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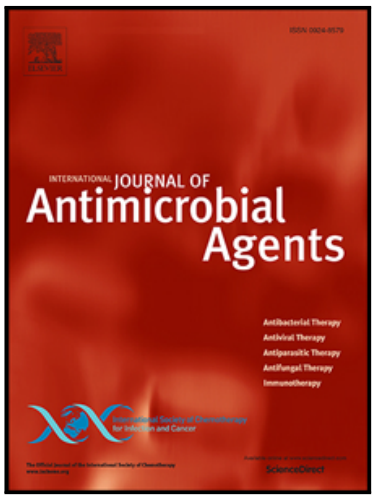

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Highlights

- We undertook a WHO-commissioned rapid systematic review of evidence to examine whether limiting the use of antimicrobials in food animals decreases antimicrobial resistance 1) in those food animals; 2) in humans
- 89 studies (3 direct, 86 indirect) provided adequate evidence that limiting antimicrobials given to animals reduces antimicrobial resistance in animals; heterogeneity precluded estimating the magnitude of effect
- 4 studies (1 direct, 3 indirect) suggested that withdrawing antimicrobials in food animals results in decreased antimicrobial resistance in humans
- The paucity of well-designed primary studies that directly answer these questions means these should be urgently commissioned to strengthen the evidence of the magnitude of the effect of stopping antimicrobial use in food animals – particularly on resistance in the bacterial flora of humans

Title

Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review.

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ABSTRACT

Background:

Large quantities of antimicrobials are given to food animals, especially in feed, potentially risking increased antimicrobial resistance in humans. However, the magnitude of this effect is unclear.

Methods:

We searched PubMed, Embase and Web of Science, for studies on interventions which limited antimicrobial use in food animals, in any setting and context, to reduce antimicrobial resistance 1) in those food animals; and 2) in humans. We validated our strategy by testing whether it identifies known relevant studies. Data from included studies were extracted into pre-designed and pilot-tested forms.

Results:

We included 104 articles containing 93 studies. Heterogeneity (from different animal species, environs, antimicrobial classes, interventions, administration routes, sampling, and methods), was considerable, precluding meta-analysis. The evidence was therefore synthesised narratively. 89 studies (3 directly, 86 indirectly) addressed the question whether limiting antimicrobial exposure in food animals led to decreased antimicrobial resistance in those animals. The evidence was adequate to conclude this, although the magnitude of the effect could not be quantified; 4 studies (1 directly, 3 indirectly) examined the question of whether withdrawal of antibiotics changed resistance of potential pathogens in retail food for human consumption, and in bacteria of humans themselves. The direct (observational) study of broiler hatchery *in ovo* antimicrobial injection found a credible effect in terms of size reduction and time sequences.

Interpretation:

Limiting antimicrobial use in food animals reduces antimicrobial resistance in food animals, and probably reduces antimicrobial resistance in humans. The magnitude of the effect cannot be quantified.

BODY TEXT

1. Background

Large quantities of antimicrobials – including those within the same class as human therapeutic drugs – are administered to food animals, to treat and prevent bacterial diseases in animals but also in some cases to promote growth.[1-4] The practice of antimicrobial use generates resistance which potentially threatens both human and animal health, with devastating downstream economic consequences.[1, 2] The World Health Organisation (WHO) reports on health consequences of foodborne diseases,[5] but not the human health burden from antimicrobial-resistant disease associated with antimicrobial use in food animals.

There is a long history of public health concern about antimicrobial use in food animals. The United Kingdom's Netherthorpe Committee in 1960 investigated whether it constituted a danger to humans. The Swann Committee in 1969 concluded that it does,[6] and subsequently many scientific, regulatory, and professional organisations elsewhere have expressed concern. A new wave of concern arose in the 1990s with the registration of fluoroquinolones and third-generation cephalosporins for therapeutic use in food animals. This led to a WHO Consultation on Medical Impact of the Use of Antimicrobials in Food Animals, which concluded that use of antimicrobials in food animals can lead to antimicrobial resistance in humans, particularly in foodborne pathogens such as *Salmonella* and *Campylobacter*, despite considerable uncertainty about the magnitude of the effect.[7]

Responding to current calls for guidelines to preserve the long-term effectiveness of antimicrobials critically important for human medicine, the WHO commissioned two systematic reviews of the evidence, which addressed the following two questions: whether a limitation on the use of antimicrobial agents in food animals reduced the presence of antimicrobial-resistant genetic elements or antimicrobial resistant bacteria (1) in food animals; and (2) in humans.

Two groups were selected to conduct the systematic reviews simultaneously, albeit independently of each other. We present our findings as one of the two groups[8] awarded funding. The WHO Guideline on the use of medically important antimicrobials in food animals – which was informed by these systematic reviews – was published recently.[9]

2. Material and methods

We undertook a rapid systematic review to meet deadlines required by the WHO guidelines development timetable, in accordance with a pre-existing protocol and using accepted

methods.[10-12] This required us to deploy 10 staff with expertise in systematic reviewing, information retrieval, antimicrobial use in humans and animals, and biostatistics.

