

The application of antibiotics in broiler production and the resulting antibiotic resistance in *Escherichia coli*: A global overview

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ABSTRACT The increase in antibiotic resistance is a global concern for human and animal health. Resistant microorganisms can spread between food-producing animals and humans. The objective of this review was to identify the type and amount of antibiotics used in poultry production and the level of antibiotic resistance in *Escherichia coli* isolated from broilers. Isolate information was obtained from national monitoring programs and research studies conducted in large poultry-producing regions: US, China, Brazil, and countries of EU—Poland, United Kingdom, Germany, France, and Spain.

The survey results clearly display the absence of a harmonized approach in the monitoring of antibiotics per animal species and the evaluation of resistances using the same methodology. There is no public long-term quantitative data available targeting the amount of antibiotics used in poultry, with the exception of France. Data on antibiotic-resistant *E. coli* are available for most regions but detection of resistance and number of isolates in each study differs among regions; therefore, statistical evaluation was not possible. Data from

France indicate that the decreased use of tetracyclines leads to a reduction in the detected resistance rates. The fluoroquinolones, third-generation cephalosporins, macrolides, and polymyxins (“highest priority critically important” antibiotics for human medicine according to WHO) are approved for use in large poultry-producing regions, with the exception of fluoroquinolones in the US and cephalosporins in the EU. The approval of cephalosporins in China could not be evaluated. Tetracyclines, aminoglycosides, sulfonamides, and penicillins are registered for use in poultry in all evaluated countries. The average resistance rates in *E. coli* to representatives of these antibiotic classes are higher than 40% in all countries, with the exception of ampicillin in the US. The resistance rates to fluoroquinolones and quinolones in the US, where fluoroquinolones are not registered for use, are below 5%, while the average of resistant *E. coli* is above 40% in Brazil, China, and EU, where use of fluoroquinolones is legalized. However, banning of fluoroquinolones and quinolones has not totally eliminated the occurrence of resistant populations.

Key words: antimicrobial, avian, *E. coli*, resistance, poultry

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INTRODUCTION

The application of antimicrobials results in the emergence and spread of antimicrobial resistance, which is a cause of worldwide concern (Garcia-Migura et al.,

2014). An antimicrobial agent is defined as a “naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kills or inhibits the growth of microorganisms) at concentrations attainable in vivo. Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition” (World Organisation for Animal Health, 2016). Although antimicrobial agents are active against bacteria, protozoa, viruses, and fungi, it is the antibacterial class that is of greatest interest for public health (Page and Gautier, 2012). Thus, the present review will exclusively focus on the antibacterial class of antimicrobial agents. The term antibiotic will be applied throughout this paper, as this term is widely used. This paper provides information on the antibiotic usage (AU) and

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antibiotic resistance (AR) in broilers. The term poultry is used in the paper if the sources cited do not clearly distinguish between the poultry and broilers. However, 87% of poultry production is broiler production (FAO, 2010).

Accelerated evolutionary trends toward AR are a major threat to human and animal health (Harbarth et al., 2015; World Health Organization, 2015; European Food Safety Authority and European Centre for Disease Prevention and Control, 2016). In addition to being essential for the treatment and prophylaxis of human infections, antibiotics are also widely applied in food-producing animals, which can serve as a reservoir of antibiotic-resistant bacteria and AR determinants that may be transferred to humans (Marshall and Levy, 2011). Subsequently, the effectiveness of antibiotics in humans decreases, resulting in treatment failures (Aarestrup et al., 2008; Mellata, 2013; European Food Safety Authority and European Centre for Disease Prevention and Control, 2016).

In recent decades, broilers have increased in relevance as a meat source. Data about AU and AR in *Escherichia coli* in broilers are shown for the largest broiler meat producers worldwide: the United States, Brazil, China, and countries of European Union—Poland, United Kingdom, Germany, France, and Spain. These regions count for approximately 60% of the total worldwide broiler production, as shown in Figure 1 (Association of Poultry Processors and Poultry Trade in the EU Countries, 2015; United States Department of Agriculture, 2016).

Broiler meat produced by these countries is exported globally. For example, broiler meat from Brazil reaches 142 countries (Ministry of Agriculture Livestock and Farming in Brazil, 2016a). The amount of exported broiler meat per country in 1,000 metric ton is as follows: Brazil, 4,090; US, 3,057; EU, 1,180; China 375 (United States Department of Agriculture, 2016). This review lists the governmental authorization and monitoring of antibiotics in use in poultry and the available data of AR in *E. coli* of broiler origin. *Escherichia coli* is regarded as indicator organism of AR for a wide range of bacteria (EFSA, 2008; Kaesbohrer et al., 2012). Data from the monitoring programs and available scientific literature about AR in *E. coli* from the US, Brazil, China, and the large poultry producers in the EU from 2000 to 2017 were considered. All sources were obtained through online database searches including the Web of Science, PubMed, Scopus, and Google using translations from Chinese, Portuguese, Polish, German, French, and Spanish.

