**Supplemental Material**

Contents

[Supplemental Discussion 1: Future impact of AMR on health 2](#_Toc16252174)

[Supplemental Discussion 2: Future impact of AMR on global economy 3](#_Toc16252175)

[Supplemental Discussion 3: Methodology for Section 4 4](#_Toc16252176)

[Supplemental Discussion 4: Trends and Projections of AMU and AMS 5](#_Toc16252177)

[Supplemental Discussion 5: Judicious-Use Policies and Regulations in the US - An Example 7](#_Toc16252178)

[Supplemental Table 1. Summary of current and projected health and economic impacts of antimicrobial resistance 8](#_Toc16252179)

[Supplemental Table 2. Total amounts of antimicrobial agents applicable mainly for food-producing animals based on electronically available country reports. 13](#_Toc16252180)

## Supplemental Discussion 1: Future impact of AMR on health

Several major reports were compiled that attempt to model the future impacts of AMR, based on projected trends of AMR and infection rates to 2050. These reports include The UK Review on AMR (O’Neill 2014) – which utilized analyses commissioned by KPMG and RAND to produce global estimates - and a report commissioned by the Organization for Economic Co-operation and Development (OECD) - which produced estimates for 33 countries in North America, Europe, and Australia. Estimates on the total worldwide deaths attributable to AMR infections ranged greatly, from an average of 60,000 deaths/year in OECD countries to 700,000 deaths/year worldwide (KPMG 2014, O’Neill 2014, OECD 2018, Taylor et al. 2014). Under multiple scenarios, premature deaths ranged from a cumulative 11 million to 700 million, attributable to AMR by 2050 (KPMG 2014, Taylor et al. 2014). The AMR Review reported that, unchecked, AMR would result in 10 million deaths per year globally in 2050, and amount to 300 million premature deaths cumulatively by 2050 (KPMG 2014, O’Neill 2014). The OECD model estimated that by 2050, AMR will have caused a cumulative 2.4 million deaths worldwide among OECD countries. The OECD report additionally projected that by 2050, 1.75 million disability-adjusted-life-years (DALYs) will be lost annually due to AMR, across all modelled countries (EU/EEA, U.S., Canada, Australia) (OECD 2018). In absolute terms, the OECD model estimated that the USA would experience the highest health burden of AMR among OECD countries, with approximately 1 million deaths attributable to AMR infections and an average of 724,000 DALY’s lost per year in the USA, by 2050 (OECD 2018).

## Supplemental Discussion 2: Future impact of AMR on global economy

The KPMG, RAND, and World Bank reports provide the most recent estimates on the current and projected global economic impact of AMR from a societal perspective (Table 1) (KPMG 2014, Taylor et al. 2014, World Bank 2017). Estimates on the indirect economic impact of AMR ranged from 0.06% to 6.08% reduced global Gross Domestic Product (GDP), in the RAND and KPMG models respectively, by 2050 (KPMG 2014, Taylor et al. 2014). The AMR Review, which incorporates both of these analyses, estimated that unchecked, AMR will result in a reduction of the worlds GDP between 2% and 3.5% by 2050, corresponding to a cumulative loss of 60-100 trillion USD worth of economic output (O’Neill 2014). For the analytical methods, assumptions, and limitations of these estimates, we refer readers to the publicly available RAND and KPMG reports (KPMG 2014, Taylor et al. 2014). The World Bank estimated a 1.1-3.8% loss in global GDP, corresponding to a loss of $2-$6.1 trillion USD annually, by 2050, due to AMR (World Bank 2017). Similar to The AMR Review, the World Bank reports that the economic burden of AMR is not distributed equally at different levels of economic status, and that the negative impacts are more pronounced in low-income countries than in high-income countries. The World Bank report also noted that AMR in animals would result from declining livestock production due to greater prevalence of untreated disease, which would also be more pronounced in low-income countries.

The OECD and World Bank reports provide the most recent estimates on the projected global economic impact of AMR from a healthcare perspective (Table 1) (OECD 2018, World Bank 2017). Estimates on the global direct economic impact of AMR ranged from an average of $3.5 billion/year among OECD countries to $1.2 trillion USD/year worldwide, in the OECD and World Bank reports respectively, by 2050, due to healthcare related costs of AMR (OECD 2018, World Bank 2017). In absolute terms the USA is projected to experience the greatest annual healthcare related expenditures as a result of AMR (OECD 2018). The OECD report does not provide any estimates on indirect societal costs. We do not attempt to make any inter-estimate comparisons on the current and projected global economic impacts of AMR, for the reasons previously stated.