A set of potentially relevant studies was built from several sources: 1) forward and backward citation searches on one relevant reference for each question;[13, 14] 2) an updated search of a recent relevant report on the subject;[1] and 3) known relevant studies provided by the WHO Group developing the guideline at our request. The resulting set consisted of 26 articles spanning the period from 1976 to 2016, which we labelled a 'validation set' (Appendix A). The common key words of the studies comprising the validation set were then used to build two searches: one search for the animal question, and one search for the human question. These search strategies were tested in PubMed, to verify that all of the articles in the validation set were found by the strategy. These final search strategies were run on 10 June 2016 without language or date restrictions, and were modified appropriately to search Embase and Web of Science. Full search strategies are presented in Appendix B.

We scoped the volume and quality of the evidence through an examination of the first 100 references found by the searches. The examination suggested that both greater volume and higher quality evidence will be found for the question addressing antimicrobial resistance in animals. Accordingly, we included only the study designs of higher quality and less prone to bias for the animal question, and relaxed the rigour by additionally including interrupted time series and before and after designs for the human question.

The inclusion and exclusion criteria were as follows:

Animal question:

- Inclusion: Studies addressing the question; study designs that were probable or certain to be: reviews (systematic, literature), RCTs, challenge trials, controlled trials, or cohort studies; published in any language and on any date
- Exclusion: studies that were certain or probable to be: case-control, interrupted time series, before and after, cross-sectional, ecological, case series.

Human question:

- Inclusion: Studies addressing the question; studies that were probable or certain to be: reviews (systematic, literature), RCTs, challenge trials, controlled trials, cohort studies, case-control, interrupted time series, before and after; published in any language and on any date

- Exclusion: studies that were certain or probable to be: cross-sectional, ecological, case series.

No restriction on the basis of ready accessibility of literature was used.

The literature search was supplemented in three ways: 1) the WHO Guidelines Group and the content experts on our team provided key known relevant references; 2) a forward (citing articles) citation search was done in Web of Science on a key identified study on the effect in humans[15] to identify studies that have subsequently cited that study; and 3) the references of a study comparing the impact of stopping antimicrobials to continuing antimicrobials in food animals[16] was hand searched. There was insufficient time to contact study authors directly, or systematically search the grey literature, although where we found grey literature, we considered it against inclusion/exclusion criteria.

Ideally, in systematic reviews, two or more authors screen titles and abstracts for inclusion,[17] but time constraints in rapid systematic reviews mean this is frequently foreshortened to a single reviewer.[12] We adopted a compromise: the entire set of references was screened by a single author, but a second author screened a random sample of 10% references. The two authors subsequently met to resolve discrepancies. Included references were then reviewed in full-text by pairs of authors working independently, with discrepancies resolved by discussion or by a third reviewer if necessary. Data from included studies were extracted using pre-piloted data extraction forms (Summary of Findings, and Table of Included Studies), and checked by a second author.

The following information was extracted from studies into a Table of Included Studies form: study location and date; species and number studied; comparison (e.g. antimicrobial vs no antimicrobial, antimicrobial vs lower dose, etc.); study design; sampling (setting, approach, proportion of subjects sampled, duration, frequency); exposure (antimicrobial, dose, duration, frequency); comparator (type, does, duration, frequency); and unit of measurement (e.g. prevalence of resistance, odds ratios, etc.) The Summary of Findings form collected the following information: study author and date; exposed and unexposed animal species; exposed and unexposed humans (professional category if applicable); method of measuring resistance; and prevalence of resistance prior, during and after exposure.

The considerable heterogeneity of the included studies precluded formal assessment for risk of bias and meta-analysis. Instead, we categorised the included studies by study-design, using a hierarchy of evidence specifically devised for animal studies, and described the results narratively.

3. Results

Database searches yielded 7,023 references, and supplementary search strategies yielded an additional 132 references. After amalgamation and de-duplication of the two sets of references, 3,709 references remained (Figure A.1). The 3,709 references were title/abstract screened by a single author, and a second author screened a random sample of 10% (n=371) references. Title/abstract screening involved checking the titles and abstracts of identified references against the inclusion and exclusion criteria. Those references whose titles and abstracts appeared to meet the inclusion criteria were included; if it was uncertain whether a reference met the inclusion criteria, we included it. Resolution of discrepancies in the two authors' decisions about inclusions and exclusions of references resulted in an inclusion of 9 previously excluded references. At this stage, 210 references were advanced to full-text screening. Full-text screening against the inclusion and exclusion criteria was conducted by pairs of authors working independently, with discrepancies resolved by discussion or by a third reviewer if necessary; 106 references were excluded, leaving 104 (Figure A.1) to be data-extracted.

3.1 Interventions influencing resistance in bacteria in animals

There were 89 studies in 97 publications relevant to answering the animal question: 24 (27%) were randomised controlled trials (RCTs) conducted under field conditions, considered a higher level of evidence than the other study designs (Figure A.2). The remainder of the studies were: other types of controlled trials and challenge studies (n=46); cohort studies (n=17); and interrupted time series (ITS) (n=2) (both of which were found by hand searching, although this study-type was not initially included). No studies meeting the inclusion criteria were systematic or literature reviews.

