WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

Web Annex B. From evidence to recommendations

World Health Organization

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CONTENTS

1. EVIDENCE PROFILES TABLE

These evidence profiles table below are taken, as written, from the University of Calgary systematic review. For details on the information provided in these tables, see full report of "University of Calgary systematic review: restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" in Web Annex A. Evidence base (WHO/NMH/FOS/FZD/17.2; available at: http://apps.who.int/iris/bitstream/10665/259241/1/WHO-NMH-FOS-FZD-17.2-eng.pdf).

PICOD Question 1: For food animal populations of any age in any setting, does a restriction compared to not having that restriction of use of antimicrobial agent(s) in food animals reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistant bacteria in **food animal** populations?									
Quality assessment						**Summary of findings**		**Quality rating**	**Comments**
Design (Number of studies)	**Limitations (Risk of bias)**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Pooled estimates[1]**	**95% CI**		
- Observational study designs, meeting abstracts, dissertations, government reports (n=179)	- Predominantly cross-sectional study designs - Minimal adjustment for important confounders - Potential for selection bias within specific studies - Stratified analysis by three quality	- Direction of effect consistent though there was substantial heterogeneity observed across included studies (as measured by the I^2 statistic for pooled results)	- Interventions varied substantially and author conclusions were at times not consistent with study findings - No discrepancy between	- Though a large number of studies were identified, the absolute risk differences varied somewhat by bacterial family and antibiotic class under investigation	- Potential publication bias present as measured by funnel plot asymmetry (but trim and fill sensitivity analysis did not change results) - No discrepancy between findings published in	Quinolone resistance in *Enterobacteriaceae*: - Faecal samples (n=17) RD=-0.01 (-0.02, -0.00) - Meat samples (n=12) RD=-0.09 (-0.17, -0.02) Cephalosporin resistance in *Enterobacteriaceae*: - Faecal samples		⊕⊕OO LOW	- Pooled estimates showed a consistent reduction in antibiotic resistance for all interventions under investigation. These findings need to be interpreted with the caveat that there was heterogeneity with respect to animal populations under investigation, interventions,

[1] Limited to analyses performed on highest priority critically important antimicrobials

Abbreviations: PICOD (Populations, Intervention, Control/Comparator, Outcome and Design); GRADE (Grading of Recommendations Assessment, Development, and Evaluation); CI (confidence interval); RD (risk difference)

	criteria suggested that lower quality studies may overestimate the risk reduction of antibiotic resistance associated with interventions that reduce antibiotic use in animals. However, though the effect appears less strong, the risk reduction in higher quality studies remained statistically significant. - For genetic analyses: majority were targeted gene detection in phenotypically resistant isolates only		findings when meta-analyses were stratified by type of intervention - Genetic data support phenotypic data of reduced prevalence of resistance genes specific to the restricted antibiotic	- The overall trend of reduced antibiotic resistance in intervention groups compared to control groups was consistent across all bacteria, sample types, and antibiotic classes	journals, abstracts, government reports	(n=17) RD=-0.01 (-0.04, 0.01) - Meat samples (n=11) RD=-0.07 (-0.14, 0.01) Macrolide resistance in *Campylobacter* spp. - Faecal samples (n=11) RD=-0.15 (-0.26, -0.04) -Meat samples (n=7) RD=-0.04 (-0.17, 0.09) Glycopeptide resistance in *Enterococcus* spp. - Faecal samples (n=12) RD=-0.22 (-0.32, -0.12) Multi-drug resistance in *Enterobacteriaceae* - Faecal samples (n=19) RD=-0.24 (-0.32, -0.17) - Meat samples (n=14) RD=-0.32 (-0.43, -0.22)		comparators, outcomes, and study design though stratification by these characteristics did not change the conclusions

<table>
<tr><td colspan="11">PICOD Question 2: Does a restriction compared to not having that restriction of use of antimicrobial agent(s) in food animals reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistant bacteria in human populations?</td></tr>
<tr><th colspan="6">Quality assessment</th><th colspan="2">Summary of findings</th><th rowspan="2">Quality rating</th><th rowspan="2">Comments</th></tr>
<tr><th>Design (number of studies)</th><th>Limitations (risk of bias)</th><th>Inconsistency</th><th>Indirectness</th><th>Imprecision</th><th>Publication bias</th><th>Pooled estimates</th><th>95% CI</th></tr>
<tr><td>- Observational study designs, meeting abstracts, government reports (n=21)

(13 studies included within a formal meta-analysis)</td><td>- Minimal adjustment for important confounders

- Limited reporting to demonstrate that intervention and control groups were comparable

- Potential for selection bias

- Limited generalizability (samples not representative of general population)</td><td>- Direction of effect consistent in pooled analysis. Heterogeneity observed across included studies (I^2=97.4%)

- Inconsistent conclusions drawn by study authors</td><td>- Lack of direct evidence to link limitations in antimicrobial agents in food animals and a 'causal' reduction in antimicrobial resistance in humans</td><td>- Absolute risk differences varied minimally by intervention under investigation, population studied, or antibiotic class tested for resistance</td><td>- Potential publication bias as measured by funnel plot asymmetry (but trim and fill sensitivity analysis did not change results)

- No discrepancy between findings when the single abstract included in meta-analysis was removed in a sensitivity analysis</td><td colspan="2">- Pooled absolute risk differences of antibiotic resistance (n=13 studies)

RD=-0.24 (-0.42, -0.06)

-Stratification by the studied human population

<u>Farm workers (n=9)</u>
RD=-0.29 (-0.54, -0.04)

<u>Not farm workers (n=4)</u>
RD=-0.09 (-0.13, -0.05)</td><td>⊕⊕OO
LOW</td><td>- Pooled estimates showed a reduction in antibiotic resistance in humans when interventions to reduce antibiotic use in animals were implemented. Most of the studies assessed this association within humans who had direct contact with animals. In this population, the risk reduction of antibiotic resistance was greater compared to those without direct contact with animals, though a statistically significant risk reduction was seen for both populations. These findings must be interpreted in light of statistical heterogeneity and in many cases indirect evidence.</td></tr>
</table>

Abbreviations: PICOD (Populations, Intervention, Control/Comparator, Outcome and Design); GRADE (Grading of Recommendations Assessment, Development, and Evaluation); CI (confidence interval); RD (risk difference).

2. EVIDENCE-TO-RECOMMENDATION TABLES

2.1 Recommendation 1

Does a restriction of antimicrobials on the WHO CIA List used in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in humans?	
Problem: Increasing antimicrobial resistance is resulting in increased morbidity and mortality in humans ***Option:*** Restriction of antimicrobials on the WHO CIA List in food-producing animals ***Comparison:*** No restriction of antimicrobials on the WHO CIA List in food-producing animals ***Setting:*** Food-producing animals production and aquaculture worldwide	***Background:*** A systematic review conducted by the WHO in 2014, as part of its Global Surveillance Report, asked the question of whether there were any differences in outcome from infections caused by resistant vs sensitive bacteria found a significantly increased risk of mortality and health care expenditures with antibiotic resistant compared to antibiotic sensitive organisms. Use of antimicrobial agents in food-producing animals results in selection and dissemination of antimicrobial-resistant bacteria and resistant determinants in the intestinal tracts of food-producing animals. Furthermore, pathogenic (e.g., *Salmonella*, *Campylobacter spp*.) and commensal (e.g., *Escherichia coli*, *Enterococcus spp.)* bacteria, including resistant bacteria with resistant determinants, are transmitted to humans through food. Infections with antimicrobial resistant bacteria, including antimicrobial resistant foodborne bacteria (such as non-typhoidal *Salmonella*, *Campylobacter spp*., and *Escherichia coli*) can contribute to more severe human health consequences, including treatment failures, increased or longer hospitalizations, and prolonged illnesses, compared with infections with susceptible bacteria. Antimicrobials are widely used in food-producing animals for treatment, prophylaxis, and growth promotion. Although the quantity of antimicrobials used in food-producing animals is not reported in many countries, it is clear that the quantity of antimicrobials used in food-producing animals is large. Some recent studies indicate that the economic benefits of certain uses, such as growth promotion, are small. A review of the information on the mechanisms of emergence and dissemination of antimicrobial resistance provides strong support for the plausibility of the observed associations between use of antimicrobials in food-producing animals and increased risks of human exposure to and infection by antimicrobial resistant bacteria originating from food-producing animals. Also, intervention studies have examined the impacts of reducing the amounts of antimicrobials used in food-producing animals and have reported associated reductions in antimicrobial resistance in food-producing animals and in humans. These studies have been undertaken in several countries, particularly in Europe, where there has been reliable monitoring of the quantity of antimicrobials used in food-producing animals. These interventions have not resulted in impacts on food animal productivity or food animal health or welfare. We thus sought to critically review the evidence and all other criteria to assess if a recommendation could be made as to whether there should be a restriction of the use of antimicrobials on the WHO CIA List (whether Important, Highly Important, or Critically Important) in food-producing animals, in order to reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in food animal populations and in humans.

	Criteria	Judgement	Research Evidence	Additional Information
Problem	1. Is the problem a priority?	Yes[1]	Antimicrobial resistance has been recognized as a major global public health threat. In the 2014 WHO Antimicrobial Resistance. Global Report on Surveillance, high proportions of resistance were reported in all regions of the world to common treatments for bacteria causing infections in both healthcare settings and in the community. Antibacterial resistance has a negative effect on patient outcomes including both morbidity and mortality and was more costly to the healthcare system. A systematic review published by the WHO in 2014 on the impact of AMR on multiple outcomes including mortality revealed for patients with third-generation cephalosporin resistant (including ESBL) *E. coli* infections there was a significant twofold increase in all-cause mortality, bacterium-attributable mortality and in 30-day mortality; for patients with fluoroquinolone-resistant *E. coli* infections there was a significant twofold increase in both all-cause mortality and 30-day mortality; for patients with third-generation cephalosporin resistant *K. pneumoniae* infections there was: a significant almost two-fold increase in all-cause mortality, bacterium-attributable mortality and 30-day mortality, and in the risk of intensive care unit (ICU) admission; for patients with carbapenem-resistant *K. pneumoniae* infections there was a significant two-fold increase in both all-cause mortality and 30-day mortality; and for patients with methicillin-resistant *S. aureus* infections there was a significant increase in all-cause mortality, bacterium-attributable mortality and ICU mortality, and septic shock. Treatment options for common infections are limited. Food-producing animals are important reservoirs and / or amplifiers of many bacterial infections of humans, including among others non-typhoidal *Salmonella*, *Campylobacter*, and *E. coli*, as well as opportunistic pathogens including *E. coli* and *Enterococcus spp.*	Reference: WHO Antimicrobial Resistance. Global Report on Surveillance 2014 http://www.who.int/drugresistance/documents/surveillancereport/en
Problem	2. Are a large number of people affected?	Yes[1]	Foodborne diseases are a major cause of human morbidity and mortality. According to recent estimates from the WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), foodborne diseases caused 600 million illnesses, 420,000 deaths, and 33 million Disability Adjusted Life Years (DALYs) in 2010 (1). Foodborne diseases are particularly important in children. According to the WHO FERG estimates, although children <5 years of age represent only 9% of the	http://www.who.int/drugresistance/documents/surveillancereport/en/ Reference: Havelaar AH, Kirk MD, Torgerson P, Gibb HJ, Hald T, Lake RJ, Praet N, Bellinger JD, de Silva

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			global population, 40% of the foodborne disease burden is borne by children in this age group. There are also considerable differences in the burden of foodborne diseases among sub-regions with the highest burden of per population observed in Africa. Exact numbers of the global population affected by AROs is difficult to define but in the recent WHO Global Surveillance Report 5 WHO Regions globally had national reports of 50% resistance or more to three of the most commonly reported bacterial strains causing infections in humans. Lord O'Neill, in his recent economic report suggesting the global financial cost of no action would be the loss of 10 million lives a year by 2050 and £ 69 trillion (US$ 100 trillion) a year. Non-typhoidal *Salmonella* caused an estimated 80 million infections and 60,000 deaths and *Campylobacter* caused 95 million infections and 21,000 deaths in 2010. Resistance among these infections is common (e.g. 0-49% resistance to fluoroquinolones among non-typhoidal *Salmonella* infections, depending on region).	NR, Gargouri N, Speybroeck N, Cawthorne A, Mathers C, Stein C, Angulo FJ, Devleesschauwer B. World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. PLoS Medicine 2015; doi: 10.1371/journal.pmed.1001923

	Criteria	Judgement	Research Evidence	Additional Information
Benefits & Harms	1. Are the desirable anticipated effects large?	Yes[1]	Summary of findings: **Outcome (from PICOT Question 1): For food animal populations of any age in any setting, does a restriction compared to not having that restriction of use of antimicrobial agent(s) in food-producing animals reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistant** | **Risk Difference (intervention compared to control groups) (n= no. studies) (95%CI)** | **Certainty of the evidence (GRADE[2])**	Of the two systematic reviews, one was a narrative summary of the findings and the other a quantitative assessment. Both revealed similar findings with respect to the reduction of resistance transfer from food-producing animals to human. Within the quantitative analysis, in the animal studies, 179 described fantibiotic resistance
Benefits & Harms	2. Are the undesirable anticipated effects small?	Yes[1]		
Benefits & Harms	3. What is the overall certainty of this evidence?	Low[3]		

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; and Varies.
[2] Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation)
[3] Selectable options are: No included studies; Very low; Low; Moderate; or High.