The objective of this study was to identify the legalized antibiotics, the amounts thereof administered, and the level of AR monitored in *E. coli* isolated from broilers originating from the large poultry-producing regions such as US, China, Brazil, Poland, United Kingdom, Germany, France, and Spain. We hypothesize that the application of antibiotics leads to high and consistent resistance levels in *E. coli* isolates, whereas ban of

(A) Broiler Meat Production worldwide (1000 MT)



(B) Broiler Meat Production in European Union (1000MT)



Figure 1. Broiler meat production in 1,000 metric tons (MT) by country worldwide (A) and in the European Union (Association of Poultry Processors and Poultry Trade in the EU Countries 2015; United States Department of Agriculture, 2016).

some classes of antibiotics results in low resistance levels. This review is the first comprehensive evaluation of data recording the authorized antibiotics for poultry production combined with AR data in *E. coli* isolates in large poultry-producing regions.

USE OF ANTIBIOTICS

Antibiotics in poultry are generally administered to the entire flock and are used for the treatment of disease (therapy), disease prevention (methaphylaxis), and growth promotion (Poole and Sheffield, 2013). Antibiotic growth promoters were banned in the EU in 2006, in the US in 2017 and are currently allowed in Brazil and China (European Commission, 2005, AccessScience Editors, 2017). Antibiotic usage for disease prevention is permitted in all large poultry-producing countries. Antibiotics are applied for the treatment of intestinal infections such as colibacillosis, necrotic enteritis, and other diseases generally caused by *Salmonella*, *E. coli*, or *Clostridium* spp. These infections are a major concern among poultry leading to enormous economic losses (United States Department of Agriculture, 2015). The type and extent of AU differ from country to country based on the country's economy, and its level of development, animal husbandry, and the animal species (Archawakulathep et al., 2014). The method of administration and the volume of antibiotic used vary

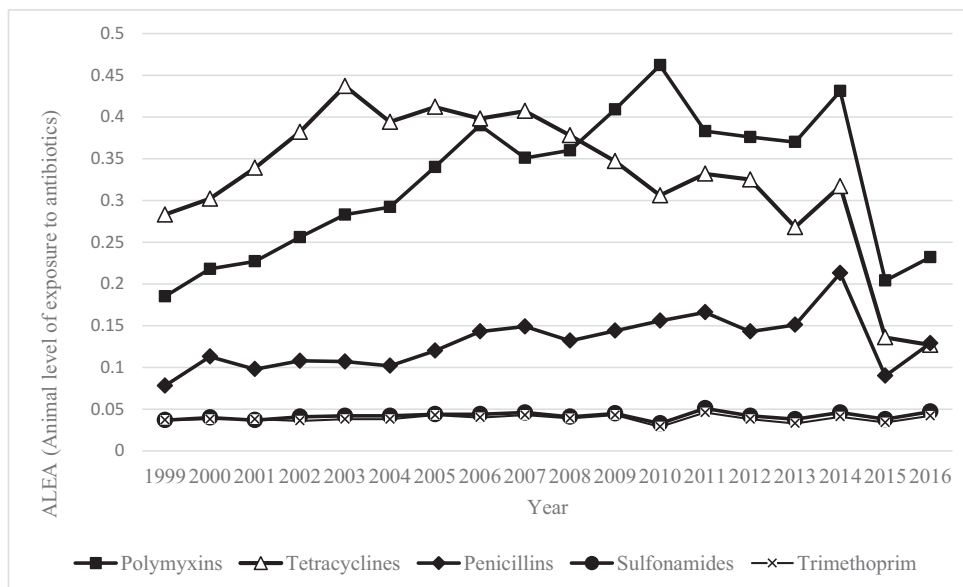


Figure 2. Sales of antibiotics for use in poultry by class between 1999 and 2013 in ALEA (France), modified from French Agency for Food Environmental and Occupational Health & Safety and French Agency for Veterinary Medicinal Products (2017). ALEA = [Live weight treated]/[Total number of animals] × [Weight of adult animals or at slaughter].

depending on the stage of production and the risk of disease (Rosengren et al., 2010). In general, there are different methods of monitoring AU: following the sales of antibiotics is one method, although long-term data for individual animal species are unavailable (with the exception of France); the detection of prescribed antibiotics per animal species; and the detection of AU in animals on farm level.

The French Agency for Veterinary Medicinal Products has monitored the sale of active antibiotic substances applied in poultry production since 1999. In 2016, 106 metric ton of active antibiotic substances were sold for use in poultry. This number represents 20% of all veterinary antibiotics and an average annual consumption of 47 mg of active ingredients per kilogram of chicken produced (French Agency for Food Environmental and Occupational Health & Safety and French Agency for Veterinary Medicinal Products, 2017). Figure 2 shows the changes in the sales of mainly applied antibiotic classes, expressed using the Animal Level of Exposure to Antimicrobials indicator for poultry between 1999 and 2016. In 2016, poultry herds were basically treated with polymyxins, penicillins, and tetracyclines, then with sulfonamides and trimethoprim (French Agency for Food Environmental and Occupational Health & Safety and French Agency for Veterinary Medicinal Products, 2017).

No quantitative monitoring data of AU in broilers are currently available in most large poultry-producing countries. Only in the US, data on AU of medically important antibiotics per animal species are available for 2016, which do not provide the complete picture on AU in broilers as it does not include non-medically important antibiotics (US Food and Drug Administration, 2017). However, the list of antibiotics that are approved

by regulatory agencies may provide an indication of the use of antibiotics in poultry production in every country considered in this report. National listings of all medical products that are approved for use for poultry in the US, Brazil, China, Poland, United Kingdom, Germany, France, and Spain were analyzed for active antibiotic substances that may be used in feed, water, or administered parenterally.