The most commonly studied animals were pigs (28 studies, including 7 RCTs, 13 other controlled trials and challenge studies, 7 cohort studies, 1 ITS) and cattle/steers/calves (28 studies, including 12 RCTs, 13 other controlled trials and challenge studies, 3 cohort). Other animals studied were chickens (23 studies, including 5 RCTs, 14 other controlled trials, 3 cohort studies, and 1 ITS) and turkeys, lambs, sheep, fish, and mixed (3 studies or fewer each).

Of the 89 included studies, 3 directly answered the question whether a limitation on the use of antimicrobial agents in food animals reduced the presence of antimicrobial-resistant

genetic elements or antimicrobial resistant bacteria in food animals; 86 studies answered the question indirectly. The studies directly answering the question included: an RCT which compared the impact of continuing exposure to oxytetracycline and neomycin versus withdrawal,[18] and two ITS studies comparing the resistance to tetracyclines before and after their withdrawal in the United Kingdom,[19] and the resistance to cephalosporin before and after the withdrawal of ceftiofur in Japan.[20]

Among the remainder of the included studies, the common comparisons were antimicrobial versus no antimicrobial, evaluated by 67 studies (22 RCTs, 32 other controlled trials and challenge studies, and 13 cohort studies). Other studies compared various doses and/or durations of antimicrobials. Some comparisons were also conducted as part of 'challenge trials', in which animals were artificially infected ("challenged") with bacteria carrying genetic material known to promote resistance. Some studies compared animals given an antimicrobial with those not given an antimicrobial, with the groups kept in isolation from one another, whereas other studies kept both groups together, and assessed transfer of resistance from animals that received antimicrobials to those that did not.

A wide range of antimicrobials or their combinations were studied. Among the 24 RCTs alone, 21 different antimicrobials or their combinations were studied. The only antimicrobials considered by more than one study (of any design), were: ceftiofur, an antimicrobial that can only be administered to animals by injection (6 studies), chlortetracycline, available in both oral and parenteral forms (9 studies); enrofloxacin, injection and water medication only (3); oxytetracycline and neomycin, oral and parenteral forms (2 studies); oxytetracycline (4 studies); tetracycline (3 studies); tylosin, oral and parenteral forms (6 studies); and virginiamycin, oral only (2 studies).

Studies also used a variety of methods to measure and quantify outcomes. 51 (57%) of the 89 animal studies used microbial culture for phenotypic assessment only, 11 (12%) PCR determination, 26 (29%) both methods, and one study did not report the method used. The comparison of resistance levels between groups was expressed as the proportion of isolates with resistance, or absolute counts of resistant isolates, or both.

In summary, the study aims and designs varied widely, with considerable heterogeneity in terms of antimicrobials, bacteria selected for challenge, or resistance measurement, animals, methods for measuring resistance, sampling timeframes, and methodology amongst studies. This precluded the possibility of a meta-analysis. However, a summary of results is

presented in Table A.1; more detailed results are presented in Appendix C and full references for all of the included studies are provided in Appendix D.

[insert table A.1 here]

Table A.1 utilises WHO's categorisation of antimicrobials that are important for human medicine into: Critically Important, Highly Important, and Important.[21] A further category – 'other' – is added to the table, to indicate studies that evaluated antimicrobials not on the WHO list.

In Table A.1, each study's result was coded in the following manner: black indicates that the study found higher resistance in bacteria isolated from animals exposed to more antimicrobial (e.g. higher resistance found in animals exposed to antimicrobials, than in animals not exposed to antimicrobials; or in animals exposed to a higher dose of antimicrobials than in animals exposed to a lower dose). Light grey indicate the opposite – that a lower resistance was found in animals exposed to more antimicrobial, or that lower resistance was found in animals exposed to antimicrobial than in animals unexposed. Finally, criss-crossed pattern indicates that the study found mixed results – e.g. animals exposed to more antimicrobials initially showed higher resistance but subsequently showed lower resistance than animals exposed to less antimicrobials, or that exposed animals showed higher resistance to one antimicrobial but lower resistance to another antimicrobial.