	Criteria	Judgement	Research Evidence			Additional Information
			bacteria in food animal populations?			outcomes in animals, of which 80 were meta-analyzed. The pooled absolute risk reduction of the prevalence of antibiotic resistance in animals, with interventions that restricted antibiotic use, varied across different antibiotic classes, bacteria, and sample types, but ranged from 0% to 39%; in general, the prevalence of antibiotic resistance was commonly 10-20% lower in intervention compared to control groups. The pooled prevalence of multi-drug resistance was 24-32% lower in bacteria isolated from intervention groups. These findings held through many different layers of stratification including by intervention type. Twenty-one studies described antibiotic resistance outcomes in humans (19 of which also reported antibiotic resistance in animals), of which 13 were meta-analyzed. In humans, the pooled prevalence of antibiotic resistance was 24% lower in intervention groups (where
			Quinolone resistance in *Enterobacteriaceae*	Faecal samples (n=17) RD=-0.01 (-0.02 to 0.00) Meat samples (n=12) RD=-0.09 (-0.17 to -0.02)	Low	
			Cephalosporin resistance in *Enterobacteriaceae*	Faecal samples (n=17) RD=-0.01 (-0.04 to -0.01) Meat samples (n=11) RD=-0.07 (-0.14 to 0.01)	Low	
			Macrolide resistance in *Campylobacter spp.*	Faecal samples (n=11) RD=-0.15 (-0.26 to -0.04) Meat samples (n=7) RD=-0.04 (-0.17 to 0.09)	Low	
			Macrolide resistance in *Enterococcus spp.*	Faecal samples (n=10) RD= -0.39 (-0.56 to -0.23)	Low	
			Penicillin resistance in *Enterobacteriaceae*	Faecal samples (n=20) RD= -0.12 (-0.18 to -0.07) Meat Samples (n=11) RD= -0.16 (-0.25 to -0.08)	Low	
			Penicillin resistance in *Enterococcus spp.*	Faecal samples (n=7) RD= -0.10 (-0.18 to -0.02)	Low	
			Tetracycline resistance in *Enterobacteriaceae*	Faecal samples (n=21) RD= -0.16 (-0.27 to -0.05) Meat Samples (n=12) RD= -0.20 (-0.36 to -0.03)	Low	

	Criteria	Judgement	Research Evidence			Additional Information
			Glycopeptide resistance in *Enterococcus spp.*	Faecal samples (n=12) RD=-0.22 (-0.32 to -0.12)	Low	interventions to reduce antibiotic use in food-producing animals were implemented) compared to comparator groups. The effect was similar, albeit weaker, when considering humans without direct contact with livestock animals, compared to farm workers. The results were similar with multiple types of stratification, adding to the robustness of the findings.
			Multi-drug resistance in *Enterobacteriaceae*	Faecal samples (n=19) RD=-0.24 (-0.32 to -0.17) Meat samples (n=14). RD=-0.32 (-0.43 to -0.22)	Low	
			Overall antibiotic resistance	With stronger interventions (n=22) RD=0.22 (-0.31 to -0.13) With weaker interventions (n=62) RD=0.16 (-0.18 to -0.14)	Low	
			Outcome (from PICOT Question 2): Does a restriction compared to not having that restriction of use of antimicrobial agent(s) in food-producing animals reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistant bacteria in human populations?	**Risk Difference (intervention compared to control groups) (n= no. studies) (95%CI)**	**Certainty of the evidence (GRADE[1])**	

[1] Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation)

	Criteria	Judgement	Research Evidence			Additional Information
			Resistance to any antimicrobial	Pooled absolute risk differences of antibiotic resistance (n=13 studies) RD=-0.24 (-0.42 to -0.06) Stratification by the studied human population Farm workers (n=9) RD=-0.29 (-0.54 to -0.04) Not farm workers (n=4) RD=-0.09 (-0.13 to -0.05) Stratification by stronger versus weaker interventions Stronger interventions (n=8) RD=-0.14 (-0.20 to -0.08) Weaker interventions (n=5) RD= -0.38 (-0.83 to 0.08)	Low	
			The nature and extent of potential harms will vary depending on the type of antimicrobial use that is restricted and could include one or more of: 1) increased use of antibiotics (such as increased need for antibiotics for treatment purposes) 2) adverse effects on human health, 3) decrease in food and protein availability, 4) food safety, 5) adverse effects on animal health and welfare, 6) adverse effects on animal production, and 7) economic consequences.			

	Criteria	Judgement	Research Evidence	Additional Information
			For details see “Supplemental report to: Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis” and “Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals”. The main conclusions of the former state “Regarding potential unintended consequences, there appears to be a recurring finding of somewhat increased use of therapeutic antibiotic courses in individual animals (though an overall reduction in the volume of antibiotics used) with interventions that restrict antibiotic use, and possible implications for food safety given the possible higher prevalence of bacterial contaminants in these food products.” The main conclusions of the latter report state: • Overall, the adverse consequences of antimicrobial growth promoter bans and other restrictions described in the literature appear to be limited and temporary. • Based on European experiences with terminating antimicrobial growth promoters (AGPs), such adverse effects that may be encountered can be reduced by taking steps to minimize disease in vulnerable classes of animals, especially weaner pigs, and supporting producers in making a transition to more targeted, prudent antimicrobial use. Such steps include improvements in veterinary advice, animal housing, non-antimicrobial disease control strategies and antimicrobial use surveillance. • For future AGP bans, particular care is needed to avoid compensatory increases in antimicrobial use for disease prophylactic or therapeutic purposes, particularly antimicrobials important for therapy in either humans or animals.	

	Criteria	Judgement	Research Evidence	Additional Information
Values	1. How certain is the relative importance of the desirable and	No important uncertainty or	The GDG gave very high ratings to desirable outcomes from restrictions on antimicrobial use in animals; it gave the highest value (median 9, with score of 9 judged of	Public health concerns about the use of antimicrobial agents in food-producing animals have been expressed for decades.

	Criteria	Judgement	Research Evidence	Additional Information
	undesirable outcomes?	variability[1]	"most importance") to the consideration that when people were infected with antimicrobial resistant bacteria, this leads to more severe health outcomes. Also rated highly were desirable outcomes related to decreases in the prevalence of antimicrobial resistant bacteria and/or antimicrobial resistant determinants in food-producing animals (median 8) and humans (median 7-8). Undesirable outcomes were rated of lower importance, including decreases in food animal health and welfare (median 4), decreases in food security (median 2), food safety (median 4), increased therapeutic antimicrobial use in animals following restrictions on growth promoters (median 4), and increased costs to producers and loss of income to national economies (median 3). However, the GDG did give value to the need to protect animal welfare by ensuring availability of antimicrobials to treat sick animals	Many groups have concluded that public health concerns warrant placing restrictions on the use of antimicrobial agents in food-producing animals given that: a. antimicrobial agents used in humans are widely used in food-producing animals, b. use of antimicrobial agents results in antimicrobial resistance, c. food-producing animals are an important source of antimicrobial-resistant bacteria for humans, and infections in humans caused by antimicrobial-resistant bacteria may have more severe health consequences compared with infections caused by antimicrobial-susceptible bacteria.
Values	2. Are the desirable effects large relative to undesirable effects?	Yes[2]	Effects of the interventions on antimicrobial resistance are large (see a summary of the findings table above), and the undesirable effects are relatively small or non-existent (See Supplemental report to: Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" and "Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals).	As mentioned in the O'Neill report, "Undesirable effects poorly quantified and in some cases hypothetical, but probably much smaller than desirable. Desirable effects potentially large"; Lord O'Neill, in his recent economic report suggests the global financial cost of no action would be the loss of 10 million lives a year by 2050 and £69 trillion (US$100 trillion) a year.

	Criteria	Judgement	Research Evidence	Additional Information
Resource	1. Are the resources	Varies[3]	In Denmark, net costs due to productivity losses from	In addition, a study by a major poultry

[1] Selectable options are: Important uncertainty or variability; Possibly important uncertainty or variability; Probably no important uncertainty or variability; No important uncertainty or variability; or No known undesirable outcomes.
[2] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.
[3] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
use	required small?		growth promoter termination were estimated to be 7.75 DKK (1.04 €) per pig produced (1%) and no net cost for poultry. Findings from a general equilibrium model of the Danish economy indicated that AGP termination lowered pig production by about 1.4% per annum and increased poultry production by 0.4% per annum. Impact of AGP termination on the Danish economy was estimated to be a reduction of 0.03% (363 million DKK (48 million €) by 2010 at 1995 prices) in real Gross Domestic Product (GDP). A recent U.S. evaluation estimated that a 1-3% increased cost of production in pigs and broilers would lead to a 1% increase in wholesale prices and drop in output of less than 1%. Another study estimated the potential loss of production and meat value following an AGP ban under two scenarios: 1) effects of AGPs are high (using growth response data from the 1980s), and 2) effects of AGPs are low (using growth response data from the 2000s). They projected that a worldwide ban on AGPs would result in a decrease of global meat production by 1.3% to 3% from its current level (1980s vs. 2000s scenarios). This corresponds to a global loss of between USD 13.5 and USD 44.1 billion in the two scenarios. The costs associated with implementation of the Yellow Card system in Denmark (for reduction in therapeutic / prophylactic use) were estimated to be approximately € 1 million per annum. Variable results from studies examining effects of therapeutic / prophylactic antimicrobial use interventions on animal production, treatment costs, veterinary costs. (For details see above reports).	producer reported little effects of removing growth promoter antimicrobials from poultry.
Resource use	2. Is the incremental cost small relative to the net benefits?	Varies[1]	According to the Lord O'Neill Report, "The value of a delay is potentially enormous": RAND Europe's study demonstrated that delaying the development of	The World Bank recently reviewed the economic impacts of failure to control antimicrobial resistance in terms of reductions

[1] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			widespread resistance by just 10 years could save 65 trillion USD of the world's output between now and 2050" Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/	in national GDP (World Bank Group, Drug-Resistant Infections A Threat to our Economic Future 2016). This analysis indicated large decreases in global economic growth. In contrast to acute economic events such as the 2008-9 financial crisis, these impacts are expected to be prolonged. This analysis indicated substantial inequities in impacts that varied inversely with per capita income such that the poorest countries would experience the greatest decreases in annual economic growth as measured by GDP (figure 3). Overall, under a more optimistic scenario (related to the magnitude of AMR) the losses of world economic output exceeded US$1 trillion annually to reach a total of US$2 trillion per year by 2050. Under a more pessimistic scenario, these losses were estimated to be US$ 3.4 trillion annually to 2030 and US$6.1 trillion annually by 2050. Economic shocks to livestock production were also anticipated due to trade restrictions and consumer fears of food safety. These impacts and associated effects on nutrition and health would also be more severe in low income countries. Health care costs in terms of extra costs associated with AMR infections would also increase significantly. Because of these disparate economic impacts, poverty is anticipated to increase markedly in low income countries

	Criteria	Judgements	Research Evidence	Additional Information
Equity	1. What would be the impact on health inequities?	Probably reduced[1]	In the O'Neill Report, it was indicated that "KPMG looked at what would happen if infection rates doubled and then stayed constant and the analysis suggested an increase in infection rates alone could mean 150 million people dying prematurely and reduce world GDP by 55 trillion USD between now and 2050, just over half the total impact they estimate for AMR." The impact would be greater on low to middle income countries and thus by acting on our recommendations health inequities would be likely reduced.	Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/ See World Bank statement above.
Acceptability	1. Is the option acceptable to key stake-holders?	Yes[2]	Key target audiences are Governments and regulatory agencies, veterinarians, farmers and other food producers, the food production industry, and consumers. Access to antimicrobials varies between countries.	
Feasibility	1. Is the option feasible to implement?	Yes[1]	Reductions in the use of antimicrobials in food-producing animals have been undertaken in several countries, particularly in Europe. The reductions in these countries demonstrate that this option is feasible.	

Balance of consequences	Desirable consequences clearly outweigh undesirable consequences in most settings.

[1] Selectable options are: Increased; Probably increased; Uncertain; Probably reduced; Reduced; or Varies.
[2] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

Reduction of overall use of antimicrobials on the WHO CIA List in food-producing animals?	
Type of recommendation[1]	Strong recommendation for the intervention
Recommendation	We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.
Justification	The evidence shows that restricting use of antimicrobials in food-producing animals reduces the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in humans. The panel determined that this recommendation should be strong despite the low quality evidence due to the large health benefits of lowered antimicrobial resistance. The beneficial human health outcomes are larger than any undesirable outcomes. Furthermore, the systematic review concluded broad restrictions covering all antibiotic classes appear to be more effective in reducing antibiotic resistance compared to narrow restrictions of one antibiotic class or drug and the literature review on mechanisms of resistance supports the biological plausibility of this conclusion. Reducing use of antimicrobials is in accordance with the WHO Global Action Plan which states that "evidence that antimicrobial resistance is driven by the volume of use of antimicrobial agents is compelling".
Implementation considerations	To reduce possible undesirable outcomes, non-antimicrobial options for disease prevention in animals should be implemented, including improved hygiene, improved biosecurity, and better use of vaccines. Some countries may need support for implementation. FAO and OIE may assist countries with implementation (e.g. governance models, taking small holders into account). FAO and OIE may assist with tools for veterinary oversight of antimicrobial use. Countries should implement antimicrobial usage monitoring in order to be able to document reductions in antimicrobial use in animals. Reductions of overall use of antimicrobials in food-producing animals may include any level of reduction of use of antimicrobials in food-producing animals including reductions of a single antimicrobial, reductions of multiple antimicrobials, or combination of reductions of use of antimicrobials. Such reductions may include complete restriction of selected uses as growth promotion use or off-label use, voluntary limitations, or requiring that antimicrobials be used only with oversight by a veterinarian.
Monitoring and evaluation	Quantities of antimicrobials used in food-producing animals should be monitored to determine trends in antimicrobial use in food-producing animals.
Research priorities	While research is compelling concerning the evidence that antimicrobial use selects for antimicrobial resistance, and that reducing antimicrobial use can lead to reduction in antimicrobial resistance, additional research would be helpful to identify the most effective disease prevention strategies for reducing antimicrobial use, alternatives to antimicrobials, and the most effective methods for implementing antimicrobial stewardship programs in food-producing animals.

[1] Selectable options are: Strong recommendation against the intervention; Conditional recommendation against the intervention; Conditional recommendation for either the intervention or the comparison; Conditional recommendation for the intervention; or Strong recommendation for the intervention.

2.2 Recommendation 2

Does complete restriction of classes of antimicrobials on the WHO CIA List used in food-producing animals for purposes of growth promotion, compared to no such restriction, reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in humans?	
Problem: Increasing antimicrobial resistance is resulting in increased morbidity and mortality in humans ***Option:*** Complete restriction of antimicrobials on the WHO CIA List for growth promotion in food-producing animals ***Comparison:*** No restriction of use of antimicrobials on the WHO CIA List for growth promotion in food-producing animals ***Setting:*** Food animal production and aquaculture worldwide	***Background:*** A systematic review conducted by the WHO in 2014, as part of its Global Surveillance Report, asked the question of whether there were any differences in outcome from infections caused by resistant vs sensitive bacteria found a significantly increased risk of mortality and health care expenditures with antibiotic resistant compared to antibiotic sensitive organisms. Use of antimicrobial agents in food-producing animals results in selection and dissemination of antimicrobial-resistant bacteria and resistant determinants in the intestinal tracts of food-producing animals. Furthermore, pathogenic (e.g., *Salmonella*, *Campylobacter spp.*) and commensal (e.g., *Escherichia coli*, *Enterococcus spp.*) bacteria, including resistant bacteria with resistant determinants, are transmitted to humans through food. Infections with antimicrobial resistant bacteria, including antimicrobial resistant foodborne bacteria (such as non-typhoidal *Salmonella*, *Campylobacter spp.*, and *Escherichia coli*) can contribute to more severe human health consequences, including treatment failures, increased or longer hospitalizations, and prolonged illnesses, compared with infections with susceptible bacteria. The use of antimicrobial agents as growth promoters in animals is concerning because such use exposes large numbers of animals for prolonged periods of time to low doses of antimicrobials for reasons related to production efficiency rather than therapy of sick animals. In some countries, members of classes of antimicrobials important to human health are (or were) used as growth promoters. For example, avoparcin, a glycopeptide antimicrobial, was widely used in Europe, Australia and other countries as a growth promoting feed additive in swine and poultry. Such use selected for resistance in enterococci to vancomycin, a glycopeptide antimicrobial use for treatment of important human infections. In some countries, tetracyclines, penicillins, macrolides, polymyxins and other drugs important to human health are used for growth promotion, and have been shown to select for resistance to these and other classes of drugs. We thus sought to critically review the evidence and all other criteria to assess if a recommendation could be made as to whether there should be complete restriction of the use of antimicrobials on the WHO CIA List (whether Important, Highly Important, or Critically Important) for purposes of growth promotion in animals, in order to reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in food animal populations and in humans.

