higher in South China than in North China, was greater for clinical mastitis than sub-clinical and increased between the two study periods (2000–2010 and 2011–2020). This pooled prevalence of CNS was higher than those of previous studies conducted in China (11.3% : Gao *et al.*, 2017). In recent years, CNS has become a major cause of frequent outbreaks and epidemics of bovine mastitis, especially for subclinical mastitis, and is often associated with persistent mammary infection (De Visscher *et al.*, 2017). In a study of 134 milk samples, Piessens *et al.* (2011) found a large number of CNS, with the highest separation rate of *Staphylococcus chromogens* (30.6%), followed by *Staphylococcus haemolyticus* (27.6%) and *Staphylococcus epidermidis* (11.9%). In another study the detection rate of CNS reached 90.0% in 300 bulk milk samples, among which *Staphylococcus*

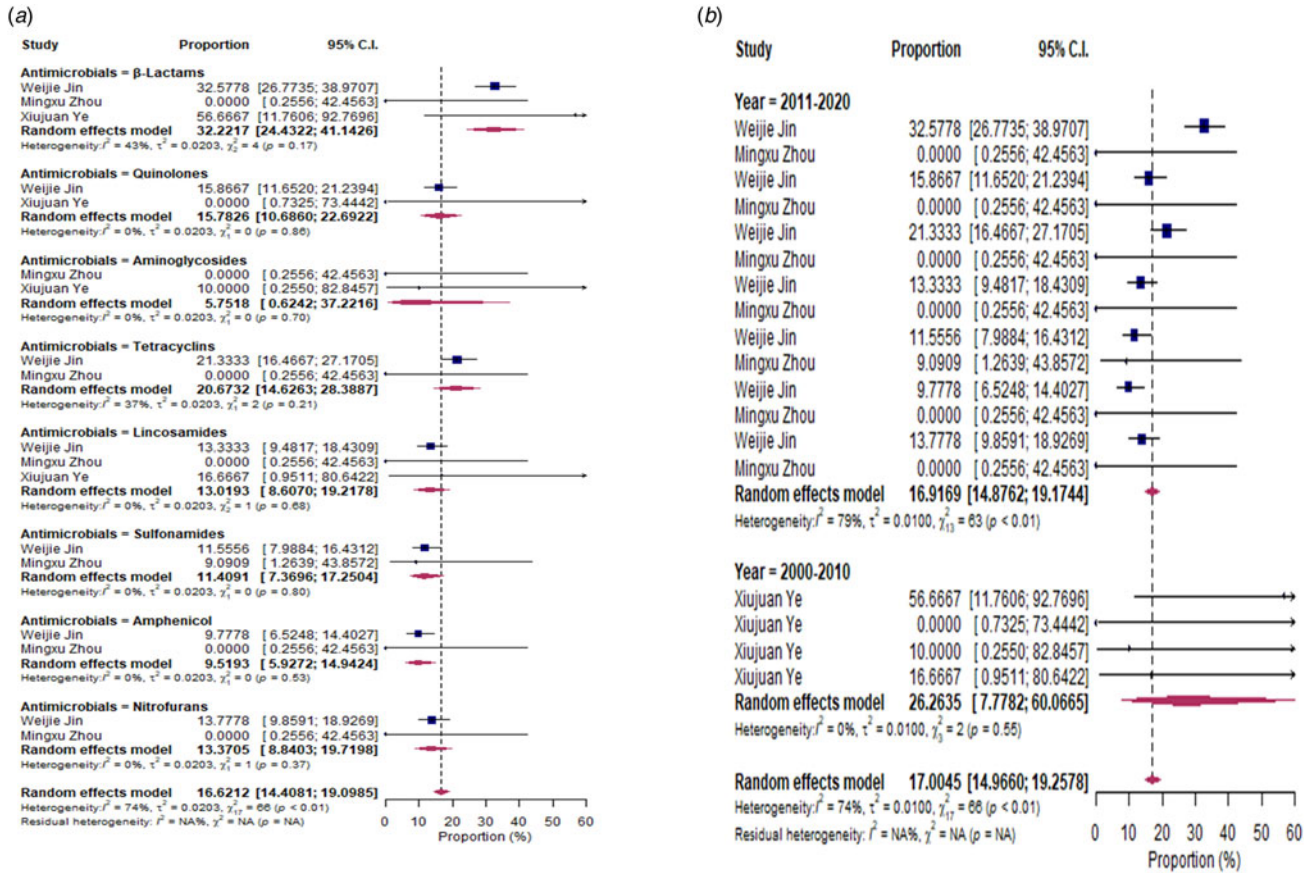


Figure 2. a: Forest plot of CNS antimicrobial resistant rate. b: Forest plot of antimicrobial resistance rates in CNS by year.