## Supplemental Discussion 3: Methodology for Section 4

Country-, regional-, and international reports, along with the scientific literature, were thoroughly researched and scrutinized to collect the total aggregated and individual antimicrobial class sales data within the animal agriculture sector. Both total antimicrobials sold and individual antimicrobial class amounts sold to the animal agriculture sector industry among country-level documents found online were tabulated and provided in Supplemental Table 2. For reports and manuscripts where antimicrobial class amounts (either through direct measurement or modeled) were unreported, aggregated values were included to offer the most comprehensive values currently available (Supplemental Table 2). Although we compare data from different years – which as a result may misrepresent the relative intensity of AMS among countries - our objective is to represent the most recent data with the greatest accuracy.

Unfortunately, many countries (primarily low- and middle-income countries) were not found to have publicly reported AMS for animal agriculture use. Therefore, global attribution and economic analyses cannot and should not be based only on data included in this review. Countries that officially reported sales were the same countries that compiled and published consumption data found in the literature (Cuong et al. 2018) (Supplemental Table 2). The region with the largest number country-level responses was Europe – 30 countries reported sales data in a comprehensive European document (EMA 2019) (Supplemental Tables 2, 3). In the Americas, only Canada and the USA were found to have publicly-available reports that described and enumerated AMS data for animal intentions; and in Asia only Japan, Korea, and Australia were identified to report similar data (Aust. Pestic. Vet. Med. Auth. 2014, CIPARS 2016, CVM & US FDA 2018, Minist. Agric. For. Fisheries 2015, QIA 2019). We did not find scientific literature, country, or regional reports that enumerated or described AMS data from African or South American countries.  Among international organizations, the OIE report offered total AMS from the same country-reports, which validated our findings (OIE 2017). Country- and regional-level documents reported both aggregated data that included total AMS in kilograms (Supplemental Table 2), and total amounts of AMS by class in kilograms, although unstandardized across countries (Supplemental Table 2). Some countries reported antimicrobial class totals (e.g. beta-lactams, 3rd generation cephalosporins, etc), while others documented AMS within class (penicillin, amoxicillin, ceftiofur, etc). One resource was found within the scientific literature that modeled global antimicrobial use using currently available sales data. Considering that in 2018, China produced 47.8% of pork, 11.8% of poultry, and 10.3% of beef in the global community, we would be remiss to ignore the country’s contribution to antimicrobial use (USDA & FAS 2019). While national level data is not publicly available, prior publications report estimates of antibiotic consumption in China for food-animal production, delineated in the main text.

## Supplemental Discussion 4: Trends and Projections of AMU and AMS

In the main text, we describe the most recent data available from reports, documents, and summaries, which elucidates a snapshot of antimicrobials sold *mainly* to the animal agriculture industry (language utilized by the European Medicines Agency). The US, EU, Canada, and Republic of Korea reports have aggregated sales data which incorporates both food-producing and non-food producing animals. For this analysis, we erred on the side of including all antimicrobial sales, with the assumption that the vast majority of antimicrobials sold to animals are within the livestock sector. This assumption was seen to be valid in comparison to total AMS in Australia, one of the two countries that that do disaggregate food- and non-food producing animals. In Australia, only 17,910 kg of the total 305,910 kg antimicrobials were sold to non-producing animals (5.63%) (Aust. Pestic. Vet. Med. Auth. 2014).

The authors also recognize the importance of historical context to understand trends. Our objective is to describe trends to project and anticipate future estimates of antimicrobials sold to the animal agriculture industry. To accomplish this, this section is divided into three parts. The first two summarize recent trends in AMS in the US and in European countries. The third part reports projected increases in AMU from 2010 to 2030 stratified by region and food-producing animals.