	Criteria	Judgement	Research Evidence	Additional Information
Problem	1. Is the problem a priority?	Yes[1]	Antimicrobial resistance has been recognized as a major global public health threat. In the 2014 WHO Antimicrobial Resistance. Global Report on Surveillance, high proportions of resistance were reported in all regions of the world to common treatments for bacteria causing infections in both healthcare settings and in the community. Antibacterial resistance has a negative effect on patient outcomes including both morbidity and mortality and was more costly to the healthcare system. A systematic review published by the WHO in 2014 on the impact of AMR on multiple outcomes including mortality revealed for patients with third-generation cephalosporin resistant (including ESBL) *E. coli* infections there was a significant twofold increase in all-cause mortality, bacterium-attributable mortality and in 30-day mortality; for patients with fluoroquinolone-resistant *E. coli* infections there was a significant twofold increase in both all-cause mortality and 30-day mortality; for patients with third-generation cephalosporin resistant *K. pneumoniae* infections there was: a significant almost two-fold increase in all-cause mortality, bacterium-attributable mortality and 30-day mortality, and in the risk of intensive care unit (ICU) admission; for patients with carbapenem-resistant *K. pneumoniae* infections there was a significant two-fold increase in both all-cause mortality and 30-day mortality; and for patients with methicillin-resistant *S. aureus* infections there was a significant increase in all-cause mortality, bacterium-attributable mortality and ICU mortality, and septic shock. Treatment options for common infections are limited. Food-producing animals are important reservoirs and / or amplifiers of many bacterial infections of humans, including among others non-typhoidal *Salmonella*, *Campylobacter*, and *E. coli*, as well as opportunistic pathogens including *E. coli* and *Enterococcus spp.*	Reference: WHO Antimicrobial Resistance. Global Report on Surveillance 2014 http://www.who.int/drugresistance/documents/surveillancereport/en/
Problem	2. Are a large number of people affected?	Yes[1]	Foodborne diseases are a major cause of human morbidity and mortality. According to recent estimates from the WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), foodborne diseases caused 600 million illnesses, 420,000 deaths, and 33 million Disability Adjusted Life Years (DALYs) in 2010 (1). Foodborne diseases are particularly important in children. According to the WHO FERG estimates, although children <5 years of age represent only 9% of the	http://www.who.int/drugresistance/documents/surveillancereport/en/ Reference: Havelaar AH, Kirk MD, Torgerson P, Gibb HJ, Hald T, Lake RJ, Praet N, Bellinger JD, de Silva

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			global population, 40% of the foodborne disease burden is borne by children in this age group. There are also considerable differences in the burden of foodborne diseases among sub-regions with the highest burden of per population observed in Africa. Exact numbers of the global population affected by AROs is difficult to define but in the recent WHO Global Surveillance Report 5 WHO Regions globally had national reports of 50% resistance or more to three of the most commonly reported bacterial strains causing infections in humans. Lord O'Neill, in his recent economic report suggesting the global financial cost of no action would be the loss of 10 million lives a year by 2050 and £ 69 trillion (US$ 100 trillion) a year. Non-typhoidal *Salmonella* caused an estimated 80 million infections and 60,000 deaths and *Campylobacter* caused 95 million infections and 21,000 deaths in 2010. Resistance among these infections is common (e.g. 0-49% resistance to fluoroquinolones among non-typhoidal *Salmonella* infections, depending on region).	NR, Gargouri N, Speybroeck N, Cawthorne A, Mathers C, Stein C, Angulo FJ, Devleesschauwer B. World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. PLoS Medicine 2015; doi: 10.1371/journal.pmed.1001923

	Criteria	Judgement	Research Evidence	Additional Information
Benefits & Harms	1. Are the desirable anticipated effects large?	Yes[1]	**Summary of findings:** **Outcome: Reduction of the presence of antimicrobial-resistant bacteria and/or genetic elements in animals and humans with a complete restriction of growth promotion use in food-producing animals of classes of** | **Risk Difference (intervention compared to control groups) (n= no. studies) (95%CI)** | **Certainty of the evidence (GRADE[2])**	Summary of findings data from the systematic reviews (SR) are provided for antimicrobials that are listed the on the current WHO CIA List. Risk differences reflect uses of these antimicrobials as reported in the papers found and analyzed related to "growth promotion". A total of 27 studies were identified in the quantitative analysis of which 15 were meta-analyzed for the outcome of
Benefits & Harms	2. Are the undesirable anticipated effects small?	Yes[1]		
Benefits & Harms	3. What is the overall certainty of this evidence?	Low[3]		

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; and Varies.
[2] Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation)
[3] Selectable options are: No included studies; Very low; Low; Moderate; or High.

	Criteria	Judgement	Research Evidence			Additional Information
			antimicrobials classified as critically important on the WHO CIA list, compared to no such restriction			animal resistance and 7 studies for humans of which 6 could be meta-analyzed.
			Antimicrobial resistance in animals	RD= -0.29 (-0.40 to -0.19) n=27 15 were meta-analysed	Low	
			Antimicrobial resistance in humans	RD = -0.13 (-0.20 to -0.06) n=7 6 were meta-analysed	Low	
			Possible harms include adverse effects on: 1) increased use of antibiotics (such as increased need for antibiotics for treatment purposes) 2) adverse effects on human health, 3) decrease in food and protein availability, 4) food safety, 5) adverse effects on animal health and welfare, 6) adverse effects on animal production, and 7) economic consequences. For details see "Supplemental report to: Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" and "Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals". The main conclusions of the former state "Regarding potential unintended consequences, there appears to be a recurring finding of somewhat increased use of therapeutic antibiotic courses in individual animals (though an overall reduction in the volume of antibiotics used) with interventions that restrict antibiotic use, and possible implications for food safety given the possible higher prevalence of bacterial contaminants in these food products." The main conclusions of the latter report state:			

	Criteria	Judgement	Research Evidence	Additional Information
			• Overall, the adverse consequences of AGP (antimicrobial growth promoter) bans and other restrictions described in the literature appear to be limited and temporary. • Based on European experiences with terminating AGPs, such adverse effects that may be encountered can be reduced by taking steps to minimize disease in vulnerable classes of animals, especially weaner pigs, and supporting producers in making a transition to more targeted, prudent antimicrobial use. Such steps include improvements in veterinary advice, animal housing, non-antimicrobial disease control strategies and antimicrobial use surveillance. • For future AGP bans, particular care is needed to avoid compensatory increases in antimicrobial use for disease prophylactic or therapeutic purposes, particularly antimicrobials important for therapy in either humans or animals.	

	Criteria	Judgement	Research Evidence	Additional Information
Values	1. How certain is the relative importance of the desirable and undesirable outcomes?	No important uncertainty or variability[1]	The GDG gave very high ratings to desirable outcomes from restrictions on antimicrobial use in animals; it gave the highest value (median 9, with score of 9 judged of "most importance") to the consideration that when people were infected with antimicrobial resistant bacteria, this leads to more severe health outcomes. Also rated highly were desirable outcomes related to decreases in the prevalence of antimicrobial resistant bacteria and/or antimicrobial resistant determinants in food-producing animals (median 8) and humans (median 7-8). Undesirable outcomes were rated of lower importance, including decreases in food animal health and welfare (median 4), decreases in food security (median 2), food safety (median 4), increased therapeutic antimicrobial use in animals following restrictions on growth promoters (median 4), and increased costs to producers and loss of income to	Public health concerns about the use of antimicrobial agents in food-producing animals have been expressed for decades. Many groups have concluded that public health concerns warrant placing restrictions on the use of antimicrobial agents in food-producing animals given that: a. antimicrobials agents used in humans are widely used in food-producing animals, b. use of antimicrobial agents results in antimicrobial resistance, c. food-producing animals are an important source of antimicrobial-resistant bacteria for humans, and infections in humans caused by antimicrobial-resistant bacteria may have more severe health consequences compared with infections caused by antimicrobial-

[1] Selectable options are: Important uncertainty or variability; Possibly important uncertainty or variability; Probably no important uncertainty or variability; No important uncertainty or variability; or No known undesirable outcomes.

	Criteria	Judgement	Research Evidence	Additional Information
			national economies (median 3).	susceptible bacteria.
Values	2. Are the desirable effects large relative to undesirable effects?	Yes[1]	Effects of the intervention on antimicrobial resistance are large (see a summary of the findings table above), and the undesirable effects are relatively small or non-existent (See Supplemental report to: Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" and "Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals).	As mentioned in the O'Neill report, desirable effects potentially large; Lord O'Neill, in his recent economic report suggests the global financial cost of no action would be the loss of 10 million lives a year by 2050 and £ 69 trillion (US$ 100 trillion) a year.

	Criteria	Judgement	Research Evidence	Additional Information
Resource use	1. Are the resources required small?	Varies[2]	The resources required to reduce [or eliminate] antimicrobial growth promotion (AGP) use of antimicrobials in food-producing animals include two general types. Governments may require some resources to direct and monitor food-production facilities, including feedmills, farms and aquaculture facilities. These resources are small. AGPs are thought to provide, in some cases, small improvements in feed efficiency, allowing farmers to reduce total inputs; and possibly to reduce heterogeneity of animal growth, thus reducing production costs. It appears that there has been a reduction in the effectiveness of AGPs over the last 50 years, for reasons that are not well understood (Laxminarayan 2015). The most probable estimate of the loss in production is approximately 1.3% to 3%, or approximately US$13.5bn to US$45.1bn annually (Laxminarayan, 2015). However, in many well-designed studies, there appear to be no benefits from AGPs (Graham 2008). It appears that the effects are smallest in countries with high biosecurity and optimized production systems; further, producers can compensate	Potential resource costs from prohibition of antimicrobial growth promoters include: • Regulatory changes (transactional costs) • Increased efforts by veterinary services and farming groups to help producers transition away from growth promoters • Added resources for monitoring of antimicrobial use Laxminarayan, R., T. Van Boeckel and A. Teillant (2015), "The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector", OECD Food, Agriculture and Fisheries Papers, No. 78, OECD Publishing. http://dx.doi.org/10.1787/5js64kst5wvl-en Stacy Sneeringer, James MacDonald, Nigel Key, William McBride, and Ken Mathews. Economics of antibiotic use in U.S. livestock

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.
[2] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			for the withdrawal of AGPs by improved biosecurity, vaccination, etc. There are no estimates of the cost of these alternatives, but the costs of eliminating AGPs are bounded by the anticipated loss in production. Generally, it appears that as production systems are re-optimized, the loss in production declines (USDA 2015). Thus, there are likely to be decreasing costs over time.	production, ERR-200, U.S. department of agriculture, economic research service, November 2015. Graham, J.P., Boland, J.J., and Silbergeld, E. (2007). Growth promoting antibiotics in food animal production: An economic analysis. Public Health Rep. 122 , 79– 87. Taylor, Jirka, Marco Hafner, Erez Yerushalmi, Richard Smith, Jacopo Bellasio, Raffaele Vardavas, Teresa Bienkowska-Gibbs and Jennifer Rubin. Estimating the economic costs of antimicrobial resistance: Model and Results. Santa Monica, CA: RAND Corporation, 2014. http://www.rand.org/pubs/research_reports/RR911.html.
Resource use	2. Is the incremental cost small relative to the net benefits?	Varies[1]	The incremental cost of eliminating the use of AGPs globally, discussed above, appears to be in the range of US$20bn per year, but likely declining over time. It is even more challenging to estimate the financial value of the net benefits. One estimate of the value of delaying widespread resistance by ten years is approximately USD65 trillion or approximately one year's global GDP (RAND 2014). AGPs, of course, are not the only contributor to resistance. Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/	The World Bank recently reviewed the economic impacts of failure to control antimicrobial resistance in terms of reductions in national GDP (World Bank Group, Drug-Resistant Infections A Threat to our Economic Future 2016). This analysis indicated large decreases in global economic growth. In contrast to acute economic events such as the 2008-9 financial crisis, these impacts are expected to be prolonged. This analysis indicated substantial inequities in impacts that varied inversely with per capita income such that the poorest countries would experience the greatest decreases in annual economic growth as measured by GDP (figure 3). Overall, under a more optimistic scenario

[1] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
				(related to the magnitude of AMR) the losses of world economic output exceeded US$1 trillion annually to reach a total of US$2 trillion per year by 2050. Under a more pessimistic scenario, these losses were estimated to be US$ 3.4 trillion annually to 2030 and US$6.1 trillion annually by 2050. Economic shocks to livestock production were also anticipated due to trade restrictions and consumer fears of food safety. These impacts and associated effects on nutrition and health would also be more severe in low income countries. Health care costs in terms of extra costs associated with AMR infections would also increase significantly. Because of these disparate economic impacts, poverty is anticipated to increase markedly in low income countries

	Criteria	Judgements	Research Evidence	Additional Information
Equity	1. What would be the impact on health inequities?	Probably reduced[1]	In the O'Neill Report, it was indicated that "KPMG looked at what would happen if infection rates doubled and then stayed constant and the analysis suggested an increase in infection rates alone could mean 150 million people dying prematurely and reduce world GDP by 55 trillion USD between now and 2050, just over half the total impact they estimate for AMR." The impact would be greater on low to middle income countries and thus by acting on our recommendations health inequities would be likely reduced.	Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/ Also see the World Bank statement mentioned above.
Acceptability	1. Is the option acceptable to key stake-	Probably yes[2]	Key target audiences are governments and regulatory agencies, veterinarians, farmers and other food producers, the food production industry, and consumers.	Concerns about possible adverse effects have been raised by farmers and veterinarians. See information above under "Are the resources

[1] Selectable options are: Increased; Probably increased; Uncertain; Probably reduced; Reduced; or Varies.
[2] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgements	Research Evidence	Additional Information
	holders?		Access to antimicrobials varies between countries.	required small?".
Feasibility	1. Is the option feasible to implement?	Yes[1]	Prohibition of use of growth promoters has been implemented in all European Union countries and additional countries are planning or recently have revoked approvals for antimicrobial growth promoters (i.e. over-the-counter, in-feed "production uses").	