Studies addressing the animal question directly suggest that a limitation of antimicrobials in food animals leads to a decrease in resistance to antimicrobials in those animals. One RCT examined the impact of discontinuation of feeding dairy calves with milk replacer containing oxytetracycline and neomycin, compared to its continuation. It found that the discontinuation was significantly associated with increased susceptibility to tetracyclines in both *E. coli* and *Salmonella*, with the effect most pronounced in the first 3 months.[18] An ITS study examined the impact of the United Kingdom's 1971 ban on the use of tetracyclines in pigs to promote growth. It showed that prior to the ban, the percentage of samples with tetracycline resistance increased from 18% (in 1956) to 64% (in 1970). The prevalence of resistance decreased to 23-41% 2-5 years after the ban.[19] Another interrupted time series study examined the impact of voluntary withdrawal, in March 2012, of off-label use of ceftiofur in chicken hatcheries in Japan. The study examined the impact on the prevalence of resistance to a broad-spectrum cephalosporin in *E coli* isolates from healthy broilers, and found a decrease from 16.4% resistance in 2010 to 4.6% resistance in 2013 (p=0.001).[20]

The majority of the studies addressing the question indirectly, showed that exposing animals to antimicrobials results in higher resistance to those antimicrobials, than exposing animals to no (or a lower dose) of those antimicrobials. This result is consistent across included study types – RCT conducted under field conditions, other controlled trial types and challenge studies, cohort study, and interrupted time series. The result also holds regardless of the WHO classification of importance to human health – critical, highly important or important. The majority of RCTs and other controlled and challenge studies focused on evaluating antimicrobials that are categorised as 'critically important' or 'highly important' to human health; very few studies evaluated antimicrobials classified as 'important.'

3.2 Interventions influencing resistance in bacteria in humans

We identified only one study which directly addressed the question of whether stopping the use of antimicrobials in food animals resulted in reduced antimicrobial resistance in bacteria in humans – the original question asked by the WHO committee.[15] The study reported data from Quebec, Canada, where injections of ceftiofur – a third generation cephalosporin – into eggs in chicken hatcheries was voluntarily withdrawn in 2005, and then partially reintroduced in 2007. The study measured the prevalence of resistance in *Salmonella enterica* serovar Heidelberg isolated from both retail chicken carcasses and clinical samples from infected humans across Canada, as well as *E. coli* samples (chickens only). The study found that the withdrawal of *in ovo* antimicrobial use in chickens was associated with a reduction in resistance in both bacterial species isolated from chicken meat for human consumption, and in clinical samples from infected humans (Figure A.3). Re-introduction of the *in ovo* antimicrobial use was similarly associated with an increase in resistance in both cohorts. The temporal pattern of changes in resistance was consistent with a causal effect. The findings of this study are expanded with national-level data from Canada, reported by the Public Health Agency of Canada[22] and the Canadian Integrated Program for Antimicrobial Resistance Surveillance[23] (Figure A.4)

Additionally, three studies addressed the human question indirectly – that is, they examined whether the *introduction* of antimicrobials was associated with *increased* resistance in animals and humans.[24-26] A cohort study of pigs and human farm residents, conducted in the Netherlands, found a significant dose-response relationship (across all farms) between the dose of antimicrobial and multi-antimicrobial-resistant livestock associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA): 16% increase in odds for a doubling of dose in pigs, and 1.2% increase in odds for a doubling of dose in humans.[24] A second study

reported resistance monitoring data among poultry in the United States, reporting that the odds ratio for resistance in human *Campylobacter* clinical isolates was 2.5 for the presence of resistance after fluoroquinolones were introduced for food animal use in 1995-6, compared to prior to introduction.[25] Similar findings from Spain showed that after fluoroquinolones were introduced for food animal use, there was an increase in prevalence of resistance in the human *Campylobacter* clinical isolates (general population) from a baseline of approximately 10% to >80%.[26, 27] In both reports of an increasing trend of fluoroquinolone resistance prevalence in *Campylobacter* it was not possible to apportion the relative contributions of human and animal use of the concurrently used fluoroquinolones.

4. Discussion

Our rapid systematic review examined whether a limitation on the use of antimicrobial agents in food animals reduced antimicrobial resistance in those food animals and in humans. The majority of studies addressed the question *indirectly* – that is, they examined whether an increase in exposure to antimicrobials increases resistance. Three (3) studies *directly* addressed the animal question, suggesting that a limitation of antimicrobial exposure in food animals leads to a decrease in resistance to antimicrobials in particular bacterial species in those animals, however the magnitude of the effect cannot be quantified. A single study – of injectable antimicrobial use – provided evidence to directly address the human question. It concluded that limiting *in ovo* antimicrobial exposure in broiler chickens reduced the burden of antimicrobial resistance in the animals themselves as well as in contact humans and consumers.[15] The size of the effect is large enough to make this study credible. Moreover, the time-courses are also credible for this to be a causal association. However, the overall body of evidence – consisting of a single study, of observational design – for the human question is thin, and on this basis, it is not possible to quantify the effect. Moreover, the effect is probably specific to the use of a critically important antimicrobial for routine injection into eggs to prevent *E. coli* infection (this is not an established practice in most poultry producing countries) and may differ for each antimicrobial, dosage, route of administration, infection type, food animal species and management system and environment.

The review has a few limitations. First, it is limited by a paucity of well-conducted primary studies that directly addressed the questions – only 3 studies (one RCT and two interrupted time series) directly addressed the animal question, and 1 study (an interrupted time series) directly addressed the human question. The majority of the included studies (86 studies of animals, and 3 studies of humans) addressed the questions only indirectly, by examining the impact of an increase in antimicrobial exposure (e.g. greater duration, higher dose,

increased frequency) compared to its decrease (no antimicrobial, shorter duration of exposure, lower dose or decreased frequency). The majority of the studies showed that increased exposure to antimicrobials leads to increased resistance – or conversely, that a lower exposure is associated with lower resistance. The paucity of well-designed primary studies that directly address these questions means these studies should be urgently commissioned to strengthen the evidence of the magnitude of the effect of stopping antimicrobial use in food animals – particularly on resistance in bacteria in humans.

