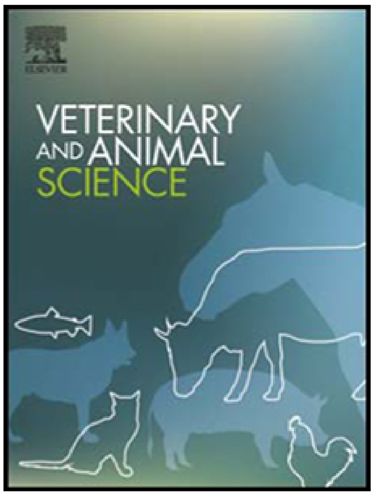

Patterns of antibiotic use in global pig production: a systematic review

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Highlights

- Many classes of antibiotic used for humans are also used in food animals, including the highest priority of the critically important antimicrobials for human medicine in the World Health Organisation's list.
- Penicillins and Tetracyclines classes were the most commonly used antibiotics in many countries.
- Improve understanding of the use of antibiotics and factors influencing antibiotic use will help promoting prudent use of antimicrobials in livestock.

Patterns of antibiotic use in global pig production: a systematic review

1. Abstract

This review assesses the evidence for patterns of antibiotic use in pig on the basis of papers published in peer-reviewed journals in English between 2000 and 2017. Thirty-six articles were identified and reviewed, of which more than 85% of studies were conducted in Europe and North America. Penicillins and Tetracyclines groups were the most commonly used antibiotics in many countries. Oral medication in suckling and post-weaning periods were the most common applications of antibiotic administration in pig production. Antibiotic use is driven by age-specific diseases and the common pathogens causing these conditions where epidemiological profiles varied greatly across countries. In addition, the type and size of farm were associated with antibiotic use with finisher and larger farms using more antibiotics than farrow-to-finish and smaller farms. There is variation in the use of the highest priority critically important antimicrobials in humans across studies. However, this review indicates that they are still commonly used in pig production, for treatment and prevention of infection. This evidence calls for global efforts on the prudent use of antibiotics in response to the emergence of antimicrobial resistance (AMR) in the agricultural sector.

Keywords: antibiotic; antimicrobial resistance; antibiotic use; pig; systematic review

2. Introduction

Antibiotics have been used routinely in farm animal production since the 1950s, in particular during intensive farming, in order to keep animals healthy and to increase productivity. The use of antibiotics in animals has raised concerns that the selective pressure on the bacteria population promotes antibiotic resistance. Despite the difficulties in demonstrating the transmission of resistant bacteria from animals to humans, many studies have shown evidence of human infection from resistant bacteria in animals (C. Liu et al., 2018; McCrackin et al., 2016; Nhung, Cuong, Thwaites, & Carrique-Mas, 2016). The discovery of a plasmid-mediated colistin resistant gene (MCR-1) in commensal *Escherichia coli* from pigs, pork products and humans in China, triggered global concern (Y.-Y. Liu et al., 2016). Colistin is considered a last resort antibiotic as it is one of the only antibiotics active in severe infections caused by hospital acquired multidrug-resistant (MDR) pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacteriaceae* (Catry et al., 2015).

Antibiotics in the same class usually have a similar mode of therapeutic action, with a range of effectiveness. Many classes of antibiotic used for humans are also used in food animals. The World Health Organisation (WHO) produces a list of all antimicrobials grouped into 3 categories based on their importance in treating human infections. (World Health Organization, 2017). The classes of drugs included in the list of critically important antimicrobials (CIA) for human medicine contain the last-resort antibiotics to treat severe infections caused by multidrug-resistant (MDR). The CIA list of Highest Priority Critically Important Antimicrobial includes Quinolones, 3rd and higher generation Cephalosporins, Macrolides and Ketolides, Glycopeptides and Polymixins class which includes colistin (World Health Organization, 2017). This WHO CIA list is referred to in the rest of this report.