Balance of consequences	Desirable consequences clearly outweigh undesirable consequences in most settings.

Complete restriction of use of antimicrobials on the WHO CIA List for growth promotion in animals?	
Type of recommendation[1]	Strong recommendation for the intervention
Recommendation	We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.
Justification	The panel determined that this recommendation should be strong despite the low quality evidence due to the potential large health benefits of lowered antimicrobial resistance in humans resulting from the complete restriction of use of antimicrobials for growth promotion. This conclusion is based upon the systematic review that found consistent evidence that restriction of growth promotion use of antimicrobials in food-producing animals reduces the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance that can be transmitted to humans. The review of molecular mechanisms also supports this conclusion since bacteria exposed to lower concentrations, as in growth promotion, have an increased efficiency for emergence and dissemination of antimicrobial resistance. Furthermore, undesirable consequences associated with complete restriction of growth promotion use of antimicrobials in food-producing animals appear to be relatively small or non-existent. Finally, complete restriction of growth promotion use of antimicrobials in food-producing animals has been accomplished successfully in multiple countries demonstrating its feasibility. Reducing use of antimicrobials is in accordance with the WHO Global Action Plan which states that "evidence that antimicrobial resistance is driven by the volume of use of antimicrobial agents is compelling".
Implementation considerations	To reduce possible undesirable outcomes, non-antimicrobial options for disease prevention in animals should be implemented, including improved hygiene, improved biosecurity, and better use of vaccines. Particular care is needed to avoid compensatory increases in antimicrobial use for disease prophylactic or therapeutic purposes, particularly antimicrobials important for therapy in either humans or animals. Experience gained in prohibition of antimicrobial growth promoters in Europe should be made widely available in other regions. A detailed WHO report of the effects of the prohibition in Denmark on antimicrobial resistance, animal production, food safety, national economy and other parameters, is available (WHO, 2002). Provision should be made to assist developing regions with implementation, which could include implementation and follow-up monitoring in AGISAR country pilot projects (e.g. Bangladesh, India, Kenya, Rwanda, Tanzania). Some countries may need support for implementation. FAO and OIE may assist countries with implementation (e.g. alternatives to growth promoters, governance models, taking small holders into account). FAO and OIE may assist with tools for veterinary oversight of antimicrobial use. Among the antimicrobials not currently used in human medicine, special consideration can be given to ionophores - which are a class of antimicrobial agents widely used in food-producing animals in some countries and which are not used in human medicine.
Monitoring and evaluation	National antimicrobial resistance and antimicrobial use surveillance programs, using the integrated One Health approach, should evaluate the effect of implementation of prohibition. Quantities of prophylactic and therapeutic antimicrobials used in food-

[1] Selectable options are: Strong recommendation against the intervention; Conditional recommendation against the intervention; Conditional recommendation for either the intervention or the comparison; Conditional recommendation for the intervention; or Strong recommendation for the intervention.

	producing animals should be monitored in food-producing animals to determine trends.
Research priorities	Alternatives to antimicrobial growth promoters (e.g. vaccines, probiotics), improved hygiene and animal health.

2.3 Recommendation 3

Does complete restriction of the routine use of antimicrobials on the WHO CIA List for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?	
Problem: Increasing antimicrobial resistance is resulting in increased morbidity and mortality in humans ***Option:*** Complete restriction of routine use of antimicrobials on the WHO CIA List for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals ***Comparison:*** No such restriction in food-producing animals ***Setting:*** Food animal production and aquaculture worldwide	***Background:*** Antimicrobials important to human health (i.e. all of those on the WHO CIA List, whether Important, Highly Important, or Critically Important) are in many countries approved for use in food-producing animals for disease prevention/prophylactic use, i.e. use of an antimicrobial(s) in healthy animals (individually or in groups) considered to be at risk of infectious diseases but prior to the onset of clinical infectious disease in those animals. More simply, such use constitutes treatment with antimicrobials in the absence of disease. Disease prevention/prophylactic use, particularly when such use is regular or routine, has been shown to select for resistance among human pathogens and commensals. We thus sought to critically review the evidence and all other criteria to assess if a recommendation could be made as to whether complete restriction of the routine use of classes of antimicrobials important to human health (i.e. all those on the WHO CIA list) in healthy animals considered to be at risk of infectious diseases but prior to the onset of clinical infectious disease in those animals, compared to no such restriction, would reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans. According to Codex Alimentarius, prophylactic use of antimicrobials in food-producing animals is defined as the use of an antimicrobial(s) in a group of healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. Prophylaxis in food-producing animals therefore includes control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals (disease control), and prevention of an infectious disease in a group of animals that has not yet been clinically diagnose (disease prevention). This restriction option being considered pertains only to the disease prevention type of prophylaxis: the use of antimicrobials in group of healthy food-producing animals considered to be at risk of infectious diseases but prior to the onset of clinical infectious disease in those animals. This can also be described as the prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals, or, more simply, prevention in the absence of disease.

	Criteria	Judgement	Research Evidence	Additional Information
Problem	1. Is the problem a priority?	Yes[1]	Antimicrobial resistance has been recognized as a major global public health threat. In the 2014 WHO Antimicrobial Resistance. Global Report on Surveillance, high proportions of resistance were reported in all regions of the world to common treatments for bacteria causing infections in both healthcare settings and in the community. Antibacterial resistance has a negative effect on patient outcomes including both morbidity and mortality and was more costly to the healthcare system .A systematic review published by the WHO in 2014 on the impact of AMR on multiple outcomes including mortality revealed for patients with third-generation cephalosporin resistant (including ESBL) *E. coli* infections there was a significant twofold increase in all-cause mortality, bacterium-attributable mortality and in 30-day mortality; for patients with fluoroquinolone-resistant *E. coli* infections there was a significant twofold increase in both all-cause mortality and 30-day mortality; for patients with third-generation cephalosporin resistant *K. pneumoniae* infections there was: a significant almost two-fold increase in all-cause mortality, bacterium-attributable mortality and 30-day mortality, and in the risk of intensive care unit (ICU) admission; for patients with carbapenem-resistant *K. pneumoniae* infections there was a significant two-fold increase in both all-cause mortality and 30-day mortality; and for patients with methicillin-resistant *S. aureus* infections there was a significant increase in all-cause mortality, bacterium-attributable mortality and ICU mortality, and septic shock. Treatment options for common infections are limited. Food-producing animals are important reservoirs and / or amplifiers of many bacterial infections of humans, including among others non-typhoidal *Salmonella*, *Campylobacter*, and *E. coli*, as well as opportunistic pathogens including *E. coli* and *Enterococcus spp*.	Reference : WHO Antimicrobial Resistance. Global Report on Surveillance 2014 http://www.who.int/drugresistance/documents/surveillancereport/en/
Problem	2. Are a large number of people affected?	Yes[1]	Foodborne diseases are a major cause of human morbidity and mortality. According to recent estimates from the WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), foodborne diseases caused 600 million illnesses, 420,000 deaths, and 33 million Disability Adjusted Life Years (DALYs) in 2010 (1). Foodborne diseases are particularly important in children. According to the WHO FERG	http://www.who.int/drugresistance/documents/surveillancereport/en/ Reference: Havelaar AH,

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			estimates, although children <5 years of age represent only 9% of the global population, 40% of the foodborne disease burden is borne by children in this age group. There are also considerable differences in the burden of foodborne diseases among sub-regions with the highest burden of per population observed in Africa. Exact numbers of the global population affected by AROs is difficult to define but in the recent WHO Global Surveillance Report five WHO Regions globally had national reports of 50% resistance or more to three of the most commonly reported bacterial strains causing infections in humans. Lord O'Neill, in his recent economic report suggested the global financial cost of no action would be the loss of 10 million lives a year by 2050 and £ 69 trillion (US$ 100 trillion) a year. Non-typhoidal *Salmonella* caused an estimated 80 million infections and 60,000 deaths and *Campylobacter* caused 95 million infections and 21,000 deaths in 2010. Resistance among these infections is common (e.g. 0-49% resistance to fluoroquinolones among non-typhoidal *Salmonella* infections, depending on region).	Kirk MD, Torgerson P, Gibb HJ, Hald T, Lake RJ, Praet N, Bellinger JD, de Silva NR, Gargouri N, Speybroeck N, Cawthorne A, Mathers C, Stein C, Angulo FJ, Devleesschauwer B. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. PLoS Medicine 2015; doi: 10.1371/journal.pmed.1001923

	Criteria	Judgement	Research Evidence	Additional Information
Benefits & Harms	1. Are the desirable anticipated effects large?	Probably yes[1]	**Summary of findings:**	Summary of findings data from the systematic reviews (SR) are provided for antimicrobials that are listed the on the current WHO CIA List. Risk differences reflect uses of these antimicrobials as reported in the papers found and analyzed related to "nontherapeutic" use which would have included prophylaxis referring to use of (an) antimicrobial(s) in
Benefits & Harms	2. Are the undesirable anticipated effects small?	Probably yes[1]		
Benefits & Harms	3. What is the overall certainty of this evidence?	Low[3]		

Outcome:Reduction of the presence of antimicrobial-resistant bacteria and/or genetic elements in animals and humans with a complete restriction of non-therapeutic use, which included prophylactic use in	Risk Difference or Odds Ratios (intervention compared to control groups) (n= no. studies) (95% CI)	Certainty of the evidence (GRADE[2])

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; and Varies.
[2] Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation)
[3] Selectable options are: No included studies; Very low; Low; Moderate; or High.

<table>
<tr><th></th><th>Criteria</th><th>Judgement</th><th>Research Evidence</th><th>Additional Information</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>food-producing animals of classes of antimicrobials classified as critically important on the WHO CIA list, compared to no such restriction</td><td></td><td></td></tr>
<tr><td>Antimicrobial resistance in animals</td><td>RD = -0.08 (-0.11 to -0.06) (n=36; 26 were meta-analyzed)</td><td>Low</td></tr>
<tr><td>Antimicrobial resistance in humans</td><td>RD = -0.08 (-0.20 to 0.04)
RD = -0.25 (-0.34 to -0.16) (n=2; not meta-analyzed due to different units of analysis)

OR 1.17 (0.98 to1.39) for antimicrobial use in animals (2 fold increase in unit exposure) for LA-MRSA in humans

OR 0.19 (0.07 to 0.53) for LA-MRSA carriage in intervention arm</td><td>Low</td></tr>
</table>
Possible harms include adverse effects on:
1) increased use of antibiotics (such as increased need for antibiotics for treatment purposes)
2) adverse effects on human health,
3) decrease in food and protein availability,
4) food safety,
</td><td>healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease, as well as for control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and growth promotion. It was not possible to identify what the percentage use of each of the categories would have been in these studies. A total of 36 studies were identified in the quantitative analysis of which 26 were meta-analyzed for the outcome of animal resistance and 2 studies for human resistance and a RD was determined for both. The two human studies could not be combined for a meta-analysis since one uses isolates as the unit of analysis and the other uses sample as the unit of analysis. Two additional studies from Group 6 where it could be discerned that prophylaxis was used with human resistance outcomes were also included but were not amenable to meta-analysis but had ORs for</td></tr>
</table>

	Criteria	Judgement	Research Evidence	Additional Information
			5) adverse effects on animal health and welfare, 6) adverse effects on animal production, and 7) economic consequences. In the case of complete restriction of routine prevention/prophylactic use of classes of antimicrobials important to human health (i.e. all those on the WHO CIA list) in healthy animals considered to be at risk of infectious diseases but prior to the onset of clinical infectious disease in those animals, the most relevant possible type of harm is 1) increased use of antibiotics (such as increased need for antibiotics for treatment purposes). For details see "Supplemental report to: Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" and "Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals". The main conclusions of the former state "Regarding potential unintended consequences, there appears to be a recurring finding of somewhat increased use of therapeutic antibiotic courses in individual animals (though an overall reduction in the volume of antibiotics used) with interventions that restrict antibiotic use, and possible implications for food safety given the possible higher prevalence of bacterial contaminants in these food products." The main conclusions of the latter report that are relevant to prophylaxis state: • Such adverse effects that may be encountered can be reduced by taking steps to minimize disease in vulnerable classes of animals, especially weaner pigs, and supporting producers in making a transition to more targeted, prudent antimicrobial use. Such steps include improvements in veterinary advice, animal housing, non-antimicrobial disease control strategies and antimicrobial use surveillance.	comparison. . Twenty-one studies described antibiotic resistance outcomes in humans (19 of which also reported antibiotic resistance in animals), of which 13 were meta-analyzed. In humans, the pooled prevalence of antibiotic resistance was 24% lower in intervention groups (where interventions to reduce antibiotic use in food-producing animals were implemented) compared to control groups. The effect was similar, albeit weaker, when considering humans without direct contact with livestock animals, compared to farm workers.

	Criteria	Judgement	Research Evidence	Additional Information
Values	1. How certain is the relative importance of the desirable and undesirable outcomes?	Probably no important uncertainty or	The GDG gave very high ratings to desirable outcomes from restrictions on antimicrobial use in animals; it gave the highest value (median 9, with score of 9 judged of "most importance") to the consideration that when	Public health concerns about the use of antimicrobial agents in food-producing animals have been expressed for decades. Many groups have concluded that public

	Criteria	Judgement	Research Evidence	Additional Information
		variability[1]	people were infected with antimicrobial resistant bacteria, this leads to more severe health outcomes. Also rated highly were desirable outcomes related to decreases in the prevalence of antimicrobial resistant bacteria and/or antimicrobial resistant determinants in food-producing animals (median 8) and humans (median 7-8). Undesirable outcomes were rated of lower importance, including decreases in food animal health and welfare (median 4), decreases in food security (median 2), food safety (median 4), increased therapeutic antimicrobial use in animals following restrictions on growth promoters (median 4), and increased costs to producers and loss of income to national economies (median 3).	health concerns warrant placing restrictions on the use of antimicrobial agents in food-producing animals given that: a. antimicrobials agents used in humans are widely used in food-producing animals, b. use of antimicrobial agents results in antimicrobial resistance, c. food-producing animals are an important source of antimicrobial-resistant bacteria for humans, and infections in humans caused by antimicrobial-resistant bacteria may have more severe health consequences compared with infections caused by antimicrobial-susceptible bacteria.
Values	2. Are the desirable effects large relative to undesirable effects?	Probably yes[2]		

	Criteria	Judgement	Research Evidence	Additional Information
Resource use	1. Are the resources required small?	Uncertain[3]	The resources required to eliminate prophylactic use of antimicrobials in food-producing animals include two general types. Governments may require some resources to direct and monitor food-production facilities, including feedmills, farms and aquaculture facilities. These resources are small. Antibiotic prophylaxis is an alternative to good hygiene practices, vaccination, and biosecurity in food production. Some studies have found that the use of vaccines could substantially replace the prophylactic use of antibiotics in food-producing animals, but there is a need for more research in this area (Bak and Rathkjen, 2009; Allen et al 2009). There are no	Bak H, Rathkjen PH, Reduced Use of Antimicrobials after Vaccination of Pigs Against Porcine Proliferative Enteropathy in a Danish SPF Herd. Acta Veterinaria Scandinavica 2009, 51(1). Allen H K, Levine UY, Looft T, Bandrick M Casey TA, Treatment, Promotion, Commotion: Antibiotic Alternatives in Food-Producing Animals. Trends in Microbiology, 2013, 21(3), 114-119.