The WHO categorizes fluoroquinolones, third- and fourth-generation cephalosporins, macrolides, glycopeptides, and polymyxins as “highest priority critically important” antibiotics for human medicine due to the limited availability of alternatives for the treatment of bacterial infections. These antibiotics are the preferred option for the treatment of serious human infections (World Health Organization, 2011). The data in Table 1 show that fluoroquinolones, third-generation cephalosporins, macrolides, and polymyxins are approved for use in poultry in the largest poultry-producing countries, with the exception of fluoroquinolones in the US and cephalosporins in the EU. The FDA banned the use of enrofloxacin in poultry in the US in 2005 (US Food and Drug Administration, 2005).

ANTIBIOTIC RESISTANCE IN *E. COLI* FROM BROILERS

The use of antibiotics in poultry production increases the selection pressure for antibiotic-resistant bacteria (Diarra and Malouin, 2014). *Escherichia coli* are commensal bacteria that are ubiquitous in animals and humans. Because of their widespread availability, monitoring of commensal bacteria allows the comparison of

Table 1. Antibiotic substances approved for use in poultry by national regulative authorities in the US, Brazil, China, Poland, United Kingdom, Germany, France, and Spain based on national reports.¹

Antimicrobial class	Compound	US	BR	CN ²	PL	GB	DE	FR	ES	
Aminoglycosides	Apramycin		x	x		x				
	Gentamicin	x	x							
	Hygromycin	x								
	Kanamycin		x							
	Neomycin	x	x	x	x		x	x	x	
	Spectinomycin	x	x	x	x		x	x		
Arsenical	Streptomycin	x	x							
	Arsanilic acid	o		x						
	Nitarsons	o								
β-lactams—penicillins	Roxarsone	o	x							
	Amoxicillin		x	x	x	x	x	x	x	
	Ampicillin		x	x			x	x		
	Benzlypenicillin	x	x				x		x	
β-lactams—1 g cephalosporins	Phenoxymethyl-penicillin		x		x		x			
	Cefalexin		x							
β-lactams—3 g cephalosporins	Ceftiofur	x	x							
Diaminopyrimidines	Ormethoprim	o								
	Trimethoprim		x	x	x	x	x	x	x	
	Florfenicol			x	x					
Fenicols	Thiamphenicol			x	x					
	Ciprofloxacin			x						
Fluoroquinolones	Difloxacin			x	x					
	Enrofloxacin		x	x	x	x	x		x	
	Flumequine				x			x	x	
	Norfloxacin		x							
	Bambermycin	x		x						
Glycophospholipid Ionophores	Hainanmycin			x						
	Lasalocid	x		x						
	Maduramicin	x	x	x						
	Monensin	x	x	x						
	Narasin	x	x							
	Salinomycin	x	x	x						
	Semduramicin	x	x							
	Lincomycin	x	x	x	x		x	x	x	
Lincosamides	Erythromycin	x		x	x			x	x	
	Tylosin	x	x	x	x	x	x	x	x	
Macrolides	Tilmicosin		x	x	x	x	x		x	
	Spiramycin				x			x		
	Tylvalosin				x		x			
	Kitasamycin		x	x						
	Avilamycin	x		x						
	Fosfomycin		x							
Pleuromutilins	Tiamulin		x		x	x	x		x	
Polypeptides	Enramycin		x	x						
	Bacitracin	x	x	x						
Polymyxmins	Colistin	x	x	x	x	x	x	x	x	
Quinolone	Halquinol		x							
	Oxolinic acid							x		
	Virginiamycin	x		x						
Streptogramins Sulfonamides	Phalysysulfathiazole		x							
	Sulfachlorpyrazine				x		x			
	Sulfachlorpyridazine	x		x						
	Sulfadiazine		x			x		x		
	Sulfaguandine		x							
	Sulfadimethoxine	x	x		x		x	x	x	
	Sulfadimidine		x				x	x		
	Sulfamerazine	x								
	Sulfamethazine	x	x							
	Sulfamethoxazole		x	x	x		x		x	
	Sulfamethoxypyridazine		x						x	
	Sulfanilamide		x							
	Sulfaquinoxaline	x	x	x			x	x		
	Sulfisoxazole		x							
	Sulfomyxin	x								
	Tetracyclines	Chlortetracycline	x	x	x	x	x	x		x
		Doxycycline		x	x	x	x	x		x
Oxytetracycline		x	x	x	x		x	x	x	

Table 1. continued

Antimicrobial class	Compound	US	BR	CN ²	PL	GB	DE	FR	ES
Thiostrepton 50S	Tetracycline	x		x	x	x		x	x
	Nosiheptide			x					

¹Following national reports were used: US—US Food and Drug Administration 2016; Brazil—Ministry of Agriculture Livestock and Farming in Brazil 2008, 2014, 2016b; China—Ministry of Agriculture of People's Republic of China, 2001, 2013; Poland—The office for registration of medicinal products medical devices and biocidal products in Poland 2016; the United Kingdom—Veterinary Medicine Directorate UK 2016; Germany—German Federal Ministry of Health 2016; France—French Agency for Food Environmental and Occupational Health & Safety 2016; Spain—Spanish Agency of Medicines and Sanitary Products 2016.