In the USA, the aggregated amount of MIA AMS to animal agriculture dropped by 33% from 2016 (8,356,340 kg) to 2017 (5,559,212 kg). Tetracyclines, the most used antibiotic in animal industry, dropped 40% between 2016 and 2017. Between 2009 to 2017, antibiotic sales to animal agriculture have decreased by an overall 33%. In terms of the type of antimicrobial prescriptions, most prescriptions require VFD for administration of antimicrobials via enriched feed. Between 2016 and 2017, there was a 1,671% increase in VFD/prescription (from 295,309 kg to 5,230,663 kg). This vast increase is consequential of the precipitous drop (96%) between 2016-2017 in MIA OTC drugs, which may have been used for production indications. In regard to sales to animal sectors, the cattle industry was sold 2,333,839 kg (42% of all antimicrobials sold), the swine industry was sold 2,022,932 kg (36%), and the chicken and turkey industry was sold 938,878 kg (17%) of antibiotics. All three industries have seen an overall decrease in consumption of 35%, 35%, and 15%, respectively (CVM & US FDA 2018).

European figures collected by the EMA indicated similar decreases in AMS. In 21/30 (70%) of the European countries, there were decreased AMS between 2015 and 2016. Overall tonnage decreased by 6.6% (8333.90 tonnes to 7787.07 tonnes). Of the 17 countries that participated from 2010 to 2016 (when the EMA began to report EU member state AMS data) – a 32% decrease in overall AMS (4467.52 tonnes to 3,039.9 tonnes). Tetracyclines and penicillins were the most sold antibiotics classes within animal agriculture. 2012 demonstrates peak sales of tetracyclines was; overall, a drop of 18% in tetracycline sales was noted from 2010 to 2016. All AMA drug class with the exception of aminoglycosides, which rose, and amphenicols 1st- and 2nd-generation cephalosporins, which was essentially unchanged, dropped in sales between 2015 and 2016 on a mg per population correction unit (mg/PCU) basis. Similarly, all classes decreased in mg/PCU between 2011 and 2016 with the exception of amphenicols, cephalosporins, fluoroquinolones, and aminoglycosides. Stratification of sales by species was launched in July 2018 and no data is yet released to determine this metric (EMA 2019).

Finally, Van Boeckel et al. predicted global antimicrobial consumption trends needed to produce animal protein from available 2010 data to the year 2030. They employed Bayesian regressions to predict total usage globally and by region and stratified by major food animal species. Van Boeckel et al. reported total global antimicrobial consumption within the food sector in 2010 of 63,151 tons, which they modeled to increase to 105,596 tons (67% increase) by 2030, with 49% of total consumption attributed to the Asian market (51,851 tons). In 2010, the top five countries who consumed the most antimicrobials were China (23%), the United States (13%), Brazil (9%), India (3%), and Germany (3%). Van Boeckel et al. predicted that by 2030, those contributions will be by China (30%), the United States (10%), Brazil (8%), India (4%), and Mexico (2%). Based upon current global eating patterns and trends, by the year 2030, chicken and pork sectors will increase antimicrobial consumption by 129% and 124% respectively (Binder et al. 1998).

## Supplemental Discussion 5: Judicious-Use Policies and Regulations in the US - An Example

For decades, the FDA has promulgated regulations and policies designed to curb uses of antimicrobials within the animal agriculture sector that may contribute to AMR in humans and/or animals and are less critical to maintain animal health. This material will describe the recent history and current regulatory environment in the US as an example of the complexities of AMU regulations in the animal agriculture sector. In 1996, the US established the National Antimicrobial Resistance Monitoring System (NARMS). In its original mandate, NARMS worked with CDC to collect foodborne illness data from humans across 14 states. In 1997, USDA joined the NARMS umbrella to collect animal carcass and fecal samples; and in 2002, the FDA began to sample retail poultry, pork, and beef (McDermott et al. 2015). NARMS’ efforts were fortified by the President’s Food Safety Initiative (FSI), released in 1997, which strengthened surveillance and coordinated activities among federal agencies to reduce foodborne illnesses country-wide (Binder et al. 1998).