[1] Selectable options are: Important uncertainty or variability; Possibly important uncertainty or variability; Probably no important uncertainty or variability; No important uncertainty or variability; or No known undesirable outcomes.
[2] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.
[3] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			known estimates of the cost-effectiveness of antibiotic prophylaxis distinct from AGPs and so it is difficult to provide clear estimates of the resources required to stop the use of prophylactic antibiotics. Because of increasing resistance, the value of prophylaxis is declining.	
Resource use	2. Is the incremental cost small relative to the net benefits?	Varies[1]	The incremental cost of eliminating the use of AGPs globally, discussed above, appears to be in the range of US$20bn per year, but likely declining over time. It is even more challenging to estimate the financial value of the net benefits. One estimate of the value of delaying widespread resistance by ten years is approximately USD65 trillion or approximately one year's global GDP (RAND 2014).	Resistance: Tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/

	Criteria	Judgements	Research Evidence	Additional Information
Equity	1. What would be the impact on health inequities?	Uncertain[2]	In the O'Neill Report, it was indicated that "KPMG looked at what would happen if infection rates doubled and then stayed constant and the analysis suggested an increase in infection rates alone could mean 150 million people dying prematurely and reduce world GDP by 55 trillion USD between now and 2050, just over half the total impact they estimate for AMR." The impact would be greater on low to middle income countries and thus by acting on our recommendations health inequities would be likely reduced. Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/	The World Bank recently reviewed the economic impacts of failure to control antimicrobial resistance in terms of reductions in national GDP (World Bank Group, Drug-Resistant Infections A Threat to our Economic Future 2016). This analysis indicated large decreases in global economic growth. In contrast to acute economic events such as the 2008-9 financial crisis, these impacts are expected to be prolonged. This analysis indicated substantial inequities in impacts that varied inversely with per capita income such that the poorest countries would experience the greatest decreases in annual economic growth as measured by GDP (figure 3). Overall, under a more optimistic scenario (related to the magnitude of AMR) the losses of world economic output exceeded US$1

[1] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.
[2] Selectable options are: Increased; Probably increased; Uncertain; Probably reduced; Reduced; or Varies.

	Criteria	Judgements	Research Evidence	Additional Information
				trillion annually to reach a total of US$2 trillion per year by 2050. Under a more pessimistic scenario, these losses were estimated to be US$ 3.4 trillion annually to 2030 and US$6.1 trillion annually by 2050. Economic shocks to livestock production were also anticipated due to trade restrictions and consumer fears of food safety. These impacts and associated effects on nutrition and health would also be more severe in low income countries. Health care costs in terms of extra costs associated with AMR infections would also increase significantly. Because of these disparate economic impacts, poverty is anticipated to increase markedly in low income countries
Acceptability	1. Is the option acceptable to key stake-holders?	Varies[1]	Key target audience are Governments and regulatory agencies, veterinarians, farmers and other food producers, the food production industry, and consumers.	Concerns about additional restrictions to antimicrobial prescribing have been raised by veterinarians.
Feasibility	1. Is the option feasible to implement?	Yes[1]		Some countries have implemented programs for substantial reduction of antimicrobial use without many problems. Feasibility of implantation in other countries depends on access to laboratory facilities for culture and sensitivity testing (to enable use when justified) as well as resistance patterns to antimicrobials classified Very Important and Important (more feasible if less resistance). In some situations, administration of antimicrobials to individual animals is not practical, and this may affect feasibility to the intervention.

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

Balance of consequences	Desirable consequences clearly outweigh undesirable consequences in most settings.

Does complete restriction of the use in the absence of disease in food-producing animals of classes of antimicrobials classified as critically important on the WHO CIA list, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?	
Type of recommendation[1]	Strong recommendation for the intervention
Recommendation	We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.
Justification	The panel determined that this recommendation should be strong despite the low quality evidence due to the potential large health benefits of lowered antimicrobial resistance in humans resulting from the complete restriction of the routine use of antimicrobials for disease prevention (i.e., the prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals). This conclusion is based upon the systematic review and evidence from documented additional observational studies, particularly the use of third generation cephalosporin for disease prevention in chickens in Canada, that found evidence from that restriction of prophylactic use of antimicrobials in food-producing animals reduces the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance that can be transmitted to humans. A review of molecular mechanisms of resistance indicated that prolonged treatment as in prophylactic conditions is more efficient for horizontal transfer of resistance genes, and therefore enhances emergence and dissemination of resistance. Furthermore, undesirable consequences associated with complete restriction of use of antimicrobials for the prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals appear to be relatively small. Finally, restriction of disease prevention use of antimicrobials in food-producing animals has been accomplished successfully in several countries demonstrating its feasibility. Reducing use of antimicrobials is in accordance with the WHO Global Action Plan which states that "evidence that antimicrobial resistance is driven by the volume of use of antimicrobial agents is compelling".
Implementation considerations	The panel acknowledges that, when in the professional judgment of a veterinary professional, prophylaxis may be used to address an elevated risk of contraction of a particular disease or infection. If antimicrobials are used for disease prevention, this should be justified on the basis of recent culture and sensitivity testing results, and the types of antimicrobials used should be used in reverse order as their importance for human health (i.e., classes not used in humans, important, and lastly highly important antimicrobials). The use of antimicrobials classified as critically important in human medicine on the WHO CIA List should only be used when justified by culture and sensitivity results of bacteria isolated in the recent past that have caused disease that is associated with the judged elevated risk and the sensitivity results indicate that the critically important antimicrobial is the only treatment option.
Monitoring and evaluation	National antimicrobial resistance and antimicrobial use surveillance programs should evaluate the effect of implementation.
Research priorities	Alternative to antimicrobials for prophylaxis, such as vaccines, hygiene, changing diets, probiotics.

[1] Selectable options are: Strong recommendation against the intervention; Conditional recommendation against the intervention; Conditional recommendation for either the intervention or the comparison; Conditional recommendation for the intervention; or Strong recommendation for the intervention.

2.4 Recommendation 4

Does complete restriction of the Critically Important Antimicrobials on the WHO CIA List for disease control and treatment in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?	
Problem: Increasing antimicrobial resistance is resulting in increased morbidity and mortality in humans ***Option:*** Restriction of the Critically Important Antimicrobials on the WHO CIA List used for disease control and treatment in food-producing animals ***Comparison:*** No such restriction in food-producing animals ***Setting:*** Food animal production and aquaculture worldwide	***Background:*** Antimicrobials deemed to be Critically Important antimicrobials on the WHO CIA List (e.g. fluoroquinolones, 3rd and 4th generation cephalosporins and macrolides) are in many countries approved for use in food-producing animals, many for therapeutic purposes in individual animals and in some cases, groups of animals. Antimicrobials are sometimes administered to an entire group of animals, even when only some of the animals in the group have clinically diagnosed infectious disease. In this situation, the antimicrobial is administered for two reasons; 1) disease treatment/therapy for the animal(s) with the clinically diagnosed infectious disease; and 2) control of the dissemination of the clinically diagnosed infectious disease to the other animals in the group. This is sometimes called "metaphylaxis". Use of antimicrobials of critical importance to human health in food-producing animals has been shown to select for resistance among human pathogens and commensals. We thus sought to critically review the evidence and all other criteria to assess if a recommendation could be made as to whether complete restriction of the Critically Important Antimicrobials on the WHO CIA List for treatment and control in food-producing animals, compared to no such restriction, would reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans. According to Codex Alimentarius, disease control is a type of prophylaxis. Codex Alimentarius defines prophylactic use of antimicrobials in food-producing animals as the use of an antimicrobial(s) in a group of healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. Prophylaxis in food-producing animals therefore includes control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals (disease control), and prevention of an infectious disease in a group of animals that has not yet been clinically diagnosed (disease prevention). In terms of prophylactic use of antimicrobials in food-producing animals, this restriction option being considered only pertains to the disease control type of prophylaxis in group of animals: the use of antimicrobials in group of food-producing animals for the control of dissemination of clinically diagnosed infectious disease.

	Criteria	Judgement	Research Evidence	Additional Information
Problem	1. Is the problem a priority?	Yes[1]	Antimicrobial resistance has been recognized as a major global public health threat. In the 2014 WHO Antimicrobial Resistance. Global Report on Surveillance, high proportions of resistance were reported in all regions of the world to common treatments for bacteria causing infections in both healthcare settings and in the community. Antibacterial resistance has a negative effect on patient outcomes including both morbidity and mortality and was more costly to the healthcare system .A systematic review published by the WHO in 2014 on the impact of AMR on multiple outcomes including mortality revealed for patients with third-generation cephalosporin resistant (including ESBL) *E. coli* infections there was a significant twofold increase in all-cause mortality, bacterium-attributable mortality and in 30-day mortality; for patients with fluoroquinolone-resistant *E. coli* infections there was a significant twofold increase in both all-cause mortality and 30-day mortality; for patients with third-generation cephalosporin resistant *K. pneumoniae* infections there was: a significant almost two-fold increase in all-cause mortality, bacterium-attributable mortality and 30-day mortality, and in the risk of intensive care unit (ICU) admission; for patients with carbapenem-resistant *K. pneumoniae* infections there was a significant two-fold increase in both all-cause mortality and 30-day mortality; and for patients with methicillin-resistant *S. aureus* infections there was a significant increase in all-cause mortality, bacterium-attributable mortality and ICU mortality, and septic shock. Treatment options for common infections are limited. Food-producing animals are important reservoirs and / or amplifiers of many bacterial infections of humans, including among others non-typhoidal *Salmonella*, *Campylobacter*, and *E. coli*, as well as opportunistic pathogens including *E. coli* and *Enterococcus spp.*	Reference: WHO Antimicrobial Resistance. Global Report on Surveillance 2014 http://www.who.int/drugresistance/documents/surveillancereport/en/
Problem	2. Are a large number of people affected?	Yes[1]	Foodborne diseases are a major cause of human morbidity and mortality. According to recent estimates from the WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), foodborne diseases caused 600 million illnesses, 420,000 deaths, and 33 million Disability Adjusted Life Years (DALYs) in 2010 (1). Foodborne diseases are particularly important in children. According to the WHO FERG estimates, although children <5 years of age represent only 9% of the	http://www.who.int/drugresistance/documents/surveillancereport/en/ Reference: Havelaar AH, Kirk MD, Torgerson P, Gibb HJ, Hald T, Lake RJ, Praet

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			global population, 40% of the foodborne disease burden is borne by children in this age group. There are also considerable differences in the burden of foodborne diseases among sub-regions with the highest burden of per population observed in Africa. Exact numbers of the global population affected by AROs is difficult to define but in the recent WHO Global Surveillance Report 5/6 WHO Regions globally had national reports of 50% resistance or more to three of the most commonly reported bacterial strains causing infections in humans. Lord O'Neill, in his recent economic report suggested the global financial cost of no action would be the loss of 10 million lives a year by 2050 and £ 69 trillion (US$ 100 trillion) a year. Non-typhoidal *Salmonella* caused an estimated 80 million infections and 60,000 deaths and *Campylobacter* caused 95 million infections and 21,000 deaths in 2010. Resistance among these infections is common (e.g. 0-49% resistance to fluoroquinolones among non-typhoidal *Salmonella* infections, depending on region). In some countries, fluoroquinolones have been approved for therapeutic treatment of bacterial infections (e.g. *E. coli*) in poultry. The fluoroquinolone was typically administered to the entire flock through drinking water. This practice has been shown to select for fluoroquinolone resistance in *Campylobacter*. A quantitative assessment of effects on human health by fluoroquinolone-resistant *Campylobacter* species associated with the therapeutic use of fluoroquinolones in poultry in the United States of America estimated that 153,580 persons were infected with fluoroquinolone-resistant *Campylobacter* species in 1999 from chicken consumption and 9261 of these people were estimated to have been treated with a fluoroquinolone. Nelson JM, Chiller TM, Powers JH, Angulo FJ (2007). Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. Clinical Infectious Disease 44:977-980.	N, Bellinger JD, de Silva NR, Gargouri N, Speybroeck N, Cawthorne A, Mathers C, Stein C, Angulo FJ, Devleesschauwer B. World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. PLoS Medicine 2015; doi: 10.1371/journal.pmed.1001923

<table>
<tr><th></th><th>Criteria</th><th>Judgement</th><th>Research Evidence</th><th>Additional Information</th></tr>
<tr><td>Benefits & Harms</td><td>1. Are the desirable anticipated effects large?</td><td>Probably yes[1]</td><td rowspan="3">Summary of findings:
<table>
<tr><th>Outcome: Reduction of the presence of antimicrobial-resistant bacteria and/or genetic elements in animals and humans with a restriction of the Highest Priority, Critically Important antimicrobials on the WHO CIA List used in food-producing animals for trestment and control compared to no such restriction</th><th>Risk Difference (intervention compared to control groups) (n= no. studies) (95% CI)</th><th>Certainty of the evidence (GRADE[2])</th></tr>
<tr><td>Quinolone resistance in Enterobacteriaceae</td><td>Faecal samples (n=16)
RD=-0.01 (-0.01 to 0.00)

Meat samples (n=12)
RD=-0.09 (-0.17 to -0.02)</td><td>Very Low</td></tr>
<tr><td>Quinolone resistance in Campylobacter spp.</td><td>Faecal samples (n=11)
RD= -0.06 (-0.16 to 0.05)

Meat samples (n=12)
RD= -0.08 (-0.17 to 0.01)</td><td>Very Low</td></tr>
<tr><td>Cephalosporin resistance in Enterobacteriaceae</td><td>Faecal samples (n=16)
RD=-0.01 (-0.04 to 0.01)

Meat samples (n=11)
RD=-0.07 (-0.14 to 0.01)</td><td>Very Low</td></tr>
</table></td><td rowspan="3">Data from a systematic review (SR) is provided for antimicrobials that are listed among the Highest Priority, Critically Important Antimicrobials on the current WHO CIA List. This data provides indirect evidence related to the designated outcome and hence the overall quality of the evidence is considered very low.