In animals, the use of antibiotics is common for not only treatment, but also for controlling the spread of infection (metaphylaxis), preventing infection (prophylaxis) particularly in periods of stress and vulnerability to infections, and improvement of feed efficiency and promotion of animal growth (Aarestrup, 2005). According to American Veterinary Medical Association, the term "therapeutic" includes treatment, control, and prevention of disease (Association American Veterinary Medical, 2019). The use of antibiotics as a growth promoter is considered non-therapeutic. Many countries including USA, Canada and Australia have implemented policies and regulations that medically important antimicrobials are prescription only medicines by licensed veterinarians (Australian Government Department of Health and Department of Agriculture and Water Resources, n.d.; Government of Canada, 2018; US Food and Drug Administration, 2011). The use of antibiotics for growth promotion has been banned in the European Union since 2006 (Regulation (EC) No 1831/2003 of the European Parliament and of the councel on additives for use in animal nutrition, 2003). In contrast, other countries - including China and Brazil which are the large livestock producing and exporting countries- do not prohibit the use of antibiotics for growth promotion (Maron, Smith, & Nachman, 2013).

Despite the concerns about the relationship between the use of antibiotics and AMR in food animals and AMR in humans, there are limited studies exploring the use of antibiotic in livestock and the factors that influence how farmers use them. To promote the prudent use of antibiotics in livestock, it is vital to have a better understanding of the current situation. This systematic review aims to analyse and synthesise the available published information on the pattern of antibiotic use in pigs.

3. Method

3.1. Scope of study and research question

This study focuses on antibiotics. Before conducting the systematic review, the terms and explanations to be included were considered as follows. According to World Organisation for Animal Health (OIE) definition, an antimicrobial is considered as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (to kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Anti-helminthic and substances classed as disinfectants or antiseptics are excluded from this definition (World Organisation for Animal Health, 2011). In this study the word 'pigs' refers to all stages of swine production including breeding and gestation, farrowing, nursery and feeding and finishing. The word 'pattern' explains the use of antibiotics in terms of active ingredient; the route of administration such as injection or medicated feed; the purpose of the use including treatment, metaphylaxis, prophylaxis and growth promotion; and the frequency of the use by different farms and different stages of life cycle of pig production. The research questions in the review is: "What are the patterns of antibiotic use in terms of classes, routes of administration and purpose of the use and its associations with pig production?".

3.2. Identifying relevant literature

The study applied the "SPIDER" tool, designed specifically to identify relevant quantitative studies (Cooke, Smith, & Booth, 2012). It covers the following: Sample: pig; Phenomenon of Interest: antibiotic use in pigs; Design: Observational studies; Evaluation: pattern of antibiotic use including active ingredient of antibiotic, route of administration, purpose of use including treatment, control, prevention and growth promotion; and Research: Quantitative research.

Literature on the use of antibiotics in pigs was systematically reviewed between July to October 2017. Relevant scientific papers published in English peer-reviewed journals were identified using the keyword combinations (antibiotic OR antimicrobial OR antibacterial) AND (livestock OR swine OR pig* OR farrow OR weaner OR finisher OR sow) AND (use OR utilisation OR consum* OR practice OR administration).

The online electronic database through LSHTM databases: MEDLINE (http://ovidsp.tx.ovid.com; 1946 until present), Scopus (http://www.scopus.com; 1823 until present) and Web of Science (http://apps.webofknowledge.com; 1970 until present) were searched with restriction of the date of publication between 2000 and 2017 to capture up-to-date data. To ensure a wide range of articles from different sources, additional searches were sourced through the reference lists of key articles.

3.3. Eligibility assessment of studies and inclusion criteria

Prior to a study being included within the review, the following criteria were considered: publication in English, and focus on antibiotic usage in pigs with high and moderate ranking of a quality assessment.

Citations of all identified studies were downloaded into a reference management software (EndNote X8.0.2). In the first screening step, the duplicated studies were removed, through consideration of the title and the abstract by comparison with the keywords. Full texts were further considered. Reviews, clinical research, pharmacokinetic, biopharmaceutical and experimental studies were excluded. In addition, studies focusing on antibiotic activity, specific diseases related to drug recommendations, associations of antibiotic use with antimicrobial resistance, relationship between interventions and antibiotic use, and effects of antibiotic treatment to AMR, animal productivity and animal management were excluded.