Although NARMS and FSI were not strictly regulatory, they increased awareness of foodborne illness and set the stage for four regulations: GFI #152, GFI #209, GFI #213, and the VFD amendments. FDA’s GFI #152, 209, and 213 documents were not legally binding guidelines, and thus required voluntary adoption by stakeholders. The first of these documents, GFI #152, was proposed in 1998 as the “Framework Document” and implemented in 2003. It urged the implementation of qualitative risk assessment to determine the potential for animal antimicrobial agents to promote AMR (CDC & US FDA 1999, CVM & US FDA 2012). GFI #152 also conceptually divided antimicrobial agents into three ordinal categories based on their potency and utility in human medicine. GFI #209, finalized in 2012, built on the ideas presented in GFI #152 and was foundational to construct “judicious use of antimicrobials” policies within the animal agriculture sector. GFI #209 contains non-binding recommendations to advance two major guiding principles. First, the MIA agents listed in GFI #152 should only be administered “judiciously” to “assure animal health” and thus prohibited for use in feed efficiency and growth promotion. And second, GFI #209 proposed that MIA should be subject to veterinary oversight to ensure appropriate use (CVM & US FDA 2012). In December 2013, FDA promulgated GFI #213, which elaborated on the types of antimicrobial access for use in animal agriculture: over-the-counter (OTC), prescription (Rx), and VFD drugs. Notably, GFI #213 recommended that animal pharmaceutical companies remove production uses from antimicrobial drug labels. In its text, GFI #213 urged animal drug companies to transition OTC drugs without production labels to either Rx or VFD status. All major animal pharmaceutical companies espoused GFI #213 (US FDA 2019). Lastly, the VFD amendment, effective in October 2015, legally required veterinary prescription to order antimicrobials labeled for administration in feed, which accomplishes the second guiding principle set forth in GFI #209 (US FDA 2015).

**Supplemental Literature Cited[[1]](#footnote-2)**

Binder S, Khabbaz R, Swaminathan B, Tauxe R, Potter M. 1998. The national food safety initiative. *Emerg. Infect. Dis.* 4(2):347–49

CVM (Cent. Vet. Med.), US FDA (Food Drug Adm.). 2012. *Guidance for industry. The judicious use of medically important antimicrobial drugs in food-producing animals*. Guid. Doc. 209, CVM, US FDA, Rockville, MD. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-209-judicious-use-medically-important-antimicrobial-drugs-food-producing-animals

McDermott P, Tate H, Friedman C, Whichard J, Dessai U, et al. 2015. *NARMS 2015 integrated report*. Rep., US Dep. Health Hum. Serv., Food Drug Adm., Laurel, MD. <https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2015-narms-integrated-report>

Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. 2007. Veteran’s affairs hospital discharge databases coded serious bacterial infections accurately. *J. Clin. Epidemiol.* 60(4):397–409

Shrestha P, Cooper BS, Coast J, Oppong R, Do Thi Thuy N, et al. 2018. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. *Antimicrob. Resist. Infect. Control* 7(1):98

US FDA (Food Drug Adm.). 2019. List of medically important antimicrobial drugs affected by GFI #213. *Food and Drug Administration*. <https://www.fda.gov/animal-veterinary/judicious-use-antimicrobials/list-medically-important-antimicrobial-drugs-affected-gfi-213>

USDA (US Dep. Agric.), FAS (Foreign Agric. Serv.). 2019. *Country production total exports livestock and poultry: world markets and trade China’s share of world meat imports to expand in 2019*. Fact Sheet, USDA, Washington, DC. https://apps.fas.usda.gov/psdonline/circulars/livestock\_poultry.pdf