An additional study which more directly addresses this outcome is also presented. Risk differences reflect uses of the Highest Priority, Critically Important Antimicrobials as reported in the literature. The effect due to the proposed intervention alone has not been determined. Risk differences for multi-drug resistance in Enterobacteriaceae and overall antimicrobial resistance are also shown, because these antimicrobials may also contribute to these</td></tr>
<tr><td>Benefits & Harms</td><td>2. Are the undesirable anticipated effects small?</td><td>Probably yes[1]</td></tr>
<tr><td>Benefits & Harms</td><td>3. What is the overall certainty of this evidence?</td><td>Very low[3]</td></tr>
</table>

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; and Varies.
[2] Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation)
[3] Selectable options are: No included studies; Very low; Low; Moderate; or High.

	Criteria	Judgement	Research Evidence			Additional Information
			Macrolide resistance in *Campylobacter spp.*	Faecal samples (n=11). RD=-0.15 (-0.26 to -0.04) Meat samples (n=7) RD=-0.04 (-0.17 to 0.09)	Very Low	outcomes through direct and co-selection. Of the two SRs one was a narrative summary of the findings and the other a quantitative assessment. Both revealed the same findings with respect to the reduction of resistance transfer from food-producing animals to humans when a limitation of antimicrobials were used in the food-producing animals. Within the quantitative analysis, in the animal studies, 179 described antibiotic resistance outcomes in animals, of which 80 were meta-analyzed. The pooled absolute risk reduction of the prevalence of antibiotic resistance in animals, with interventions that restricted antibiotic use, varied across different antibiotic classes, bacteria, and sample types, but ranged from 0% to 39%; in general, the prevalence of antibiotic resistance was commonly 10-20% lower in intervention compared to control groups. The pooled prevalence of multi-drug resistance was 24-32%
			Macrolide resistance in *Enterococcus spp.*	Faecal samples (n=10). RD= -0.39 (-0.56 to -0.23)	Very Low	
			Multi-drug resistance in *Enterobacteriaceae*	Faecal samples (n=19) RD=-0.24 (-0.32 to -0.17) Meat samples (n=14). RD=-0.32 (-0.43 to -0.22)	Very Low	
			Overall antibiotic resistance	With stronger interventions (n=22) RD=0.22 (-0.31 to -0.13) With weaker interventions (n=62) RD=0.16 (-0.18 to -0.14)	Very Low	
			Resistance to any antimicrobial	Pooled absolute risk differences of antibiotic resistance (n=13 studies) RD=-0.24 (-0.42 to -0.06) Stratification by the studied human population Farm workers (n=9) RD=-0.29 (-0.54 to -0.04) Not farm workers (n=4)	Very Low	

	Criteria	Judgement	Research Evidence	Additional Information
			RD=-0.09 (-0.13 to -0.05) Stratification by stronger versus weaker interventions* Stronger interventions (n=8) RD=-0.14 (95% CI -0.20 to -0.08) Weaker interventions (n=5) RD= -0.38 (-0.83 to 0.08) In the Netherlands, implementation of a requirement whereby the use of a 3rd generation cephalosporin or fluoroquinolone in food-producing animals is only allowed when culture and susceptibility test results show that this is the only available drug, substantially decreased use of the drug and resistance in bacteria from animals (Mevius, 2013). Complete restriction on the use of Antimicrobials Critically Important for Human Use in food-producing animals could lead to animal health and welfare problems in the case of an infectious disease outbreak where these antimicrobials were the only effective treatment.	lower in bacteria isolated from intervention groups. These findings held through many different layers of stratification including by intervention type. Twenty-one studies described antibiotic resistance outcomes in humans (19 of which also reported antibiotic resistance in animals), of which 13 were meta-analyzed. In humans, the pooled prevalence of antibiotic resistance was 24% lower in intervention groups (where interventions to reduce antibiotic use in food-producing animals were implemented) compared to control groups. The effect was similar, albeit weaker, when considering humans without direct contact with livestock animals, compared to farm workers. In some countries, fluoroquinolones have been approved for therapeutic treatment of bacterial infections (e.g. *E. coli*) in poultry. The fluoroquinolone was typically administered to the

	Criteria	Judgement	Research Evidence	Additional Information
				entire flock through drinking water. This practice has been shown to select for fluoroquinolone resistance in *Campylobacter*. In 2005, approval of use of fluoroquinolones for therapeutic treatment of bacterial infections in poultry in the U.S. was withdrawn. Since the withdrawal, fluoroquinolone resistance has persisted in *Campylobacter* from poultry in the U.S. Nelson JM, Chiller TM, Powers JH, Angulo FJ (2007). Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. Clin Infect Dis. 2007 Apr 1;44(7):977-80. Nannapaneni R, Hanning I, Wiggins KC, Story RP, Ricke SC, Johnson MG. Ciprofloxacin-resistant *Campylobacter* persists in raw retail chicken after the fluoroquinolone ban. Food Addit Contam Part A Chem Anal Control Expo Risk

	Criteria	Judgement	Research Evidence	Additional Information
				Assess. 2009 Oct;26(10):1348-53. Price LB, Lackey LG, Vailes R, Silbergeld E. The persistence of fluoroquinolone-resistant *Campylobacter* in poultry production. Environ Health Perspect. 2007 Jul;115(7):1035-9. Complete restriction on the use of Antimicrobials Critically Important for Human Use in food-producing animals could lead to increased resistance to antimicrobials of lesser importance to human health (i.e. given a need to treat, the intervention determines which antimicrobial to use). Mevius, D. & Heederik, D. J. Verbr. Lebensm. Reduction of antibiotic use in animals “let’s go Dutch”. J. Verbr. Lebensm. (2014) 9: 177. doi:10.1007/s00003-014-0874-z. http://link.springer.com/article/10.1007/s00003-014-0874-z

	Criteria	Judgement	Research Evidence	Additional Information
Values	1. How certain is the relative importance of the desirable and undesirable outcomes?	Probably no important uncertainty or variability[1]	The GDG gave very high ratings to desirable outcomes from restrictions on antimicrobial use in animals; it gave the highest value (median 9, with score of 9 judged of "most importance") to the consideration that when people were infected with antimicrobial resistant bacteria, this leads to more severe health outcomes. Also rated highly were desirable outcomes related to decreases in the prevalence of antimicrobial resistant bacteria and/or antimicrobial resistant determinants in food-producing animals (median 8) and humans (median 7-8). Undesirable outcomes were rated of lower importance, including decreases in food animal health and welfare (median 4), decreases in food security (median 2), food safety (median 4), increased therapeutic antimicrobial use in animals following restrictions on growth promoters (median 4), and increased costs to producers and loss of income to national economies (median 3).	Public health concerns about the use of antimicrobial agents in food-producing animals have been expressed for decades. Many groups have concluded that public health concerns warrant placing restrictions on the use of antimicrobial agents in food-producing animals given that: a. antimicrobials agents used in humans are widely used in food-producing animals, b. use of antimicrobial agents results in antimicrobial resistance, c. food-producing animals are an important source of antimicrobial-resistant bacteria for humans, and infections in humans caused by antimicrobial-resistant bacteria may have more severe health consequences compared with infections caused by antimicrobial-susceptible bacteria
Values	2. Are the desirable effects large relative to undesirable effects?	Probably yes[2]	Reduction in resistance to highest priority drugs more desirable than reduction to lower priority drugs.	

	Criteria	Judgement	Research Evidence	Additional Information
Resource use	1. Are the resources required small?	Varies[3]	The resources required to limit use of critically important antimicrobials for treatment of disease in food-producing animals include two general types. Governments may require some resources to direct and monitor food-production facilities, including feedmills, farms and aquaculture facilities. In addition, governments may require resources to support	Potential resource costs from restriction include laboratory costs (culture and sensitivity testing)

[1] Selectable options are: Important uncertainty or variability; Possibly important uncertainty or variability; Probably no important uncertainty or variability; No important uncertainty or variability; or No known undesirable outcomes.
[2] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.
[3] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgement	Research Evidence	Additional Information
			susceptibility testing facilities. These resources are relatively small. Antibiotic treatment with critically important antibiotics is an alternative to good hygiene practices, vaccination, and biosecurity in food production, as well as treatment with alternative antibiotics. Because there are many alternatives, including treatment with critically important antibiotics when justified, the costs for food production should be small.	
Resource use	2. Is the incremental cost small relative to the net benefits?	Varies[1]	The main cost involved in reduced therapeutic use of critically important antibiotics relates to supporting an infrastructure for susceptibility testing. The incremental costs are likely in the millions of dollars, but such testing facilities would provide many other benefits. (Incremental costs are likely very small in countries with established facilities.) These costs are much smaller than the net benefits caused by reduced resistance to critically important antibiotics.	Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014 https://amr-review.org/

	Criteria	Judgements	Research Evidence	Additional Information
Equity	1. What would be the impact on health inequities?	Uncertain[2]	In the O'Neill Report, it indicated that "KPMG looked at what would happen if infection rates doubled and then stayed constant and the analysis suggested an increase in infection rates alone could mean 150 million people dying prematurely and reduce world GDP by 55 trillion USD between now and 2050, just over half the total impact they estimate for AMR." The impact would be greater on low to middle income countries and thus by acting on our recommendations health inequities would be likely reduced. Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance	The World Bank recently reviewed the economic impacts of failure to control antimicrobial resistance in terms of reductions in national GDP (World Bank Group, Drug-Resistant Infections A Threat to our Economic Future 2016). This analysis indicated large decreases in global economic growth. In contrast to acute economic events such as the 2008-9 financial crisis, these impacts are expected to be prolonged. This analysis indicated substantial inequities in impacts that varied inversely with per capita income such that the poorest countries would experience

[1] Under "Judgement" for criteria 1 and 2, selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.
[2] Selectable options are: Increased; Probably increased; Uncertain; Probably reduced; Reduced; or Varies.

	Criteria	Judgements	Research Evidence	Additional Information
			Chaired by Jim O'Neill December 2014 https://amr-review.org/	the greatest decreases in annual economic growth as measured by GDP (figure 3). Overall, under a more optimistic scenario (related to the magnitude of AMR) the losses of world economic output exceeded US$1 trillion annually to reach a total of US$2 trillion per year by 2050. Under a more pessimistic scenario, these losses were estimated to be US$ 3.4 trillion annually to 2030 and US$6.1 trillion annually by 2050. Economic shocks to livestock production were also anticipated due to trade restrictions and consumer fears of food safety. These impacts and associated effects on nutrition and health would also be more severe in low income countries. Health care costs in terms of extra costs associated with AMR infections would also increase significantly. Because of these disparate economic impacts, poverty is anticipated to increase markedly in low income countries
Acceptability	1. Is the option acceptable to key stake-holders?	Varies[1]	Key target audience are Governments and regulatory agencies, veterinarians, farmers and other food producers, the food production industry, and consumers.	Concerns about additional restrictions to antimicrobial prescribing have been raised by veterinarians.
Feasibility	1. Is the option feasible to implement?	Uncertain[1]	Feasibility difficulties could arise from the potential problems identified above under "Are the resources required small?".	Some countries have implemented programs for substantial reduction of antimicrobial use without many problems. Feasibility of implantation in other countries depends on access to laboratory facilities for culture and sensitivity testing (to enable use when justified) as well as resistance patterns to antimicrobials classified Very Important and Important (more feasible if less resistance). In

[1] Selectable options are: No; Probably no; Uncertain; Probably yes; Yes; or Varies.

	Criteria	Judgements	Research Evidence	Additional Information
				some situations, administration of antimicrobials to individual animals is not practical, and this may affect feasibility to the intervention.

Balance of consequences	Desirable consequences probably outweigh undesirable consequences in most settings.

Does complete restriction of the Critically Important Antimicrobials on the WHO CIA List for disease treatment and control in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?	
Type of recommendation[1]	Conditional recommendation for the intervention
Recommendation	a) We suggest that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals. b) We suggest that antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease.
Justification	The GDG concludes that the recommendation on treatment of individual sick animals should be conditional on susceptibility results demonstrating that the selected drug is the only treatment option, and treatment is given to individual animals. This conclusion is based upon the indirect evidence from the systematic review, evidence from documented additional observational studies, and the review of molecular mechanisms. Furthermore, undesirable consequences associated with such a restriction of use of antimicrobials appear to be relatively small or non-existent. Finally, such a restriction of antimicrobials in food-producing animals has been accomplished successfully in several countries demonstrating its feasibility. The GDG also concludes that the recommendation on disease control (prophylaxis in a group of animals in the presence of disease) should also be conditional on culture and sensitivity results demonstrating that the selected drug is the only treatment option. Again, this conclusion is based upon the indirect evidence from the systematic review, evidence from documented additional observational studies, and the review of molecular mechanisms. Furthermore, undesirable consequences associated with such a restriction of use of antimicrobials appear to be relatively small or non-existent. Finally, such a restriction of antimicrobials in food-producing animals has been accomplished successfully in several countries demonstrating its feasibility. These recommendations are in accordance with the WHO Global Action Plan which states that "evidence that antimicrobial resistance is driven by the volume of use of antimicrobial agents is compelling".
Implementation considerations	The use of antimicrobials classified as critically important in human medicine on the WHO CIA List should only be used when justified by culture and sensitivity results indicate that the critically important antimicrobial is the only treatment option. Feasibility is therefore dependent on access to culture and sensitivity testing. The requirement for culture and sensitivity has been implemented in some countries including the Netherlands. There may be some inequity introduced by requirement for culture and sensitivity testing but would be marginal compared to the gains. Veterinarians should have access to culture and sensitivity testing. Provision should be made to assist developing regions with implementation, which could include implementation and follow-up monitoring in AGISAR country pilot projects (e.g. Bangladesh, India, Kenya, Rwanda, Tanzania).

[1] Selectable options are: Strong recommendation against the intervention; Conditional recommendation against the intervention; Conditional recommendation for either the intervention or the comparison; Conditional recommendation for the intervention; or Strong recommendation for the intervention.

Monitoring and evaluation	National antimicrobial resistance and antimicrobial use surveillance programs should evaluate the effect of implementation.
Research priorities	More research is needed to assess the effectiveness, benefits and costs of the intervention.