Second, the conduct and reporting of the included studies were highly heterogeneous: there was a wide range of animal species studied; whether resistance was measured in index animals alone or in others to which resistance might have been transmitted; a variety of micro-organisms used to assess resistance (some of which are pathogens to humans); antimicrobial drugs investigated (with some 'critical for human use'); the purpose of antimicrobial use (as growth promoters or for prophylaxis to a whole population or to treat individually sick animals); and measures of resistance (most using bacterial culture susceptibility testing, while a minority used individual resistance gene detection by PCR). Reporting methods were also difficult to compare, as some studies reported the difference between exposed and unexposed groups as the proportion of individuals with resistance, some as the proportion of samples with resistance (which may include multiple samples per individual) and some as the proportion of resistant isolates (which may include multiple isolates per sample, or per individual). A systematic review commissioned by the WHO to be conducted in parallel with the present one, found statistical heterogeneity of this evidence to be greater than 90%.[8] Since we do not know the distribution of resistance in multiple samples or isolates from the same individual, these measurements cannot be combined in meta-analysis with those from studies concerning measures in individuals, we considered it inappropriate to undertake meta-analysis. Instead we summarise the data descriptively without a summary estimate as a pragmatic and less misleading approach.[17]

The finding that use of one antimicrobial can result in selection for resistance to a different antimicrobial class,[18, 28, 29] and the apparent spontaneous appearance of resistance without any direct exposure to the implicated antimicrobial,[18, 29-32] may have a number of causes and may represent an un-observed exposure to the drug, a spontaneous horizontal transfer of genes on integrative conjugative elements (ICEs), or activation of associated genes. If the latter, the implication is that use of one antimicrobial may carry potential problems for other antimicrobials, particularly if co-selection is occurring favouring acquisition and maintenance of multidrug-resistant plasmids, transposons or other integrative conjugative elements. Furthermore the role of other potential co-selective agents

such as biocides and heavy metals (e.g. copper, zinc) requires further investigation,[33-35] particularly where they are used as replacements for traditional antimicrobials in food animals for growth promotion and/or therapeutic or prophylactic purposes.[36, 37]

5. Conclusion

Despite the paucity of evidence, it seems biologically plausible to conclude that the use of antimicrobials in animals can result in the selection and dissemination of antimicrobial resistance determinants to bacteria in other food animals, including their carcasses and meat for human consumption, and to humans themselves. More primary studies are required to strengthen the research evidence, a conclusion also reached recently by the Food and Agriculture Organisation of the United Nations.[38] Importantly, several countries (e.g. Canada CIPARS, Denmark DANMAP; United States NARMS) now have comprehensive and well-established surveillance and reporting systems for monitoring antimicrobial resistance in food, animal and human pathogens and food animal commensals, as well as antimicrobial use in both human and veterinary sectors. These and emerging programmes in other countries, will allow for more integrative studies to correlate resistance levels with antimicrobial use and can be expected to provide substantial insights and evidence in answering important questions to guide antimicrobial risk management options. Such programmes are also critical to maintain the longevity of currently registered shared drug classes, as new human-only and animal-only drug classes are developed.

Declarations

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Competing Interests: Anna Mae Scott is employed by the Centre for Research Excellence in Minimising Antimicrobial Resistance from Acute Respiratory Infections (CREMARA).
Elaine Beller reports no conflicts of interest.
Paul Glasziou reports NHMRC grant to study antibiotic usage in primary care.
Justin Clark reports no conflict of interest.
Respati W. Ranakusuma reports no conflict of interest.
Oyungerel Byambasuren reports no conflict of interest.
Mina Bakhit reports no conflict of interest.

Stephen W. Page reports personal fees for presentations from Zoetis Animal Health, Bayer Animal Health, patent US20150366797 for methods of treating microbial infections, including mastitis; Australian Government Department of Health and Department of Agriculture contract to facilitate meeting on antimicrobial resistance.
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List of Figures and Tables