Studies included in the qualitative synthesis were those that presented the pattern of antimicrobial use, and medium (50-75%) and high-ranking quality assessment (>75%). If a study explored data over many periods of time, then the updated data was selected for the review.

3.4. Quality assessment

The Critical Appraisal Skills Programme (CASP) was applied for quality assessment)(Critical Appraisal Skills Programme, n.d.). They were aggregated into a quality score based on four criteria: aim, method, result and application of the literature; Yes, No and Cannot tell are the assessment outcomes. With eleven questions, the score was categorised into three groups: weak means <50% having "yes" answers, moderate means 50-75% having "yes" answers, and high means >75% having "yes" answers (see Table A2 of annex). If the assessment by the reviewer was 'no' or 'cannot tell', the score for that question was zero; the score for yes was one. In this review, the studies were ranked by quality criteria. The quality ranking was classified into three groups: High meant >75% of all eleven sub-criteria were met, moderate meant 50-75% were met and weak meant <50% of criteria were met.

3.5. Data extraction and synthesis

Figure 1 shows the review process. All relevant articles in full texts were reviewed and summarised using a standardised data extraction table in an Excel spreadsheet.

4. RESULTS

4.1. *Eligible studies*

Our search strategies identified a total of 2,588 articles (Appendix 1). After duplicates were removed and an initial review of titles and abstracts for relevance was conducted and 118 articles were found to be eligible for full-text screening on the basis of the inclusion criteria. Sixty-eight studies were found to be relevant and retained. Further screening excluded 31 papers; of which 16 papers were not related to pattern and factors influencing antibiotic use; two papers had inappropriate study design; four papers focused on specific diseases using recommended antibiotics and relationship between interventions and antibiotic use; and ten papers were not related to pigs. Finally, 36 studies were included in this systematic review. Figure 1 showed the flow diagram of the process in screening papers.

4.2. *Study characteristics*

As shown in table 1, twenty-seven of studies (75%) were conducted between 2010 and 2017; the remaining 9 studies were conducted between 2000 and 2010 (25%). Most studies (72%) were conducted in Europe, with four studies in North America (11%), three in Asia (8%), and one each in Africa (3%) and Australia (3%). Diverse sources of data were used for the study such as farm surveys (39%), national databases (19%), farm-based survey and prescription data (14%), prescription data (8%), antibiotic application records (8%), veterinary survey (6%), pharmaceutical producer survey (3%) and farm-based survey and national data (3%). Among total studies reviewed, 9 studies (25%) were nationally representative. The result of the quality assessment of 36 studies showed that 21 (58%) and 15 (42%) of studies are of high and medium quality respectively (see table 2A in Annex).

4.3. Patterns of antibiotic use in pigs

4.3.1 Patterns of antibiotic use

4.3.1.1 Classes and active ingredients of antibiotic

Some studies reported antibiotic use by active ingredient and others only by the class. In many studies the most common used antibiotic classes were the Penicillins and Tetracyclines. Benzylpenicillins consisted 61% of total use in a farm study in Sweden (Sjölund et al., 2016). Aminopenicillins were commonly reported accounting for 30-40% of total antibiotic use in studies from Sweden, Germany and Canada. (Glass-kaastra et al., 2013; Sjölund et al., 2016; Van Rennings et al., 2015). Twelve studies reported that Tetracyclines class was the most commonly used including studies from Denmark, Japan, Netherlands, Australia, Spain and France (Bondt, Jensen, Puister-Jansen, & van Geijlswijk, 2013; Bos et al., 2013; Casal, Mateu, Mejía, & Martín, 2007; Chauvin, Beloeil, Orand, Sanders, & Madec, 2002; Dupont, Diness, Fertner, Kristensen, & Stege, 2017; Hosoi, Asai, Koike, Tsuyuki, & Sugiura, 2014; Jordan et al., 2009; Vieira, Pires, Houe, & Emborg, 2011), and was as high as 54.4% in a study from Germany (Merle et al., 2013). Within the Tetracyclines class, doxycycline was used 62.3% of total use in the study in Austria (Moreno, 2012). The share of chlortetracycline use was 23.9% in a farm study in Vietnam (Van Cuong et al., 2016), and formed the majority of antibiotics use in all pig stages in the United States (Apley, Bush, Morrison, Singer, & Snelson, 2012). In the farm study in Switzerland, the most common antibiotic class was the reductase inhibitors and combinations class" of drugs, specifically sulfadimidine, sulfathiazole and trimethoprim, accounting for 62.1%. (Arnold, Gassner, Giger, & Zwahlen, 2004) while Bacitracin was the most reported of antibiotic use (24.8%) in the farm study in Vietnam (Van Cuong et al., 2016). Fattening farms in the study from Austria applied Lincosamides in 71.9% of antibiotic use (Trauffler, Griesbacher, Fuchs, & Köfer, 2014).