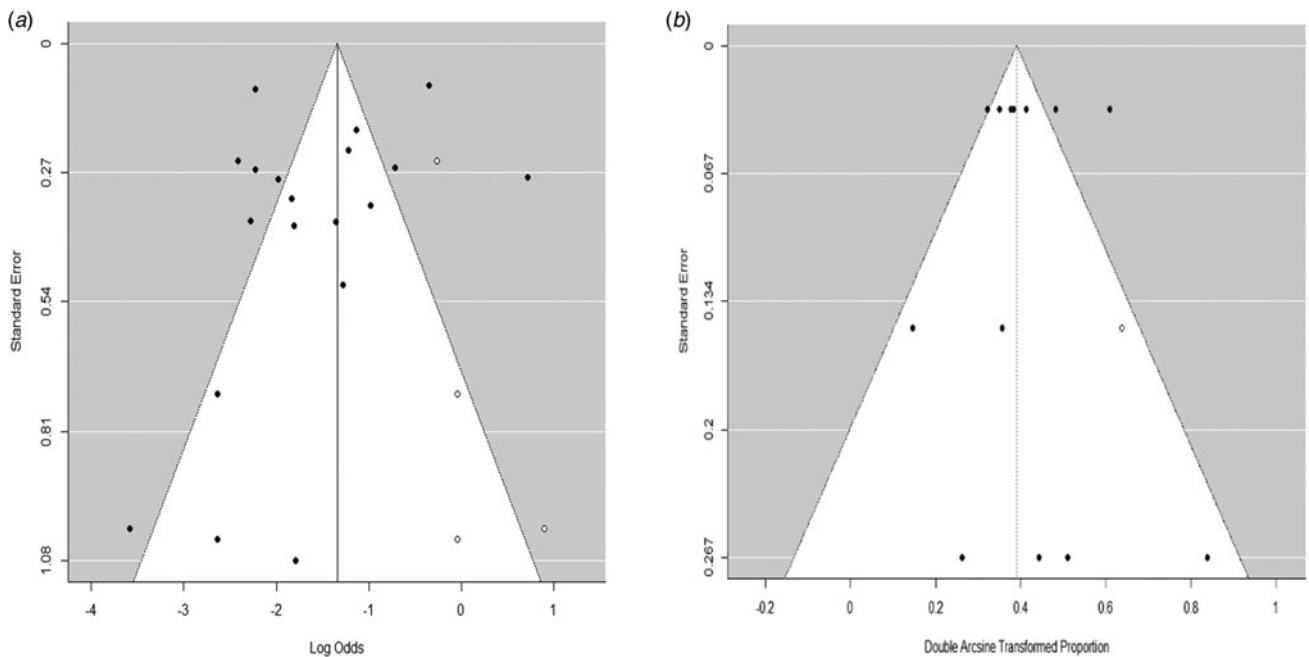


Figure 3. a: Publication bias graphics of CNS prevalence. b: Publication bias graphics of CNS antimicrobial resistant rate.

asteus was the dominant strain of CNS, accounting for 24.1% of the separation rate, followed by *Staphylococcus hemolyticus* and *Staphylococcus epidermidis*, for which the detection rate was 12.9% and 7.5%, respectively (De Visscher *et al.*, 2017). CNS

causes both clinical and subclinical mastitis, primarily affecting the teat and proliferating in the milk ducts. Primiparous heifers are more susceptible than multiparous cows (Pyörälä and Taponen, 2009). Our results are consistent with those of Gao

et al. (2017) in that the prevalence of CNS in northern China is lower than that in southern China, which may be due to the humid climate in southern China and the low degree of large-scale rearing in southern regions compared to northern regions. These factors probably contribute to a poor rearing environment, such as wet bedding not being replaced in a timely manner, and easily harboring pathogenic bacteria (Gao *et al.*, 2017).

In China, few CNS isolated from bovine mastitis have been further identified as species, but many different species of CNS have been isolated from milk samples, cow hair, breast skin and nipple tubes. Clinical bovine mastitis caused by CNS bacteria is usually treated with antibiotic. Once a CNS infection is established, in humans or animals, it is very difficult to cure completely, because CNS usually produce biofilms on the surface of objects or tissues, resulting in resistance to multiple antibiotics (Becker *et al.*, 2014). Biofilm production can increase resistance to CNS antibiotics by a factor of 1000 (Donlan, 2002). Moreover, the emergence of a large number of antimicrobial resistant strains has brought great difficulties to the treatment of bovine mastitis. The misuse of antimicrobials can increase the risk of AMR and threaten public health. Research suggests that CNS species can also act as reservoirs of antibiotic-resistant genes that can be transferred to more disease-causing species, such as *Staphylococcus aureus*, increasing their resistance to drug treatments (Côté-Gravel and Malouin, 2019). We determined the AMR of CNS against 8 kinds of frequently used antimicrobials. The resistance rate against β -lactams was the highest, followed by tetracyclines, quinolones, nitrofurans, lincosamides, sulfonamides, amphenicol and aminoglycosides.