## Supplemental Table 1. Summary of current and projected health and economic impacts of antimicrobial resistance

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **AMR-pathogens** | **Site of infection** | **Region** | **Year** | **Health burden** | **Economic burden** |
| ***Global- and regional- level estimates*** | | | | | | |
| The AMR Review (O’Neill 2016) | MRSA, 3GCR-E. coli, 3GCR-K. pneumoniae, Resistant HIV, Resistant malaria, MDR-TB | BSI, UTI, Lower RTI, SSTI | Global | 2015-2050 | ***Excess deaths attributable to AMR by 2050:***  10 million deaths per year, resulting in a cumulative 300 million premature deaths | **Societal perspective**  ***Impact on GDP by 2050:***  2-3.5% decrease in global GDP, depending on scenario  ***Cumulative worldwide loss:***  $60 trillion - $100 trillion USD |
| RAND Europe (Taylor et al. 2014) | MRSA, 3GCR-E. coli, 3GCR-K. pneumoniae, Resistant HIV, Resistant malaria, MDR-TB | BSI, UTI, Lower RTI, SSTI | Global, including OECD, EU, EEA, Latin America, Middle East and North Africa, Eurasia, and Sub-Saharan Africa | 2010-2050 | ***Excess death attributable to AMR by 2050:***  11-444 million reduction in world population, depending on scenario | **Societal perspective**  ***Impact on GDP by 2050:***  0.06-3.1% decrease in global GDP, depending on scenario  ***Cumulative worldwide loss by 2050:***  $2.1 trillion - $124.5 trillion USD |
| KPMG (2014) | MRSA, 3GCR-E. coli, 3GCR-K. pneumoniae, Resistant HIV, Resistant malaria, MDR-TB | BSI, Lower RTI, SSTI, UTI | Global, 156 countries | 2012-2050 | ***Excess death attributable to AMR by 2050:***  200-700 million reduction in world population, depending on scenario | **Societal perspective**  ***Impact on GDP by 2050:***  1.66-6.08% decrease in global GDP, depending on scenario  ***Cumulative worldwide loss by 2050:***  $14.2 trillion USD under worst case scenario |
| World Bank (2017) | MRSA, 3GCR-E. coli, 3GCR-K. pneumoniae, Resistant HIV, Resistant malaria, MDR-TB | BSI, Lower RTI, SSTI, UTI | Global, including OECD, EU, EEA, Latin America, Middle East and North Africa, Eurasia, and Sub-Saharan Africa | 2017-2050 | NA | **Societal perspective**  ***Impact on GDP by 2050:***  1.1-3.8% decrease in global GDP, depending on simulation  ***Cumulative worldwide loss by 2050:***  $2 trillion - $6.1 trillion USD, depending on simulation  **Healthcare perspective**  ***Impact on healthcare costs by 2050:***  0.33 trillion-$1.2 trillion USD, depending on simulation |
| OECD (2018) | 8 bacteria and a total of 17 AMR-bacteria combinations  Bacteria included:  *Acinetobacter spp.*  *S. pneumoniae*  *S. aureus*  *E. coli*  *K. pneumoniae*  *P. aeruginosa*  *Enterococcus faecalis*  *Enterococcus faecium* | Five body sites including:  BSI  UTI SSI | EU/EEA countries, USA, Canada, Australia | 2015-2050 | ***Excess death attributable to AMR (current):***  60,000 deaths per year  ***Excess death attributable to AMR by 2050:***  2.4 million deaths per year  1.75 million DALYs lost per year | **Healthcare perspective**  ***Cumulative worldwide loss by 2050:***  $3.5 billion USD per year, resulting in a cumulative $134 billion USD  ***Loss by 2050 (EU/EEA* *countries only)*:**  $1.5 billion USD per year, resulting in a cumulative $60 billion USD |
| Temkin et al. 2018 | 3GCR-*E. coli*  CarR-*E. coli*  3GCR-*K. pneumonia*  CarR-*K. pneumonia* | Serious infections, BSI | 193 member states of the United Nations | 2014 | ***Cases of serious infection with 3GCR-Ec and 3GCR-Kp:***  50.1 million (27.5-72.8; additive model)  28.9 million (15.8-41.9; 75% replacement model)  ***Cases of BSI with 3GCR-Ec and 3GCR-Kp:***  6.4 million (3.5-9.2; additive model)  3.7 million (2.0-5.3; 75% replacement model)  ***Cases of serious infection with CarR-Ec and CarR-Kp:***  3.1 million (1.8-4.5; additive model)  2.7 million (1.5-3.8; 75% replacement model)  ***Cases of BSI with CarR-Ec and CarR-Kp:***  0.5 million (0.3-0.7; additive model)  0.4 million (0.2-0.6; 75% replacement model) | NA |
| ***Country- level estimates*** | | | | | | |
| Cassini et al. 2019 | CR-A  CarR-A  MDR-A  VR-E. faecalis  VR-E. faecium  CR-Kp  CarR-Kp  3GCR-Kp  CR-Pa  CarR-Pa  MDR-Pa  MRSA  PR-Sp  MR-Sp | BSI, UTI, RTI, SSI,  Other infections,  Secondary BSI | Member states of the European Union and European Economic Area | 2015 | ***Cases of infection:***  671,689 (95% UI: 583,148-763,966)  ***Attributable mortality:***  33,110 (28,480-38,430)  ***DALYs:***  *874,541 (768,837-989,068)*  ***Incidence:***  131 (113-149) infections per 100,000  **Incidence of attributable mortality:**  6.44 (5.54-7.48) deaths per 100,000 population  ***Incidence of DALYs:***  170 (150-192) DALYs per 100,000 population | NA |
| Thorpe et al. 2018 | Pathogens in CDC report (2013)  Clinically validated list of bacterial infections from Schneeweiss et al., 2007 | Complicated intra-abdominal infection  Bacteremia/sepsis  Cellulitis  Encephalitis  Intestinal infection  Osteomyelitis/septic arthritis  Pneumonia  UTI  Unspecified bacterial infection | USA | 2002-2014 | ***Total cases of AMR infections:***  1.2 million infections per year (average, 2002-2014)  1.6 million infections per year (2014) | **Payer perspective:**  ***Average incremental healthcare cost per case:***  1,383.15 USD (SD = 170.08)  ***Average national expenditure:***  2.2 billion USD per year |
| CDC Report (2013, 2019) | CarR-E  MDR-A  FR-C  ESBL+E  VR-*Enterococcus*  MDR-Pa  DR-Ng  DR-C  DR-NTS  DR-ST  DR-Shigella  MRSA  VRSA  DR-Sp  ER-GAS  CR-GBS | Various | USA | 2017 | ***Estimated minimum number of illnesses due to AMR-infections:***  2,868,700  ***Estimated deaths due to AMR-infections:***  35,900 | **Healthcare perspective**  ***Excess direct healthcare costs (2011):***  $20 billion USD annually  **Societal perspective**  ***Excess societal costs (2011):***  $35 billion USD annually |
| Shrestha et al. 2018 | MRSA  3GCR-*E. coli*  3GCR-*K. pneumonia*  CarR-*A. baumanii*  CarR-*P. aeruginosa* | BSI  UTI  RTI  SSI  SSTI  Endocarditis  Pneumonia  Bone and joint infection (BJI)  Other infections | USA  Thailand | USA: 2011  Thailand: 2010 | **Total infections**  ***USA:*** 129,761  ***Thailand:*** 87,751  **Excess deaths attributable to AMR**  ***USA:*** 14,535  ***Thailand:*** 19,122 | **Healthcare perspective**  **Direct healthcare cost due to human antibiotic consumption:**  ***USA:*** $68 million USD  ***Thailand:* $**52 million USD  **Societal perspective**  **Indirect societal cost due to human antibiotic consumption:**  ***USA:*** $2.81 billion USD  ***Thailand:* $.**44 billion USD  **Total economic cost (direct + indirect)**  ***USA:*** $2.9 billion USD  ***Thailand:* $**0.5 billion USD  **Externality**  **Cost of AMR per SU of antibiotic consumed:**  ***USA:*** $0.1 USD per SU for carbapenems - $0.6 USD per SU for quinolones, cephalosporins and broad spectrum penicillins  ***Thailand***: $0.1 USD per SU for macrolides - $0.7 USD per SU for quinolones, cephalosporins and broad spectrum penicillins |
| ***Meta-analysis of AMR-pathogen specific estimates*** | | | | | | |
| Wozniak et al. 2019 | A review of 14 studies/reports which concludes high quality estimates for: MRSA, 3GCR-E, ESBLP-E | BSI | Various | 2012-2016 | NA | **Healthcare perspective**  ***LOS:***  **MRSA**: +2.54 days (-3.19-8.27) (Stewardson 2016)  **3GCR-E**: +4.89 days (1.11-8.68) (Stewardson, 2016)  **ESBLR-E:** +6.8 days **(**Stewardson 2013)  ***Excess healthcare cost:***  **MRSA**: €1600 EUR  **3GCR-E**: €3200 EUR  **ESBLR-E:** 9473 CHF |
| Naylor et al. 2018 | Reviewed 214 studies, which included estimates on various AMR-pathogens | BSI  Pneumonia  Meningitis  Various | Various | 2013-2015 | ***Patient burden of AMR:***  48% (85/177) of studies found that AMR had a significant impact on mortality | ***LOS:***  69% (44/64) of studies found that AMR had a significant impact on LOS.  LOS ranged from +2.5 days to +20 days depending on AMR-pathogen and country  ***Incremental healthcare cost per case:***  Estimates ranged from non-significant to 88,150 USD depending on AMR-pathogen and country |