Figure A.1: PRISMA[39] Flow Diagram

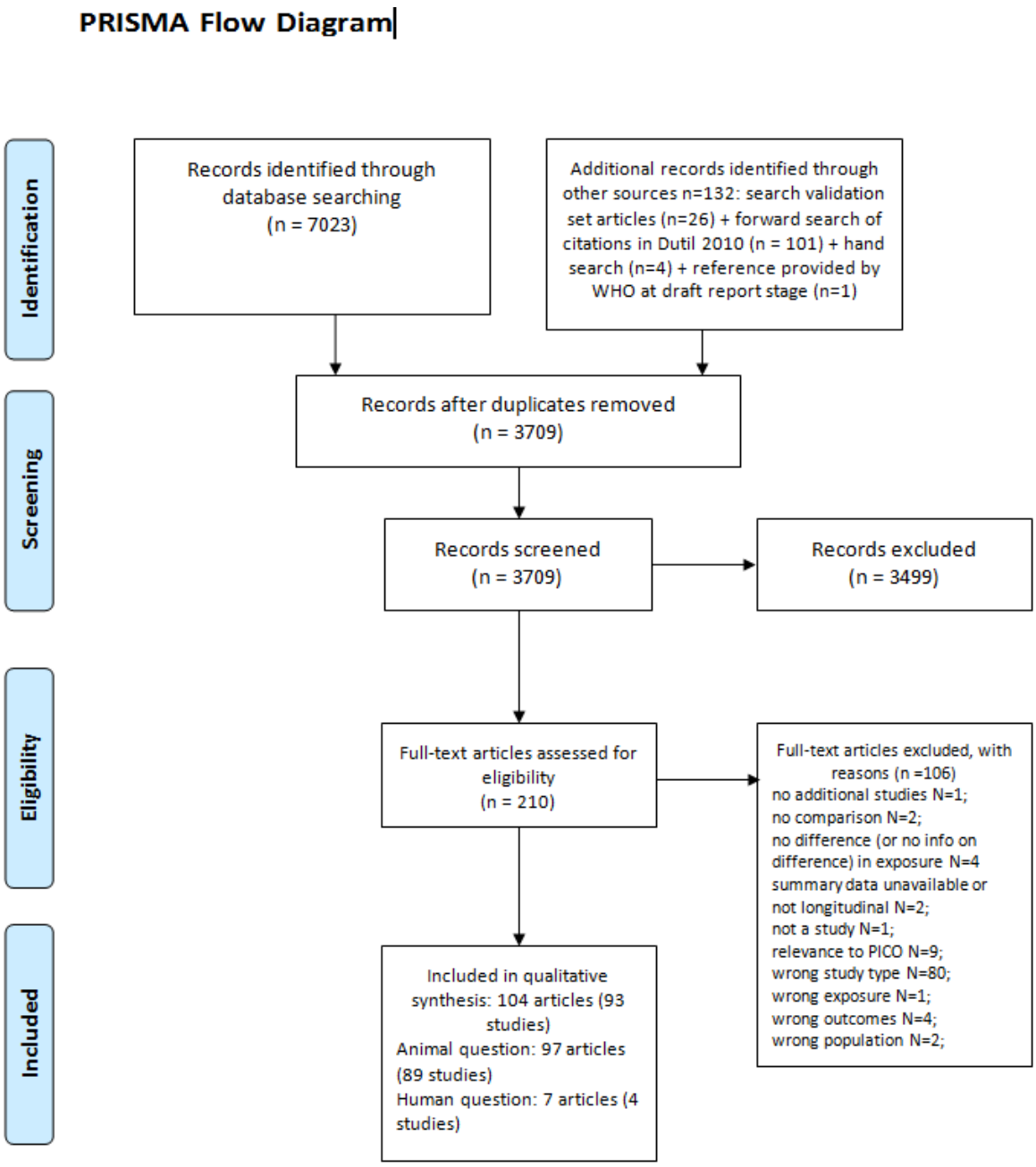

Figure A.2: Hierarchy of evidence for animal studies (modified from original) in Sergeant 2014 [40]

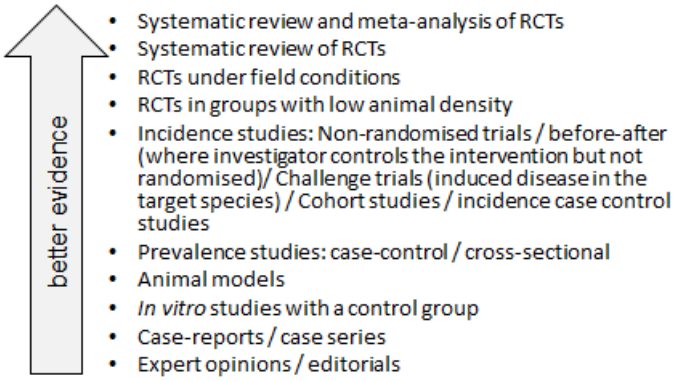

Figure A.3: Resistance to ceftiofur over time in Quebec, Canada (redrawn from data in Dutil 2010[15])