3. SUMMARY-OF-FINDINGS TABLES

For details on the information provided in the evidence profile tables, see full report of "University of Calgary systematic review: restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" in Web Annex A. Evidence base (WHO/NMH/FOS/FZD/17.2; available at: http://apps.who.int/iris/bitstream/10665/259241/1/WHO-NMH-FOS-FZD-17.2-eng.pdf).

3.1 Recommendation 1

Does a restriction of antimicrobials on the WHO CIA List used in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in humans?	
Population: Food-producing animals **Settings:** Food animal production sites and aquaculture **Intervention:** Restricting any use of antimicrobials in the WHO CIA list **Comparison:** Not restricting the use of antimicrobials in the WHO CIA list	**Recommendation:** We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
1. Antimicrobial resistance in humans	**Overall:** RD= -0.24 (-0.42 to -0.06) **Farm workers** RD= -0.29 (-0.54 to -0.04)	13 studies (2701 samples) 9 studies	Low[2]	Total n = 21 studies of which 13 could be pooled 12 examined farm-workers and 9 non-farm-workers. The RDs were higher among farm workers (high-risk) than non-farm workers (low-risk) suggesting a potential dose-response relationship. 9 well-defined strong interventions (externally imposed

[1] Only listed outcomes considered critical or important for decision-making.

[2] The default starting quality grading for observational studies in GRADE is low. We did not further downgrade the quality grading due to the consistency of findings across different bacterial groups, animal species, antibiotic classes, sample types, baseline risk of population, a potential dose-response relationship and because of the similarity of findings when considering human and animal outcomes and mechanistic data.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
	Non-farm workers RD= -0.09 (-0.13 to -0.05)	4 studies		bans): RD -0.14 (-0.20 to -0.08) 5 weak interventions (voluntary bans) RD -0.38 (-0.83 to 0.08) In 2 studies in farm-workers, genetic data suggested resistant bacteria came from animals. *See narrative summary of the remaining 8 studies below.
2. Antimicrobial resistance in animals	**Restriction of the use of all antibiotics in animals** RD= -0.18 (-0.22 to -0.14) **Restriction (various measures) of the use of antimicrobials in food-producing animals and effect on resistance to specific classes of antimicrobials in faecal and meat samples** Quinolone resistance *Enterobacteriaceae* Faecal samples, n= 17 RD= -0.01 (-0.02 to 0.00) Meat samples, n= 12 RD= -0.09 (-0.17 to -0.02) Quinolone resistance in *Campylobacter spp.* Faecal samples (n=11) RD= -0.06 (-0.16 to 0.05) Meat samples (n=12) RD= -0.08 (-0.17 to 0.01)	39 studies N/A (number of samples provided for each measure)	Low[1] Low[1]	Total n =179 studies, of which 69 studies restricted all uses of antibiotics in food-producing animals.

[1] The default starting quality grading for observational studies in GRADE is low. We did not further downgrade the quality grading due to the consistency of findings across different bacterial groups, animal species, antibiotic classes, sample types, baseline risk of population, a potential dose-response relationship and because of the similarity of findings when considering human and animal outcomes and mechanistic data.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
	Cephalosporin resistance *Enterobacteriaceae* Faecal samples, n=17 RD= -0.01 (-0.04 to -0.01) Meat samples, n=11 RD= -0.07 (-0.14 to 0.01) Penicillin resistance *Enterobacteriaceae* Faecal samples, n= 20 RD= -0.12 (-0.18 to -0.07) Meat Samples, n= 11 RD= -0.16 (-0.25 to -0.08) Tetracycline resistance *Enterobacteriaceae* Faecal samples, n= 21 RD= -0.16 (-0.27 to -0.05) Meat Samples, n= 12 RD= -0.20 (-0.36 to -0.03) Multi-drug resistance *Enterobacteriaceae* Faecal samples, n=19 RD= -0.24 (-0.32 to -0.17) Meat samples, n=14 RD= -0.32 (-0.43 to -0.22) Macrolide resistance *Campylobacter spp.* Faecal samples, n=11 RD= -0.15 (-0.26 to -0.04)			

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
	Meat samples, n=7 RD= -0.04 (-0.17 to 0.09) Macrolide resistance *Enterococcus spp.* Faecal samples, n=10 RD= -0.39 (-0.56 to -0.23) Glycopeptide resistance *Enterococcus spp.* Faecal samples, n=12 RD= -0.22 (-0.32 to -0.12)			

Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation); CI (confidence interval); RD (risk difference)

3.2 Recommendation 2

Does complete restriction of classes of antimicrobials on the WHO CIA List used in food-producing animals for purposes of growth promotion, compared to no such restriction, reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in humans?	
Population: Food-producing animals **Settings:** Food animal production sites and aquaculture **Intervention:** Complete restriction of antimicrobials in the WHO CIA list for growth promotion **Comparison:** Not restricting the use of antimicrobials in the WHO CIA list for growth promotion	**Recommendation:** We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
1. Antimicrobial resistance in humans	RD=-0.13 (-0.20 to -0.06)	6 studies	Low[2]	Total of 7 studies of which 6 could be pooled where there was complete restriction of the use of antimicrobials for growth promotion.
2. Antimicrobial resistance in animals	RD=-0.29 (-0.40 to -0.19)	15 studies	Low[2]	Total of 27 studies of which 15 studies could be pooled with complete restriction of the use of antimicrobials for growth promotion.

Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation); CI (confidence interval); RD (risk difference)

[1] Only listed outcomes considered critical or important for decision-making.

[2] The default starting quality grading for observational studies in GRADE is low. We did not further downgrade the quality grading due to the consistency of findings across different bacterial groups, animal species, antibiotic classes, sample types, baseline risk of population, a potential dose-response relationship and because of the similarity of findings when considering human and animal outcomes and mechanistic data.

3.3 Recommendation 3

Does complete restriction of the routine use of antimicrobials on the WHO CIA List for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?	
Population: Food-producing animals **Settings:** Food animal production sites and aquaculture **Intervention:** Complete restriction of antimicrobials in the WHO CIA list for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals (includes growth promotion, prophylaxis and metaphylaxis) **Comparison:** Not restricting the use of antimicrobials in the WHO CIA list for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals (includes growth promotion, prophylaxis and metaphylaxis)	**Recommendation:** We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.

Outcomes[1]	**Risk differences (95% CI)**	**Number of studies pooled (number of samples)**	**Quality of the evidence (GRADE)**	**Comments**
1. Antimicrobial resistance in humans	RD= -0.08 (-0.20 to 0.04) RD= -0.25 (-0.34 to -0.16)	None	Low[2]	Two studies for human resistance were found and a RD was determined for both. The two studies (Huijbers 2015 and Dutil 2010) could not be combined for a meta-analysis since one used isolates as the unit of analysis and the other used sample as the unit of analysis. Two additional studies

[1] Only listed outcomes considered critical or important for decision-making.
[2] Based on 2 studies: one from Canada (Dutil 2010) where the Canadian Integrated Program for Antimicrobial Resistance Surveillance described a strong correlation (r = 0.9, p<0.0001) between ceftiofur-resistant Salmonella enterica serovar Heidelberg isolated from retail chicken and incidence of ceftiofur-resistant Salmonella serovar Heidelberg infections in humans across Canada with a significant decline after withdrawal of ceftiofur from hatcheries where it was being injected in ovo to control Escherichia coli omphalitis; and one 1 longitudinal study from The Netherlands (Huijbers 2015) collecting samples from farmers, farm residents and family members, farm employees after an organic intervention. Samples were nasal and faecal from human (27) and the residential environment (75).

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
				were identified (Group 6 in the Tang et al. systemic review) where it could be discerned that prophylaxis was used with human resistance outcomes and were also included but were not amenable to meta-analysis but ORs were available (OR 1.17 (0.98-1.39) for antibiotic use in animals [2 fold increase in unit exposure] for LA-MRSA in humans and OR 0.19 (0.07-0.53) for LA-MRSA carriage in intervention arm.
2. Antimicrobial resistance in animals	RD= -0.08 (-0.11 to -0.06)	26 studies	Low[1]	Total n=36 studies, of which 26 studies could be pooled with complete restriction of the use of antimicrobials for prevention of infectious diseases that have not yet been clinically diagnosed and outcomes measured in animals.

Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation); CI (confidence interval); RD (risk difference); LA-MRSA (Livestock-associated methicillin-resistant *S. aureus*)

[1] The default starting quality grading for observational studies in GRADE is low. We did not further downgrade the quality grading due to the consistency of findings across different bacterial groups, animal species, antibiotic classes, sample types, baseline risk of population, a potential dose-response relationship and because of the similarity of findings when considering human and animal outcomes and mechanistic data.

3.4 Recommendation 4

Does complete restriction of the Critically Important Antimicrobials on the WHO CIA List for disease control and treatment in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?	
Population: Food-producing animals **Settings:** Food animal production sites and aquaculture **Intervention:** Complete restriction of antimicrobials in the Critically Important Antimicrobials for Human Medicine on the WHO CIA List for disease control and treatment in food-producing animals **Comparison:** Not restricting of antimicrobials in the Critically Important Antimicrobials for Human Medicine on the WHO CIA List for disease control and treatment in food-producing animals	**Recommendations:** a) We suggest that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals. b) We suggest that antimicrobials classified as highest-priority critically important antimicrobials for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
1. Antimicrobial resistance in humans	**Overall:** RD= -0.24 (-0.42 to -0.06) **Farm workers** RD= -0.29 (-0.54 to -0.04) **Non-farm workers** RD= -0.09 (-0.13 to -0.05)	13 studies (2701 samples)	Very low[2]	Total n= 21 studies of which 13 could be pooled 12 examined farm-workers and 9 non-farm-workers. The RDs were higher among farm workers (high-risk) than non-farm workers (low-risk) suggesting a potential dose-response relationship. 9 well-defined strong interventions (externally imposed bans): RD -0.14 (-0.20 to -0.08) 5 weak interventions (voluntary bans) RD -0.38 (-0.83 to 0.08) In 2 studies in farm-workers, genetic data suggested resistant bacteria came from animals.

[1] Only listed outcomes considered critical or important for decision-making.
[2] The default starting quality grading for observational studies in GRADE is low. We further downgraded the quality due to indirectness with respect to the question posed, related to disease control and treatment in food animals.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
				*See narrative summary of the remaining 8 studies below.
2. Antimicrobial resistance in animals	**Restriction of the use of all antibiotics in animals** RD= -0.18 (-0.22 to -0.14) **Restriction (various measures) of the use of antimicrobials in food-producing animals and effect on resistance to specific classes of antimicrobials in faecal and meat samples** Quinolone resistance *Enterobacteriaceae* Faecal samples, n= 17 RD= -0.01 (-0.02 to 0.00) Meat samples, n= 12 RD= -0.09 (-0.17 to -0.02) Quinolone resistance in *Campylobacter spp.* Faecal samples (n=11) RD= -0.06 (-0.16 to 0.05) Meat samples (n=12) RD= -0.08 (-0.17 to 0.01) Cephalosporin resistance *Enterobacteriaceae* Faecal samples, n=17 RD= -0.01 (-0.04 to -0.01) Meat samples, n=11 RD= -0.07 (-0.14 to 0.01) Penicillin resistance	39 studies N/A (number of samples provided for each measure)	Very low[2] Very low[2]	Total n=179 studies, of which 69 studies restricted all uses of antibiotics in food-producing animals. Total n=179 studies, of which 160 studies reported on outcomes of antimicrobial resistance and of which 81 studies had faecal and meat samples available. One additional study was found which was relevant for this question (Nelson JM, Chiller TM, Powers JH, Angulo F, 2007). In some countries, fluoroquinolones have been approved for therapeutic treatment of bacterial infections (e.g. E. coli) in poultry. The fluoroquinolone was typically administered to the entire flock through drinking water. This practice has been shown to select for fluoroquinolone resistance in Campylobacter species. In 2005, approval of use of fluoroquinolones for therapeutic treatment of bacterial infections in poultry in the United States (US) was withdrawn. Since the withdrawal, fluoroquinolone resistance has persisted in Campylobacter from poultry in the US.

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
	Enterobacteriaceae Faecal samples, n= 20 RD= -0.12 (-0.18 to -0.07) Meat Samples, n= 11 RD= -0.16 (-0.25 to -0.08) Tetracycline resistance *Enterobacteriaceae* Faecal samples, n= 21 RD= -0.16 (-0.27 to -0.05) Meat Samples, n= 12 RD= -0.20 (-0.36 to -0.03) Multi-drug resistance *Enterobacteriaceae* Faecal samples, n=19 RD= -0.24 (-0.32 to -0.17) Meat samples, n=14 RD= -0.32 (-0.43 to -0.22) Macrolide resistance *Campylobacter spp.* Faecal samples, n=11 RD= -0.15 (-0.26 to -0.04) Meat samples, n=7 RD= -0.04 (-0.17 to 0.09) Macrolide resistance *Enterococcus spp.* Faecal samples, n=10 RD= -0.39 (-0.56 to -0.23) Glycopeptide resistance			

Outcomes[1]	Risk differences (95% CI)	Number of studies pooled (number of samples)	Quality of the evidence (GRADE)	Comments
	Enterococcus spp. Faecal samples, n=12 RD= -0.22 (-0.32 to -0.12)			

Abbreviations: GRADE (Grading of Recommendations Assessment, Development, and Evaluation); CI (confidence interval); RD (risk difference)

4. NARRATIVE EVIDENCE SUMMARIES OF SYSTEMATIC REVIEWS

4.1 University of Calgary: restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis

University of Calgary systematic review in March 2017 (Tang K et al. Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals – a systematic review and meta-analysis).

For more details, see a full report of "University of Calgary systematic review: restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" in Web Annex A. Evidence base (WHO/NMH/FOS/FZD/17.2; available at: http://apps.who.int/iris/bitstream/10665/259241/1/WHO-NMH-FOS-FZD-17.2-eng.pdf).

Human Studies (n=8)

1. **Coalition for animal health (NR)**

Aim: This report used data available in the DANMAP reports to compare resistance patterns in humans and animals from 1997 to 2005.
Findings: For *E. faecium* there was an increase in resistance in samples from healthy humans. Resistance to virginiamycin, vancomycin, and tetracycline increased from 29 to 54%, 0 to 2% and 8 to 16% respectively. There was a 4.3% increase in ciprofloxacin resistant *E. coli* isolates from urine. In *S. Typhimurium*, resistance to ampicillin, and ciprofloxacin increased from 11 to 45% and 1 to 4% respectively between 1997 and 2005. In *C. jejuni*, resistance to ciprofloxacin and tetracycline increased from 12-14 to 28% and 9 to 25% respectively between 1997 and 2005. The ban on the use of antibiotic growth promoters in animals in Denmark was reported not to have reduced antibiotic resistance in humans.