## Supplemental Table 2. Total amounts of antimicrobial agents applicable mainly for food-producing animals based on electronically available country reports.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Class of Antimicrobials | Amount of active antimicrobial ingredients used by country/region (kg) | | | | | |
| US (2017) | EU (2016) | AUS (2010) a | CAN (2016) | JAP (2015) a | ROK (2012) |
| Medically Important | Aminoglycosides | 232,504 | 399,300 | 5,880 | 14,952 | 35,467 | 46,071 |
| Amphenicols | 49,321 | 99,700 | 900 | - | 29,728 | 83,423 |
| Cephalosporinsb | 29,369 | 19,700 | 3,300 | 6,766 | 5,895 | 7,759 |
| Quinolonesc | 22,904 | 198,800 | 280 | 378 | 9057 | 49,149 |
| Lincosamides | 152,497 | 237,500 | 6,480 | 48,083 | 28,660 | 9,172 |
| Macrolides | 468,794 | 546,600 | 10.7d | 97,453 | 98,408 | 55,924 |
| Penicillins | 690,889 | 2,009,800 | 31,830 | 133,722 | 94,725 | 189,748 |
| Polymyxins | - | 397,200 | - | - | - | - |
| Pleuromutilinse | - | 218,300 | - | - | - | 17,740 |
| Sulfas | 274,112 | 897,900 | 20,030 | - | 96,670 | 102,273 |
| Tetracyclines | 3,535,701 | 2,251,000 | 59,010 | 513,890 | 333,858 | 281,974 |
| Trimethoprim | - | 148,300 | - | - | 12,146 | - |
| NIRf | 76,440 | 93,100 | 171,870 | 187,070 | 49,366 | 44,916 |
| SUBTOTAL | 5,559,212 | 7,787,100 | 299,580 | 1,002,313 | 756,498 | 888,149 |
| Non -medically Important | Ionophores | 4,394,850 | - | 11,700 | 487,733 | - | 47,618 |
| NIRg | 979,306 | - | 12,300 | 85,935 | - | 602 |
| SUBTOTAL | 5,374,156 | - | 24,000 | 573,668 | - | 48,220 |
| GRAND TOTAL | 10,933,367 | 7,787,200 | 323,580 | 1,575,982 | 756,498 | 936,369 |