²CN—the list of licensed antibiotics in China does not include parenterally administered antibiotics.

US—USA, BR—Brazil, CN—China, PL—Poland, GB—United Kingdom, DE—Germany, FR—France, ES—Spain, o—antibiotic was voluntarily withdrawn by producers.

the selective pressure effects in all relevant populations and is considered useful as an early alert system, for tracking emerging resistance in livestock and possible spread to animal-derived food (EFSA, 2008). Due to this prevalence, they are widely accepted as indicator bacteria for AR in Gram-negative bacteria populations and serve as a model for studying the emergence of AR (Kaesbohrer et al., 2012). Additionally, *E. coli* as well as other bacteria of the commensal flora can form a reservoir of AR genes that may be transferred between bacterial species, including organisms capable of causing disease in both humans and animals. The effects of antibiotics used and the trends in the prevalence of AR in food-producing animals can be more accurately investigated in this indicator bacterium, than in food-borne pathogens (European Food Safety Authority, 2008). Reflecting the awareness of the AR problem and the need for research on the triggers that cause AR development and spreading, some countries established strategies for surveillance and monitoring programs that concern AR and its determinants. Usually, national monitoring studies publish data yearly and use the same criteria for the determination of antibiotic resistances (European Food Safety Authority and European Centre for Disease Prevention and Control, 2018; US Food and Drug Administration, 2018). However, there is no harmonized evaluation of AR in different monitoring programs, which makes the comparison between regions impossible.

An overview of the prevalence of AR in *E. coli* is given for the US, Brazil, China, Poland, the United Kingdom, Germany, France, and Spain by using the results of their national monitoring programs as well as the scientific literature. Each scientific study evaluates AR using different methodology (and number of isolates); therefore, the statistical comparison is not possible. However, descriptive presentation of available data is possible. The source of AR data from each country is provided below in the description of each country. Additionally resistance rates and their evaluation from national monitoring systems of Poland, the United Kingdom, Germany, France, and Spain are presented in the section Supplementary material, due to the large volume of data. All cited resistance rates from 2000 to 2017 are presented with the support of GraphPad PRISM (2016). The outcome of the evaluation is the plot diagram (Figures 4 and 5), which is presented in the section overarching view.

Because of the harmonized sampling and detection of AR at the national levels, the AR results are shown in the form of figures, allowing the comparison of AR in *E. coli* over time. The data regarding AR in *E. coli* that is reported in scientific publications are presented in tabular format and includes the number of *E. coli* isolates that were tested and the average percentages of detected AR (Tables 2 and 3). If more than one set of data were indicated, data on the minimal and maximal AR rates in *E. coli* are additionally presented in

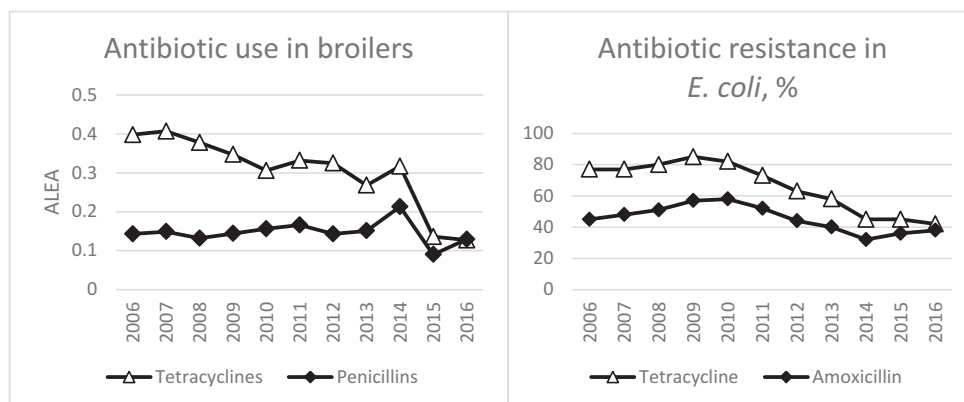


Figure 3. Tetracycline and penicillins use in poultry and resistance in *E. coli* isolates from broilers in France. ALEA (Animal level of exposure to antibiotics) = Animal level of exposure to antibiotics.