The use of highest priority Critically Important Antimicrobials in humans was also reported differently across countries. The studies from France and Austria reported the use of Macrolides at 20% and at 7.4% of total use (Chauvin et al., 2002) (Trauffler, Obritzhauser, Raith, Fuchs, & Köfer, 2014). Based on the electronic drug application records from 75 pig farms in Austria, Fluoroquinolones were reported at 2.4% of total use, third and fourth generation Cephalosporins were 2.2% of total use (Trauffler, Obritzhauser, et al., 2014), while the use of Fluoroquinolones at 5 % and third generation Cephalosporins at 11% were reported from 47 pig farms in the study in Belgium (Sjölund et al., 2016). The study in 60 French pig herds received colistin in 30% of total antibiotic use (Sjölund et al., 2016), 12.2% in the study in Vietnam using the internet-based survey of commercial feed producer (Van Cuong et al., 2016), 33% and 61% in the survey in 45 farrow-to-finish farms and 67 fattening farms in Spain (Moreno, 2012) and 34.4% in fattening farms in 75 pig farms in Austria (Trauffler, Griesbacher, et al., 2014).

4.3.1.2 Routes of administration

Generally, oral medication was the most common route of antibiotic administration in pig production. Several studies reported more than 90% of antibiotic substances were administered orally via both feed and water (Merle et al., 2012; Van Rennings et al., 2015; Rajić et al., 2006; Chauvin et al., 2002). About 70-90% of the oral use was reported in many countries, for example 87% in the study from France (Sjölund et al., 2016), 86% in the study from Austria (Trauffler, Griesbacher, et al., 2014), 73% in the study from Denmark (Dupont et al., 2017), 71% in the study from Germany (Sjölund et al., 2016) and 70% in the study from Belgium (Sjölund et al., 2016). In the UK farm study, 60-75% of the farmers had used medicated feeds for their weaners (Stevens et al., 2007). Another study indicated that oral use of antibiotics was higher than parenteral indication (97.43% VS 2.46%) (Merle et al., 2013).This is in contrast to another study that farmers applied very low levels of oral antibiotics, 13% of all routes (Sjölund et al., 2016).

A wide range of active ingredients was commonly used for oral medication, including: colistin (Filippitzi, Callens, Pardon, Persoons, & Dewulf, 2014; Moreno, 2012; Timmerman et al., 2006), amoxicillin(Filippitzi et al., 2014; Timmerman et al., 2006), sulfonamides (Bondt et al., 2013; Timmerman et al., 2006), oxycycline (Bondt et al., 2013), doxycycline (Moreno, 2012; Timmerman et