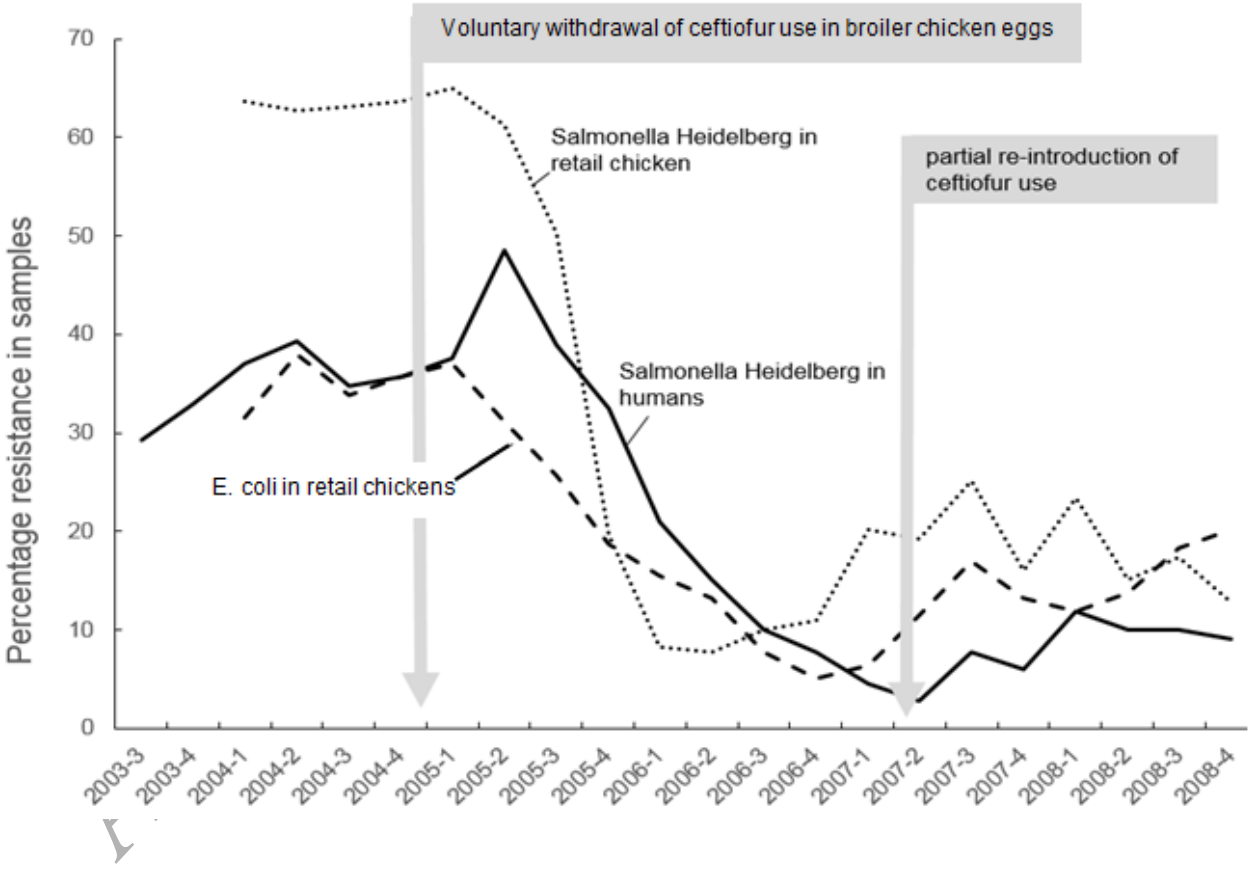

Figure A.4: Resistance to ceftiofur over time in Canada (redrawn from data in Public Health Agency of Canada [22] and Canadian Integrated Program for Antimicrobial Resistance Surveillance [23]

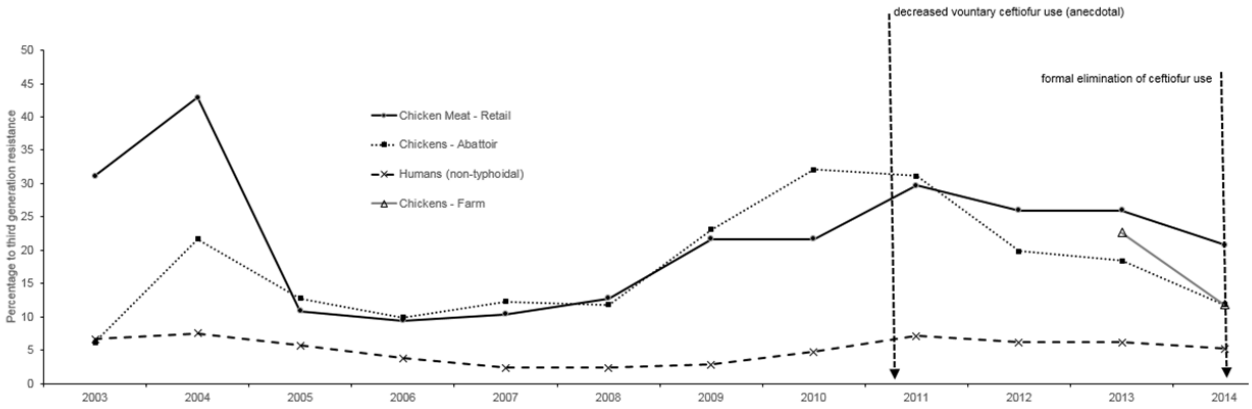

Table A.1: Resistance to antibiotics important to human health: studies comparing animals exposed to (more) antibiotics, and animals exposed to no/less of those antibiotics.