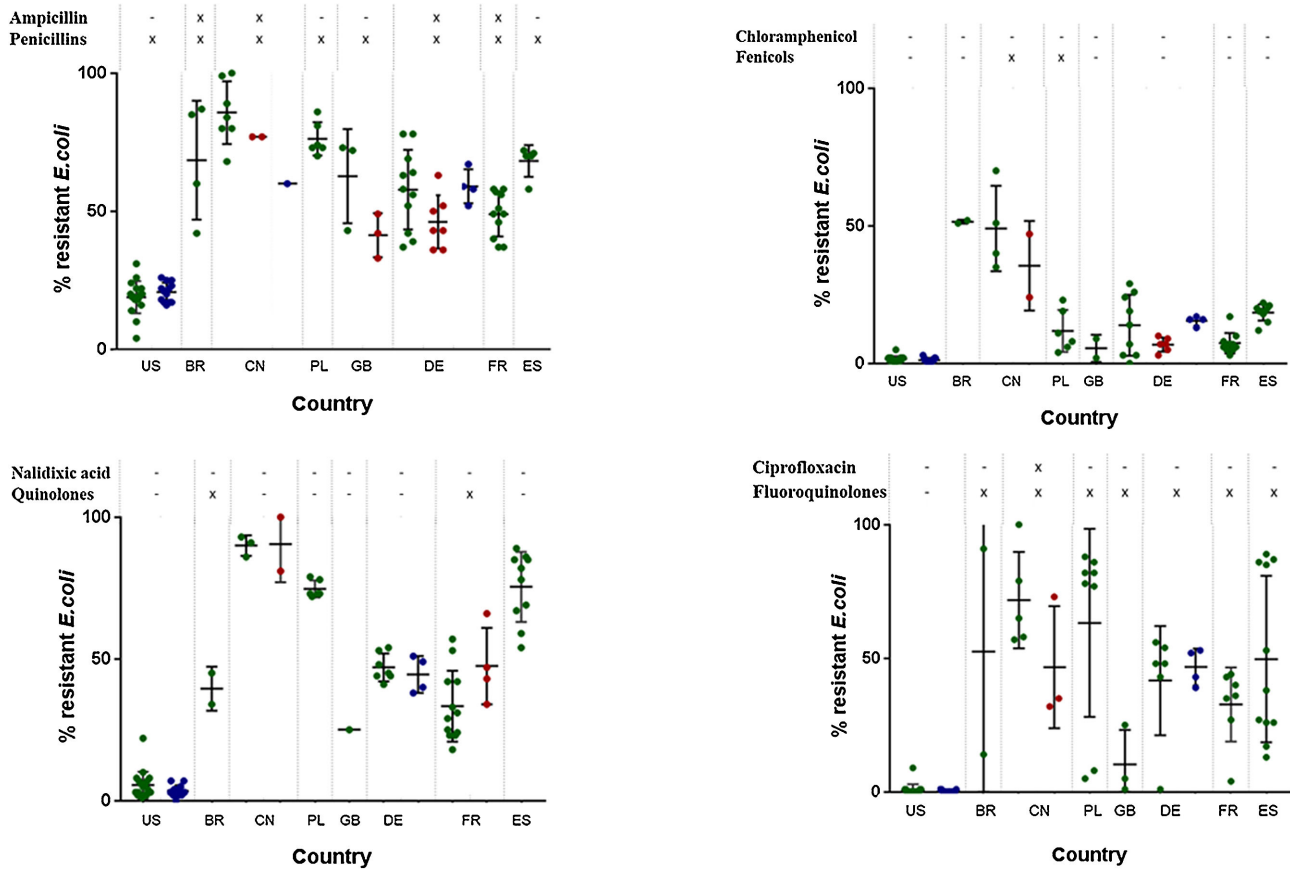


Figure 4. Resistance rates in *E. coli* to antibiotics from healthy animals (green dots), chicken retail meat (blue dots), and diseased chickens (red dots) detected within scientific studies or national monitoring programs. Each dot represents 1 study or data set in 1 yr. On the top of the figure, status of approval for the specific antibiotic tested for resistance (first line), the antimicrobial class (second line).

the tables. Throughout the paper, the percentage of AR is defined as the percentage of resistant *E. coli* as proportion of the number of tested *E. coli* isolates.

The literature analyzed in this review uses different breakpoints to determine AR; additionally, resistance levels of *E. coli* were determined in the different time points. Therefore, any interpretation of these results should consider this issue/fact. Nevertheless, surveillance systems, together with scientific literature, provide valuable contribution for the overview of the occurrence of AR in the indicator organism *E. coli* combining this data with possible AU in large poultry-producing regions. The evaluation of data is included in the description of each country and it shows the need for global harmonized approach in the detection of AU and AR.

United States of America

Established in 1996, the National Antibiotic Resistance Monitoring System (NARMS) is a national public health surveillance system in the US. The United States Department of Agriculture (USDA) reports each year AR in *E. coli* isolates from retail raw chicken meat, caecal *E. coli* isolates from slaughtered animals, and isolates from processing plants collected as part of the

Hazard Analysis Critical Control Point (HACCP). All data are available and easy to compare on NARMS interactive database (US Food and Drug Administration, 2018). NARMS uses similar methods and defined protocols, which supports the analysis. The monitoring of AR in the US shows similar resistance rates in *E. coli* from retail meat, slaughterhouse, and intestinal samples. The testing of AR from different sources to the same antibiotics makes this comparison possible. Antibiotic resistance rates in *E. coli* remain on the same level from 2000 to 2015, only resistance to streptomycin decreases from 78 to 46%. Independent from the source of the isolates, resistance rates of approximately 45% were detected for streptomycin, tetracycline, and sulfamethoxazole-sulfisoxazole. Antibiotic resistance percentages of *E. coli* from broilers in the US obtained by scientific publications show similar resistance rates for streptomycin and tetracycline as detected in the monitoring programs (Johnson et al., 2007; Smith et al., 2007; Zhang et al., 2011; Millman et al., 2013; Rothrock et al., 2016). However, this comparison cannot be statistically evaluated due to the different methodologies of AR determination in scientific studies and national monitoring. Streptomycin and tetracycline are approved for use in poultry. In contrast, sulfamethoxazole and sulfisoxazole are not licensed, but there are other sulfonamides that are approved and therefore may influence the