2. **Dorado-García (2015b)**

Aim: This work presents the results and experiences from an intervention study aimed at reducing MRSA in animals and humans on veal farms.
Findings: In 193 humans assessed, the proportion of MRSA-positive people was highest in control farms (20.9%), followed by RAB-CD farms (17%). The proportion of MRSA was lowest (7.2%) in RAB farms. The difference in the proportion of MRSA between intervention groups RAB-CD and Control was only significant in the group of farmers working 20 or more hours per week ($p<0.01$). There was no statistically significant association between prevalence of MRSA in calves and MRSA in humans (OR per 10% increase in animal prevalence=1.06, 95% CI=0.94 – 1.18, p=0.34). In humans working on veal farms, MRSA prevalence decreased in parallel in all study arms, with no significant difference in the decline across groups.

3. **Dutil (2010)**

Aim: This study examined the effect of a voluntary withdrawal of ceftiofur from hatcheries in the province of Quebec, Canada.
Findings: Following a voluntary withdrawal of ceftiofur by hatcheries in 2005 the prevalence of ceftiofur resistance significantly decreased from 2004 to 2006 among chicken (62% to 7%; p <0.001) and human (36% to 8%; p <0.0001) *Salmonella* Heidelberg isolates. Resistance to ceftiofur among *Salmonella* Heidelberg isolates increased from 2006 to 2008 (chicken (7% to 18%) and human (8% to 12%) although this increase was not significant (p=0.41). The decline in ceftiofur resistance in Quebec retail chicken meat was consistent with the voluntary withdrawal of ceftiofur use in hatcheries. There appeared to be a re-emergence of ceftiofur resistance among *E. coli* but at lower levels than baseline, when partial reinstitution of ceftiofur use in Quebec hatcheries occurred.

4. **Johnson (2007)**

Aim: This study used phylogenetic analysis and virulence genotyping to assess whether drug resistant human isolates resemble susceptible human isolates or resemble poultry isolates, with the purpose of identifying methods for transmission of antimicrobial resistance.
Findings: Findings upon examination of phylogenetic group distribution and virulence gene prevalence were that drug susceptible human ExPEC isolates were different from poultry isolates. Findings also indicated that in general, drug resistant human ExPEC isolates were more similar overall to poultry isolates than to drug susceptible human isolates. Antibiotic resistant *E. coli* isolated from humans were similar to poultry isolates, suggesting poultry origin of resistance. The presence of poultry source *E. coli* in both vegetarians and those who do consume meat products suggests that antibiotic resistant *E. coli* of poultry origin may spread through the general human population without requiring individual direct contact to poultry or poultry products.

5. **Gallay (2007)**

Aim: This study describes trends in antimicrobial resistance in *Campylobacter spp.* isolates from 1986 to 2004. The European Union recommended that the use of fluoroquinolones in poultry be limited in 1999.
Findings: From 2002 – 2004, resistance to quinolones decreased in *C. jejuni* isolated from both humans and broilers. The decline in resistance was less substantial in humans, suggesting that a longer period of time is required to detect the reduction in antibiotic resistance in humans after an intervention is implemented in food-producing animals to reduce antibiotic use. No change to quinolone resistance occurred over the same time period in C. coli isolated from humans and boilers. Reduction in fluoroquinolone use in broilers may result in reduced fluoroquinolone resistance in *C. jejuni* isolated from humans.

6. **Osadebe (2012)**

Aim: This study examined the prevalence and characteristics of *S. aureus* in pigs and pig farmers.
Findings: Of the human participants, two humans (22%) were MRSA positive though the author did not specify whether they were from conventional or organic farms. MRSA-positive persons had other risk factors for colonization including recent hospitalization or contact with a household member with recent hospitalization. Both human strains of MRSA were similar to known healthcare associated MRSA strains. Genetic analysis suggested presence of human-animal transmission, or reverse zoonosis. There should be improved biosafety measures to reduce spread of resistant bacteria between animals and humans.

7. **Skjøt-Rasmussen (2009)**

Aim: The aim of this study was to use DANMAP data to look at trends in occurrence of resistance among *C. jejuni* isolated from broiler chickens, broiler chicken meat, and human domestically acquired cases and travel-associated cases in Denmark from 1997-2007.
Findings: The prevalence of resistance to fluoroquinolones in domestically acquired human *C. jejuni* infections was higher than that found in Danish broiler chicken meat, but similar to the prevalence found in imported chicken meat. The prevalence of antibiotic resistance was also higher in travel-associated *C. jejuni*

isolated from humans compared with domestically acquired *C. jejuni* isolates. There remains high prevalence of fluoroquinolone resistant *C. jejuni* in human infections despite the withdrawal of fluoroquinolones for animal use in Denmark. The source of these resistant organisms may be through human travel or consumption of imported chicken meat.

8. Smith (2013)

Aim: This study examined the prevalence of MRSA in pigs and farm workers on conventional and antibiotic-free pig farms in several US states.
Findings: Out of a total of 148 farm workers, 31 were MRSA-positive (20.9%). Of these 31 individuals, 27 (87%) worked on farms where there were MRSA positive pigs present. The majority of samples came from the two farms where there was highest prevalence of MRSA in pigs. Exposure to pigs for 7 or more hours per day was associated with an increased risk for carrying MRSA-positive isolates (OR 5.2 [95% CI 4.2 – 6.5]). Humans that have close contact with animals that are MRSA positive have a high risk of MRSA carriage themselves.

Animal Studies (n=68)

1. Most studies focused on *Enterobacteriaceae*.
2. For *Enterobacteriaceae*, *Enterococcus spp.*, and *Staphylococcus spp.*, most studies reported a reduction in the absolute risk difference of antibiotic resistance with any intervention that aimed to reduce antibiotic use in animals, across all antibiotic classes and sample types. There were also many studies that reported no statistically significant difference between intervention and control groups, and proportionately few studies that reported an increase of antibiotic resistance with interventions that aimed to reduce antibiotic use in animals.
3. Antibiotic resistance in *Campylobacter spp.* appeared to follow a different pattern compared to the other bacterial groups. Specifically, in most studies, no statistically significant difference in antibiotic resistance was detected in animals with interventions that reduced antibiotic use. There were only a small number of studies showing decreased *Campylobacter spp.* antibiotic resistance with interventions that aimed to reduce antibiotic use in animals.

4.2 University of Calgary: supplemental analysis of systematic review for unintended consequences

From Table 6: Potential harms reported by animal and human studies - Calgary team systematic review March 2017 Supplemental Report. Tang K et al. Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals – a systematic review and meta-analysis)

For more details, see a full report entitled "Supplemental report to: restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans – a systematic review and meta-analysis" in Web Annex A. Evidence base (WHO/NMH/FOS/FZD/17.2; available at: http://apps.who.int/iris/bitstream/10665/259241/1/WHO-NMH-FOS-FZD-17.2-eng.pdf).

Potential harms	**Number of animal studies (N=179)**	**Number of human studies (N=21)**
Increased use of antimicrobials	5	2
Adverse effects on human health	0	0
Decrease in food or protein availability for human consumption	0	0
Food safety	34	0
Adverse effects on animal health	5	1
Animal production	4	1
Economic (cost of animal production or national economy)	3	1
No data reported on potential harms	131	19

Antibiotic use: Five studies reported on potential unintended consequences regarding the total amount of antibiotics used. One study (Aarestrup 2001) reported compensatory increase in another permitted promoter when one was banned. The other four studies reported that when antibiotic use was restricted, this resulted in increased administration of antibiotics to individual animals for therapeutic purposes, but that the total amount or volume of antibiotics used nevertheless decreased.

Food safety: Most widely reported with 34 studies. Of these, 14 (41%) found that interventions that restricted antibiotic use resulted in increased contamination with bacteria (including *Salmonella spp*., *Campylobacter spp*., and *Enterobacteriaceae*) in the retail meats produced. Fifteen of 34 studies (45%) reported no difference in contamination rates between food products from intervention and comparator groups. A smaller percentage of studies (12%) demonstrated either variable results within studies or a lower level of contamination of meats in intervention versus comparator groups. The clinical and public health significance of these findings are unclear, especially as to what extent adequate preparation and cooking can mitigate the risk of bacterial contamination of raw retail meat, and whether higher bacterial contamination translates into increased clinical and zoonotic disease.

Animal health: Five studies reported potential adverse effects on animal health. Three such studies were specific to dairy herds, showing variable results. Two of the three reported higher prevalence of intra-mammary infections when the use of antibiotics is restricted (though one study indicated that the higher prevalence was significant only at parturition but not the dry-off period) while the third study showed no difference in the prevalence of mastitis between intervention and comparator groups. Berge et al. reported an increase in respiratory disease but decrease of diarrhea in calves where antibiotics used for prophylaxis and growth promoters were restricted. Lastly, Dorado-Garcia et al. reported no difference in mortality or mean mortality age in intervention versus comparator groups.

Animal production: One study indicated that such interventions resulted in greater weight gain (from reduced diarrhea) in intervention groups, while two studies indicated that animal production was adversely affected by antibiotic restriction, with increased feeding time (to achieve a target weight) or increased production cycle duration in intervention groups. There may also be effects on parity and milk yield, with antibiotic restriction being associated with increased parity but lower milk yield in one study.

Costs and economics: Only three studies reported potential economic consequences of antibiotic restriction interventions. One study showed that restriction in antibiotic use, in combination with restrictions in the uses of hormone implants and anti-helmintics, may increase feeding time to reach target weight in animals, leading to increases in the need for land for disposal of waste, and increases in energy consumption for animal food production. It is difficult to disentangle the extent to which these unintended consequences in animal production and costs are attributable to the antibiotic restrictions themselves, versus the co-interventions that were implemented in this study. Other studies show variable economic implications to treatment and veterinary costs, with one study showing an increase while another showing a decrease in such costs.

4.3 Bond University: use in food animals of critically important antimicrobial agents for human medicine – a systematic review

Bond University systematic review entitled "Use in food animals of critically important antimicrobial agents for human medicine". (Scott A et al. October 2016)

For more details, see a full report entitled "Use in food animals of critically important antimicrobial agents for human medicine. WHO Systematic Review, May-October 2016" in Web Annex A. Evidence base (WHO/NMH/FOS/FZD/17.2; available at: http://apps.who.int/iris/bitstream/10665/259241/1/WHO-NMH-FOS-FZD-17.2-eng.pdf).

Overall results

Provided as a summary since the review was a narrative and no combined quantitative results or meta- analysis were provided.

Evidence to address PICOT questions difficult to analyze:
- paucity of good primary studies
- heterogeneous reporting methods
- variety of antibiotics
- wide range of animals
- different isolates
- methodology for measuring resistance (culturing, genetics)
- Various time intervals studied

More primary studies required to strengthen the research evidence for the specific Q's.

PICOT 1: Animal Studies

24 Randomized controlled trials (RCTs) under field conditions (22 report results by treatment group)
Antimicrobial resistance increased with use in 15/22 studies

Evidence insufficient to quantify extent to which limiting antimicrobials reduces resistance. Effect size may be specific to: antimicrobial, dose, animal, environment

- 4/22: mixed results

- 3/22: no difference or no significant difference

Remarks

- Heterogeneity: explained by different study types, animals, comparisons, antibiotics, isolates, animal housing/contexts.
- Use of one antibiotic in animals often resulted in development of resistance to another antibiotic - Chen 2008; Coe 2008; Platt 2008
- Often high baseline antibiotic resistance in food-producing animals even before administration of antibiotic - Alexander 2015/14; Checkley 2010; Coe 2008; Kaneene 2008
- Control animals in adjoining environment often developed antibiotic resistance over time with no direct exposure - da Costa 2009; Beyer 2015; Kanwar 2014

Evidence at a glance – PICOT 1				
Study types	RCTs (field cond.) = 24	Other controlled trials & challenge studies = 46	Cohort = 17	Interrupted Time Series = 2
Comparison	Antibiotic vs. none : 22 Antibiotic vs. w/d : 1 Antibiotic vs. intermittent vs. none : 1	Antibiotic vs. none : 32 Antibiotic vs. none; challenge: 10 Antibiotic vs. different dose of AB; challenge : 1 Antibiotic vs. different dose : 3 Antibiotic vs. different dose vs. none : 1 N=47 because 1 study reported 2 different experiments	Antibiotic vs. none : 13 Antibiotic vs. none vs. withdrawal :1 Association of exposure / prevalent (regression) : 1 Antibiotic stopped vs. never exposed : 1 Antibiotic vs. different dose :1	Before and after withdrawal of Antibiotic: 2
Animal studied	Pigs: 7 Chickens: 5 Cattle/ steers/ calves: 12	Pigs: 13 Chickens: 14 Cattle/steers/calves: 13 Lambs: 1 Turkeys: 3 Multiple (pigs, calves, chickens): 1 Non-extractable data: 1	Pigs: 7 Chickens: 3 Cattle/steers/calves: 5 Sheep: 1 Integrated fish farm: 1	Pigs: 1 Chickens: 1
Antibiotics studied	21 different antibiotics or combinations of antibiotics studied	28 different antibiotics or combinations of sntibiotics studied	7 different Antibiotics or combination of Antibiotics 10 studies looking at multiple Antibiotics (not always clear which)	2 different antibiotics studied

PICOT 2: Human Studies

Dutil 2010
Impact of withdrawal and subsequent reintroduction of ceftiofur
Association between the resistance in animals fed antibiotics and resistance in humans
Withdraw antibiotics in animals reduced resistance in animals and in humans
Re-introduction in animals increased in resistance in animals and in humans
Changes in resistance effects occur in humans after they appear in animals

- Large effect size: credibility of study
- Timeline credible: changes in resistance occur after changes in antibiotic practices
- Re-introduction of antibiotic caused re- emergence of resistance rates
- Withdrawal of ceftiofur resulted in reduction of resistance in both chickens and humans
- Sequential intervention with same results adds epidemiologic strength

Evidence at a glance – PICOT 2				
Study types	RCTs (field cond.) = 0	Other CTs & challenge studies = 1	Cohort = 4	Interrupted Time Series = 3
Comparison	--	High vs. med vs. low exposure to Antibiotic: 1	Association of dose / resistance: 2 Antibiotic vs. none: 2	Before & after ceasing antibiotic: 1 Before & after intro antibiotic: 2
Animal studied	--	Chicken: 1 -- --	Chickens: 1 Pigs: 2 Various: 1	Chickens: 2 -- Various: 1
Antibiotics studied	--	Tetracycline and sulfadimidine: 1	Amoxicillin & Tetracycline: 1 Tetracycline : 1 Vancomycin : 1 Various: 1	Ceftiofur: 1 Fluoroquinolone :2

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