- lincosamides	4 (Apley et al., 2012; Merle et al., 2014; Rajić et al., 2006; Sjölund et al., 2016)	1 (Merle et al., 2014; Rajić et al., 2006; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	4 (Apley et al., 2012; Jensen et al., 2017; Rajić et al., 2006; Sjölund et al., 2016)	4 (Apley et al., 2012; Merle et al., 2014; Rajić et al., 2006; Sjölund et al., 2016)
- lincosamides and spectinomycin	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)	1 (Sjölund et al., 2016)	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)
Polymyxin colistin	5 (Jensen et al., 2012, 2017, Sjölund et al., 2016, 2015; Van Rennings et al., 2015)	3 (Jensen et al., 2012; Sjölund et al., 2016; Van Rennings et al., 2015)	3 (Sjölund et al., 2016, 2015; Van Rennings et al., 2015)	5 (Jensen et al., 2012, 2017, Sjölund et al., 2016, 2015; Van Rennings et al., 2015)	3 (Jensen et al., 2012; Sjölund et al., 2016; Van Rennings et al., 2015)
Aminoglycosides	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	3 (Jensen et al., 2012, 2017; Sjölund et al., 2016)	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)
Amphenicols	2 (Jensen et al., 2012; Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)	1 (Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)
Cephalosporins	2 (Jensen et al., 2012; Merle et al., 2014)	2 (Jensen et al., 2012; Merle et al., 2014)	1 (Merle et al., 2014)	1 (Jensen et al., 2012)	2 (Jensen et al., 2012; Merle et al., 2014)
-3rd & 4th generation cephalosporins	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)

Fluoroquinolones	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)
- enrofloxacin	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)

APPENDIXES

Appendix 1

I. Search Strategy

Structured Database Search (Search terms and results)

- MEDLINE: *N= 703 articles*
  - (Antibiotic.mp. or exp Anti-Bacterial Agents) (704,921)
  - (Antimicrobial agents.mp. or Anti-Infective Agents) (61,091)
  - (livestock or swine or pig* or farrow or weaner or sow).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (519,570)
  - (Use* or usage or consume or consumption or practiceor or administration or oral or feed or injection).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6,635,975)
- Scopus: *N= 808 articles*

  (TITLE-ABS-KEY (antibiotic OR antimicrobial OR antibacterial) AND TITLE-ABS-KEY (livestock OR swine OR pig* OR farrow OR weaner OR finisher OR sow) AND TITLE-ABS-KEY (use OR utilisation OR consum* OR practice OR administration)) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "sh")) AND (LIMIT-TO (SUBJAREA , "AGRI") OR LIMIT-TO (SUBJAREA , "VETE")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))
- Web of Science: *N= 1,070 articles*

  TOPIC: (antibiotic or antimicrobial or antibacterial) AND TOPIC: (livestock or swine or pig or farrow or weaner or finisher or sow) AND TOPIC: (use or utilisation or consum* or practice or administration)

  Refined by: PUBLICATION YEARS: (2016 OR 2006 OR 2015 OR 2005 OR 2014 OR 2004 OR 2012 OR 2002 OR 2013 OR 2003 OR 2017 OR 2000 OR 2011 OR 2001 OR 2009 OR 2010 OR 2007 OR 2008) AND WEB OF SCIENCE CATEGORIES: (VETERINARY SCIENCES) AND DOCUMENT TYPES: (ARTICLE)

  Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1970-2018

Table A1 Search terminology to be used in literature review.

	Search term
I	antimicrobial (Free text) OR antimicrobial (MeSH term) OR antibacterial (Free text) OR antibacterial (MeSH term) OR antibiotic (Free text) OR antibiotic (MeSH term)
II	livestock (Free text) OR swine (Free text) OR pig* (Free text) OR farrow (Free text) OR weaner (Free text) OR finisher (Free text) OR sow (Free text)
III	use (Free text) OR utilisation (Free text) OR consum* (Free text) OR practice (Free text) OR administration (Free text)