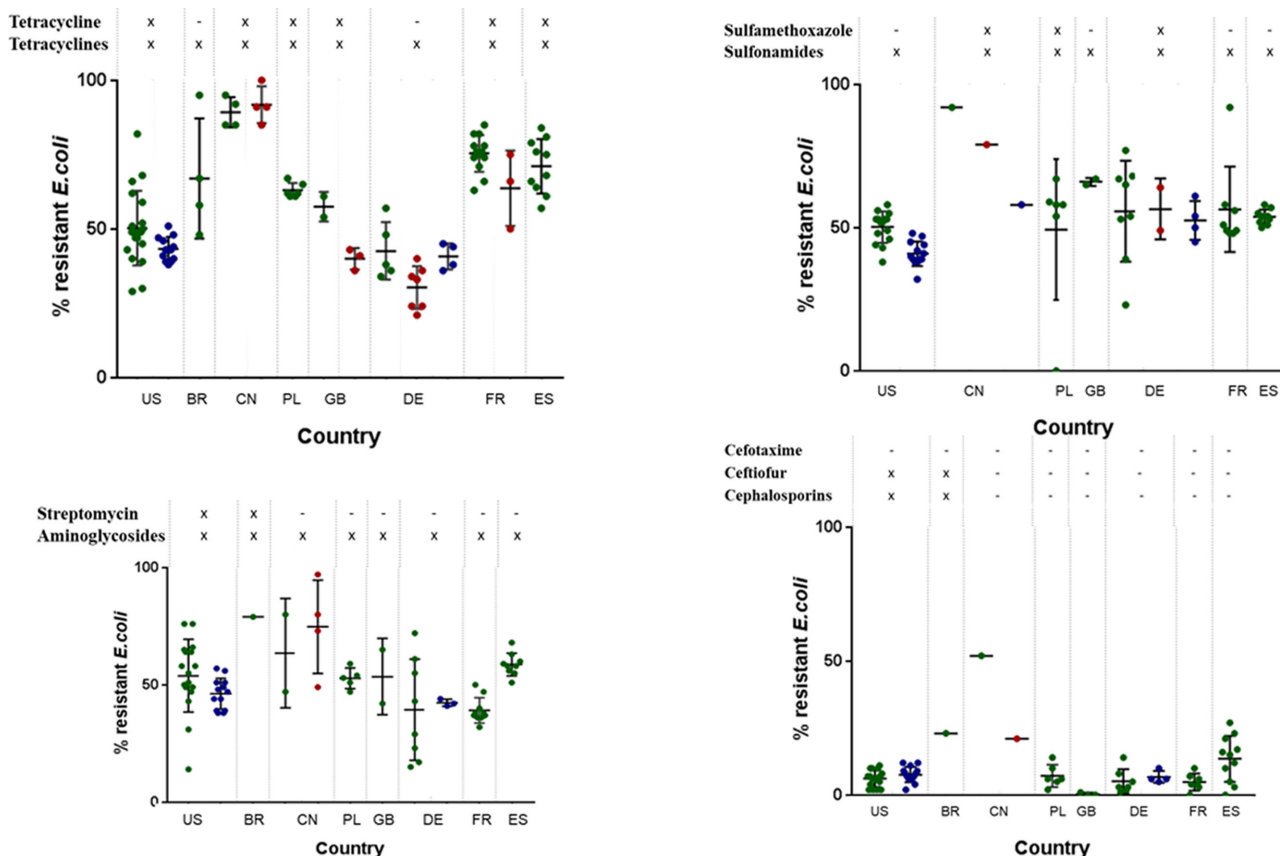


Figure 5. Resistance rates in *E. coli* to antibiotics from healthy animals (green dots), chicken retail meat (blue dots), and diseased chickens (red dots) detected within scientific studies or national monitoring programs. Each dot represents 1 study or data set in 1 yr. On the top of the figure, status of approval for the specific antibiotic tested for resistance (first line), the antimicrobial class (second line).

resistance rates. Resistance rates to gentamicin (approved for use) and ampicillin (not approved, but penicillins approved) are approximately 40 and 20%, respectively. Consequently, detected higher resistance rates in *E. coli* may be driven by the use of antibiotics, but quantitative data on AU would be needed in order to confirm this hypothesis.

Brazil

Brazil does not have any central microbiology reference laboratory. Therefore, no regular AR-monitoring data are available (Rossi, 2011). An overview of the scientific publications that presents the percentages of AR in *E. coli* isolates from broilers in Brazil since 2001 is shown in Table 2.