Systematic and continuous monitoring of antimicrobial agent consumption and resistance in animals, food and humans has been carried out in Denmark since 1995 (Hammerum *et al.*, 2007). The total use of antimicrobials for intramammary therapy in Denmark is low, declining from 2005 to 2013, followed by a slight increase in 2014. At present, penicillin is the main antibiotic used to treat mastitis in Danish dairy cows, accounting for 81% of the total antibiotics, with cephalosporins and aminoglycosides used to a lesser extent. Antibiotics that can systematically treat bovine mastitis could not be found in food (DANMAP-2016, 2017). In addition to Denmark, relevant tests have also been conducted in Norway, Sweden, the Netherlands, Canada and the United States, (Hammerum *et al.*, 2007).

Since the beginning of the 21st century, total drug expenditures (TPE) in China has been between 40% and 50% of total national health expenditures. Between 2000 and 2013, TPE rose significantly despite a stable consumer price index. In 2006, TPE reached 43.5%, well above the median for low-income countries and twice the global median (Cui *et al.*, 2017). Our results showed that CNS in China had the highest resistance to β -lactams, similar to earlier reports (Xu *et al.*, 2015). According to this epidemiological investigation, the CNS strains in this area (Jiangsu province) were severely resistant to penicillin, with a drug resistance rate of 86.8%. Breser *et al.* (2018) showed that CNS isolates from chronic bovine mastitis were 85% resistant to penicillin. Clinical CNS β -lactam antibiotic resistance is widespread, which may be caused by long-term and broad-field use of β -lactam antibiotics, which are thought to mediate penicillin resistance since strains carrying the antimicrobial resistant gene *Blaz* produce β -lactamase (Murphy *et al.*, 2008). However, it has also been suggested that the resistance of *Blaz*-free strains to β -lactam is related to penicillin-binding protein 2a, a cell-wall transpeptidase, which has a low affinity for β -lactam antibiotics.

β -lactam antibiotics do not have any effect on the strains that normally synthesize cell wall peptidoglycan (Deurenberg *et al.*, 2007).

The mechanism of bacterial antimicrobial resistance to tetracycline includes efflux pump, ribosomal protective protein and enzyme inactivation, of which efflux pump is the most important mechanism. Bal *et al.* (2010) determined a by-level resistance rate of 14% for milk from sub-clinical mastitis cases, and our results showed a somewhat similar tetracycline resistance of 20.67% whilst others have shown higher values up to 39.5% (Xu *et al.*, 2015). The most commonly used antibiotics to treat several infections in cattle are tetracycline and erythromycin, and tetracycline resistance is also the most common antibiotic resistance in nature, achieved through active outflow of tetracycline from the cell or through ribosomal protection. Tetracyclines are also considered as growth-promoting factors in animal production (Chopra and Roberts, 2001), a practice that is banned in Europe since it can promote resistance selection, as exemplified by the increase of vancomycin-resistant enterococci in animals through the use of the glycopeptide avoparcin (van den Bogaard *et al.*, 2000). China banned antibiotic growth promoters in animal feed from July 2020, specifically banning 11 antibiotics as feed additives (Wen *et al.*, 2022).

According to the research results, although the incidence rate of CNS AMR in China is not very high, the causes of AMR of bovine mastitis are very complex, and the incidence rate varies with different countries/regions (Chantziaras *et al.*, 2014). There are also national guidelines for the proper use of antibiotics, veterinary prescribing models and drug marketing strategies (Cheng *et al.* 2019). Therefore, our results should raise concerns about AMR of bovine mastitis NCS in Chinese dairy herds.

In conclusion, the pooled prevalence of CNS was 17.28%, subgroup analysis revealed that the prevalence was higher in South China, increased with time and was higher in clinical bovine mastitis cases. CNS were most resistant to β -lactams, which should raise the most concern when used in treating bovine mastitis. Our data can provide a theoretical basis for the prevention and treatment of bovine mastitis of CNS origin in clinical practice. However, our study failed to identify the main causes of CNS prevalence, for which further research is needed.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0022029923000365>

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