Study type	Reference*	Isolate	Resistance to antibiotics important to human medicine			
			Critically Important Antibiotics	Highly Important Antibiotics	Important Antibiotics	Other Antibiotics
RCTs under field conditions	Usui 2014	Campylobacter				
	Amachawadi 2015	Enterococcus				
	Beyer 2015	Escherichia				
	da Costa 2008, 2009, 2010	Various				
	Le Devendec 2015	Various				
	Kanwar 2013, 2014	Escherichia				
	Pereira 2014	Escherichia				
	Kaneene 2008	Various				
	Wagner 2008	Various				
	Chen 2008	Various				
	Davies 1999	Enterococcus				
	McDermott 2005	Enterococcus				
	Agga 2014, 2015	Escherichia				
	Checkley 2010	Escherichia				
	Delsol 2003	Various				
	Edrington 2014	Various				
	Platt 2008	Various				
	Alexander 2008, Mirzaagha 2011	Escherichia				
	Butaye 2005	Enterococcus				
	Chambers 2015	Various				
	Olumeyan 1986	Various				
Study type	Reference	Isolate	Resistance to antibiotics important to human medicine			
			Critically Important Antibiotics	Highly Important Antibiotics	Important Antibiotics	Other Antibiotics
Other controlled trials and challenge studies	Farnell 2005	Campylobacter				
	Ladely 2007	Campylobacter				
	Lin 2007	Campylobacter				
	Logue 2010	Campylobacter				
	Stapleton 2010	Campylobacter				
	Takahashi 2005	Campylobacter	XXXXXXX			
	Cameron-Veas 2015	Escherichia				
	Cavaco 2008	Escherichia				
	Herrero-Fresno 2016	Escherichia				
	Huang 2014	Escherichia				
	Jimenez-Belenguer 2016	Escherichia				
	Jiang 2006	Salmonella				
	Aarestrup 1998	Various				
	Alali 2009b	Various				
	Daniels 2009	Various				
	Zaheer 2013	Various				
	van der Horst 2013	Escherichia				
	Alali 2004	Escherichia				
	Berge 2006	Escherichia				
	Kim 2005	Escherichia				
	Ebner 2000	Salmonella				
	Johnson 2015	Escherichia				
	Khachatryan 2004	Escherichia		XXXXXXX		
	Khachatryan 2006	Escherichia				
	Kobe 1995	Escherichia				
	Bauer-Garland 2006	Salmonella				
	DeGeeter 1976	Salmonella				
	Evangelisti 1975	Salmonella				
	Funk 2006	Salmonella				
	Moodley 2011	Staphylococcus				
	Molitoris 1986	Streptococcus		XXXXXXX		
	Finlayson 1973	Various				
	Wierup 1975	Escherichia				
	Alexander 2010; Beukers 2015	Escherichia				
	Sharma 2008, Wu 2011	Escherichia				
	Inglis 2005	Various				
	Kobe 1996	Escherichia				
	Cassenego 2011	Enterococcus				
	Brunton 2014	Escherichia				
	Benazet 1980	Salmonella				
	Delsol 2005	Various				
	Edrington 2003	Various				
	Kempf 2013	Various				
Study type	Reference	Isolate	Resistance to antibiotics important to human medicine			
			Critically Important Antibiotics	Highly Important Antibiotics	Important Antibiotics	Other Antibiotics
Cohort studies	Juntunen 2010	Campylobacter				
	Heuer 2002a	Enterococci				
	Andersen 2015	Escherichia				
	Baron 2014	Escherichia				
	Callens 2015	Escherichia				
	Sato 2004	Campylobacter				
	Petersen 2002	Acinetobacter				
	Akwar 2008	Escherichia				
	Benedict 2015	Escherichia				

	Duse 2015	Escherichia				
	Mathew 1999	Escherichia				
	Morley 2011	Escherichia				XXXXXXXXX
	Alali 2010b	Salmonella				
	Keelara 2013; Quintana-Hayashi 2012	Salmonella				
	Rajala-Schultz 2009	Staphylococci				
	Nulsen 2008	Various				
	Scott 2012	Various				XXXXXXXXX
			Resistance to antibiotics important to human medicine			
Study type	Reference	Isolate	Critically Important Antibiotics	Highly Important Antibiotics	Important Antibiotics	Other Antibiotics
ITS	Hiki 2015	Escherichia				
	Smith 1975	Escherichia				

*References to these studies are provided in Appendix D

Legend:
Antibiotics to which resistance is measured by each study are classified using WHO's taxonomy of antibiotics important for human medicine: Critically Important, Highly Important, Important [92]. 'Other' category indicates that a study evaluated resistance to antibiotic not on the WHO list.

Coding scheme:

	Higher resistance in animals exposed to more antibiotic, than those exposed to less antibiotic.
XXX	Mixed results (e.g. animals exposed to more antibiotic had more resistance initially but less resistance subsequently, than animals exposed to less antibiotic).
	Lower resistance in animals exposed to less antibiotic, than those exposed to more antibiotic