In general, the low number of studies as well as use of different numbers of isolates in each study does not allow any proper conclusions about resistance rates, which shows the necessity of national monitoring. According to Table 2, the highest detected resistance rates of *E. coli* from broilers were identified in the study of Barros et al. (2012) for lincomycin, erythromycin, and oxolinic acid, with 100, 97, and 88% of resistant isolates, respectively. Lincomycin is registered for use in Brazil, while erythromycin and oxolinic acid are not allowed, but other representatives of macrolides (tylosin

and tilmicosin) and quinolones (halquinol) are registered for use. Resistance rates to penicillins and ampicillins are around 75 and 65%, respectively. Representatives of both antibiotic classes may be used for poultry in Brazil. More studies found variations in the AR rates of *E. coli* from broilers to the antibiotic combination of sulfamethoxazole and trimethoprim. Hence, 1 study reports that 100% of the 174 isolates that were tested were resistant (Bezerra et al., 2016), while 3 other studies detected resistance rates of 66 and 68% in 66 and 91 isolates, respectively (Cardoso et al., 2002; Stella et al., 2013). Moreover, 2 additional studies present resistance rates of 27 and 28% in 70 and 120 tested isolates, respectively (Pessanha and Filho, 2001; Korb et al., 2015). The variation of resistance rates may be explained by different locations of studies as well as different times of detections.

China

There is no national monitoring of AR in *E. coli* isolates from poultry in China. Table 3 presents an overview of the percentages of AR in *E. coli* isolates from healthy and diseased broilers in China from available scientific literature from 2004 to 2017.

The results presented in Table 4 indicate that the AR rates in *E. coli* to sulfonamides and tetracyclines

Table 2. Percentages of *E. coli* isolates from broilers in Brazil exhibiting resistance to antibiotics published in scientific literature based on Cardoso et al. (2002), Barros et al. (2012), Bezerra et al. (2016), Pessanha and Filho (2001), Stella et al. (2013), and Korb et al. (2015).

Class	Compound	% res average	% res min	% res max	No. of studies	No. of isolates
Aminoglycosides	Gentamycin	27	26	28	2	244
	Streptomycin	79			1	91
Cephalosporines	Cefalexin	31	0	61	1	35
	Cefepime	10			1	120
	Cefotaxime	23			1	120
	Ceftazidime	3			1	120
	Ceftiofur	43			1	174
	Ceftriaxone	24			1	120
	Cephalothin	65	51	78	2	161
Fosfomycins	Fosfomicin	29	10	45	3	360
Lincosamides	Lincomycin	100	100	100	1	35
Macrolides	Azithromycin	49			1	174
	Erytromycin	97			1	91
Nitrofurans	Nitrofurantoin	13			1	120
Penicillines	Amoxicillin	65	50	84	2	101
	Ampicillin	69	42	87	4	455
Phenicol	Chloramphenicol	52	51	52	2	244
	Thiamphenicol	51	25	77	1	35
Polymyxins	Polymyxin B	1			1	174
Quinolone	Ciprofloxacin	53	14	91	2	294
	Enrofloxacin	40	13	76	2	155
	Nalidixic acid	40	34	45	2	199
	Norfloxacin	59	38	76	2	101
	Oxolinic acid	88			1	66
Tetracyclines	Chlortetracycline	74	63	84	1	35
	Oxitetracycline	81	62	100	1	35
	Tetracycline	67	48	95	4	455
Combination of compounds	Trimethoprim-Sulfamethoxazole	60	27	100	6	556

% res—average value of percentages of antibiotic resistant *E. coli* found in referenced studies.

% res min—minimal value of percentages of antibiotic resistant *E. coli* found in referenced studies.

% res max—maximal value of percentages of antibiotic resistant *E. coli* found in referenced studies.

are around 80%, and 40% to phenicol. Representatives of all 3 antibiotic classes are approved for the use in poultry. The resistances vary in the ranges of 50 to 100% for quinolones, 30 to 80% for penicillins, 20 to 70% for aminoglycosides, and 4 to 45% for cephalosporins. Quinolones and penicillins are registered for the use in poultry, while cephalosporins are not. However, it has to be taken into account that listed licensed antibiotics in China do not include parenterally administered antibiotics.

Antibiotic susceptibility testing of 326 *E. coli* isolates from food animals collected in China over the last 4 decades showed that AR in *E. coli* in the country has increased since the 1970s (Song et al., 2010). Furthermore, an evaluation of 540 *E. coli* isolates from broilers showed that resistance to amikacin, ampicillin, aztreonam, ceftazidime, cefotaxime, cephalothin, chloramphenicol, ciprofloxacin, fosfomicin, levofloxacin, norfloxacin, nalidixic acid, piperacillin, and trimethoprim-sulfamethoxazole increased significantly from 1993 to 2013 (Chen et al., 2014). Liu et al. (2016) observed a major increase of the relevance of colistin resistance in *E. coli* in China due to the detection of the plasmid-mediated colistin resistance mechanism MCR-1.

European Union

The European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) jointly analyzed data submitted by EU Member States regarding AR in *E. coli* from broilers. The organizations presented the results in the annual “European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food”. Last report evaluates AR in bacteria isolated in 2016 (EFSA/ECDC, 2018). Antibiotics were selected based on their relevance to public health and/or their epidemiological relevance. Epidemiological cut-off values were used for the AR interpretation (European Food Safety Authority, 2008). France, Germany, Poland, and Spain have participated in the monitoring since 2008. An overview of the prevalence of resistance for the largest poultry-producing countries in the EU for 2015 is shown in Table 4.