1. Australia and Japan reports allow for disaggregation of food and non-food producing animals, whereas the other country-reports may include non-food producing animals in their estimates. For comparison, this includes non-food producing animals.
2. Cephalosporins class include all generations of cephalosporins (i.e. 1st, 2nd, 3rd, and 4th)
3. Quinolones class include both “Fluoroquinolones” and “Other Quinolones”
4. Australia lists macrolides and streptogrammins for therapeutic uses and streptogrammins together, therefore grouped with “NIR”. This amount reflects macrolides administered for growth-protant purposes
5. Pleuromutlilins class is listed as WHO “important” to human medicine, although other countries (e.g. United States) considers this drug non-medically important.
6. “Not Independently Reported” includes other antimicrobial classes not listed, “other” categories from country-wide reports, and combination antimicrobial classes reported (e.g. Trimethoprim and Sulfonamides aggregated data: (US: Diaminopyrimidines, Polymyxins, and Streptogramins; EU: 2 Bacitracin, fosfomycin, furaltadone, lincosamides, macrolides metronidazole, novobiocin, paromomycin, polymyxins, pleuromutilins, rifaximin, and spectinomycin; AUS: aminocoumarins, macrolides and streptogrammins, nitroimidazoles, polypeptides, and “others”; CAN: Trimpethroprim, sulfonamides, avilamycin, bacitracins, bambermycin, chloramphenicol, chlorhexidine gluconate, florfenicol, fusidic acid, nitarsone, nitrofurantoin, nitrofurazone, novobiocin, polymixin, tiamulin, and virginiamycin; JAP: furan and derivatives, ormethoprim, tiamulin (derivatives), valnemline, bicozamycin (derivatives), Fosfomycin (derivatives), fosforycin; ROK: novobiocin, polypeptides, streptogrammins, and “others”)
7. “Not Independently Reported” includes other non-medically important antimicrobial classes including glycopeptides, polypeptides, quinoxalines, and orthosomycins. However, discrepancies exist between what constitutes medically important, therefore some countries may incorporate antimicrobials into “other” as non-medically important, while WHO considers it to be important. (US: aminocoumarins, glycolipids, orthosomycins, pleuromutilins, Polypeptides, and Quinoxaline; AUS: glycopeptides, oligosaccharides, and quinoxaline; CAN: chemical coccidiostats; ROK: orthomycins, glycopeptides.

1. Citations that do not appear in the Supplemental Literature Cited can be found in the Literature Cited to the main article. [↑](#footnote-ref-2)