Appendix 2

Table A2 Quality assessment of included studies

Author, year	Q1	Method					Result			A
		Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q1
2017										
Dupont, et al. (Dupont, Diness, Fertner, Kristensen, & Stege, 201	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jensen, et al. (Jensen, Jorsal, & Toft, 2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2016										
Cuong, et al. (Van Cuong et al., 2016)	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Sjölund, et al. (Sjölund et al., 201	Y	Y	N	N	Y	Y	Y	Y	Y	Y
2015										
Fertner et al (Fertner et al., 2015	Y	CT	N	N	Y	N	Y	Y	Y	Y
Van Rennings, et al. (Van Rennin et al., 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Visschers, et al. (Visschers et al., 2015)	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Sjölund, et al. (Sjölund, Backhan Greko, Emanuelson, & Lindberg, 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
2014										
Filippitzi et al. (Filippitzi, Callens, Pardon, Persoons, & Dewulf, 201	Y	Y	CT	N	CT	CT	Y	Y	Y	Y
Hosoi, et al. (Hosoi, Asai, Koike, Tsuyuki, & Sugiura, 2014)	Y	Y	CT	N	N	N	Y	N	Y	Y
Merle, et al. (Merle et al., 2014)	Y	Y	N	N	Y	N	Y	Y	Y	Y
Trauffler et al. (Trauffler, Obritzhauser, Raith, Fuchs, & Köfer, 2014)	Y	Y	N	N	Y	N	Y	Y	Y	Y
Trauffler et al. (Trauffler, Griesbacher, Fuchs, & Köfer, 201	Y	Y	N	N	Y	N	Y	Y	Y	Y
Visschers, et al (Visschers et al., 2014)	Y	Y	CT	Y	Y	Y	Y	Y	Y	Y
2013										
Bondt, et al. (Bondt, Jensen, Puister-Jansen, & van Geijlswijk, 2013)	Y	Y	Y	CT	CT	Y	Y	Y	Y	Y
Bos, et al. (Bos et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Glass-Kaastra, et al. (Glass-kaast et al., 2013)	Y	Y	N	N	Y	CT	Y	Y	Y	Y
Kim, et al. (Kim et al., 2013)	Y	Y	N	N	Y	CT	Y	Y	Y	Y
Merle, et al. (Merle et al., 2013)	Y	Y	N	N	Y	N	Y	Y	Y	Y
2012										
Apley, et al. (Apley, Bush, Morrison, Singer, & Snelson, 201	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Callens, et al. (Callens et al., 201	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Eltayb, et al (Eltayb, Barakat, Marrone, Shaddad, & Sta, 2012)	Y	Y	CT	N	Y	CT	Y	N	Y	Y

Merle, et al. (Merle et al., 2012)	Y	Y	N	N	Y	N	Y	Y	Y	Y
Moreno, et al (Moreno, 2012)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
2011										
Jensen, et al (Jensen, Emborg, & Aarestrup, 2012)	Y	Y	N	N	Y	Y	Y	Y	Y	Y
van der Fels-Klerx, et al. (van der Fels-Klerx, Puister-Jansen, van Asselt, & Burgers, 2011)	Y	Y	Y	N	Y	Y	N	Y	N	Y
Vieira, et al. (Vieira, Pires, Houe, Emborg, 2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Aarestrup, et al. (Aarestrup, Vibeke, Jacobsen, & Wegener, 2010)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2009										
Jordan, et al. (Jordan et al., 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2008										
Rosengren, et al (Rosengren et a 2008)	Y	CT	N	N	Y	N	Y	Y	Y	Y
2007										
Casal, et al (Casal, Mateu, Mejía, Martín, 2007)	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Stevens, et al (Stevens et al., 20(	Y	Y	N	N	Y	N	Y	Y	Y	Y
2006										
Rajic, et al. (Rajić, Reid-Smith, Deckert, Dewey, & McEwen, 20(	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Timmerman, et al. (Timmerman al., 2006)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2004										
Arnold, et al. (Arnold, Gassner, Giger, & Zwahlen, 2004)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
2002										
Chauvin, et al (Chauvin, Beloeil, Orand, Sanders, & Madec, 2002)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

*score >75 = high (H), 50-74 = medium (M) and <50 = low (L) *score >75 = high (H), 50-74 = medium (M) and <50 = low (L)

Note:

Q1 = Did the study address a clearly focused issue?
Q2 = Did the authors use an appropriate method to answer their question?
Q3 = Were the subjects recruited in an acceptable way?
Q4 = Were the measures accurately measured to reduce bias?
Q5 = Were the data collected in a way that addressed the research issue?
Q6 = Did the study have enough participants to minimize the play of chance?
Q7 = How are the results presented and what is the main result?
Q8 = Was the data analysis sufficiently rigorous?
Q9 = Is there a clear statement of findings?
Q10 = Can the results be applied to the local population?
Q11 = How valuable is the research?
Y = Yes (clearly described)
N = No (Not described)
CT = Cannot tell (described but with limited detail