In addition to this EU monitoring, Poland, the UK, Germany, and France have national AR-monitoring systems. Some data from national monitoring are used for EU monitoring. Thus, they correspond to each other. There is a variation in resistance rates in

Table 3. Percentages of *E. coli* isolates from broilers exhibiting resistance to antibiotics in China, based on Dai et al. (2008), Chen et al. (2014), Ho et al. (2011), Gai et al. (2015), Lei et al. (2010), Jiang et al. (2011), Lu et al. (2010), Wu et al. (2015), Yang et al. (2004), Yu et al. (2012), and Zhang et al. (2012a,b, 2014, 2016).

Class	Compound	% res	% res min	% res max	No. of studies	No. of isolates
Aminoglycosides	Amikacin	18	3	46	10	2,784
	Apramycin	68			1	45
	Gentamycin	50	9	82	11	2,302
	Kanamycin	59	24	97	5	951
	Neomycin	26	7	50	3	705
	Spectinomycin	26	15	42	3	403
	Streptomycin	71	47	97	6	1,480
	Tobramycin	14			1	389
Carbapenems	Meropenem	0			1	540
Cephalosporines	Cefalexin	8	5	11	2	553
	Cefazoline	33	9	92	4	1,157
	Cefotaxime	37	21	52	2	627
	Ceftazidime	18			1	540
	Ceftiofur	45	0	90	2	116
	Ceftriaxone	4	2	8	3	647
	Cefalothin	32	27	41	4	1,206
Fluoroquinolones	Difloxacin	91			1	71
	Ciprofloxacin	62	32	100	8	2,272
	Enrofloxacin	71	38	100	7	1,479
	Gatifloxacin	67			1	71
	Levofloxacin	44	21	63	4	1,187
	Norfloxacin	53	21	100	5	1,322
	Ofloxacin	37	24	50	2	476
	Orbifloxacin	76			1	71
	Sarafloxacin	100			1	71
	Sulfadimidine	100			1	45
	Fosfomycins	Fosfomycin	16			1
Monobactams	Aztreonam	10			1	540
Nitrofurans	Nitrofurantoin	3			1	540
Penicillines	Amoxicillin	54			1	389
	Ampicillin	81	60	100	10	2,581
	Piperacillin	30			1	540
Phenicol	Chloramphenicol	44	24	69	6	1,854
	Florfenicol	41	15	78	4	682
Quinolone	Nalidixic acid	91	81	94	5	1,465
Polymyxins	Colistin	9	5	13	2	251
	Polymyxin B	1			1	389
Sulfonamides	Sulfamethoxazole	76	58	92	3	294
	Sulfisoxazole	83			1	87
	Doxycycline	79	48	93	6	1,594
Tetracyclines	Tetracycline	87	85	100	9	2,164
	Amoxicillin/clavulanate	50	0	100	5	1,156
Combination of antimicrobials	Cefoperazone-Sulbactam	51			1	373
	Trimethoprim-Sulfamethoxazole	78	66	93	8	2,314

% res—average value of percentages of antibiotic resistant *E. coli* found in referenced studies.

% res min—minimal value of percentages of antibiotic resistant *E. coli* found in referenced studies.

% res max—maximal value of percentages of antibiotic resistant *E. coli* found in referenced studies.

E. coli among the mentioned EU countries. Nevertheless, comparing the obtained averages of resistance, that of ampicillin (70%) was the highest one. Approximately 60% resistance rates were detected for ciprofloxacin, sulfamethoxazole, tetracycline, and nalidixic acid (European Food Safety Authority and European Centre for Disease Prevention and Control, 2018).

Poland Poland began to implement a national monitoring program for AR in commensal *E. coli* isolates from broilers in 2009 (Wasył et al., 2012). Antibiotic resistance levels to several antibiotics in *E. coli* isolates from broilers at slaughterhouse level from 2009 to 2014

are available (Wasył et al., 2013; European Food Safety Authority and European Centre for Disease Prevention and Control, 2015, 2016). Data show high AR rates (from 70 to 90%) to ciprofloxacin, nalidixic acid, and ampicillin, and 50 to 70% to tetracycline, sulfamethoxazole, and streptomycin. Wasył et al. (2013) detected increasing trends of ampicillin and cefotaxime resistance in the observed *E. coli* isolates.

United Kingdom Antibiotic resistance data for *E. coli* isolated from broilers in the United Kingdom are available from 2 distinct AR-monitoring programs: the EU-monitoring and the clinical monitoring programs (Veterinary Medicines Directorate, 2015). The

Table 4. Percentage of antibiotic resistant *E. coli* isolated from broilers in selected European countries in 2016 (EFSA/ECDC, 2018).

Antibiotic class	Compound	PL	GB	DE	FR	ES	Average
Number of isolates		173	190	177	188	171	
Aminoglycosides	Gentamicin	10	7	7	3	36	13
β-lactam cephalosporines	Cefotaxime	3	0	1	4	9	3
	Ceftazidime	3	0	1	2	8	3
β-lactam penicillines	Ampicillin	91	67	56	56	63	67
Diaminopyrimidines	Trimethoprim	62	43	38	47	37	45
Fenicols	Chloramphenicol	25	4	10	7	17	13
Fluoroquinolone	Ciprofloxacin	90	22	60	36	91	60
Macrolides	Azithromycin	5	0	2	0	11	4
Polimyxmins	Colistin	3	0	4	3	1	2
Quinolone	Nalidixic acid	78	21	45	34	88	53
Sulfonamides	Sulfamethoxazole	71	53	47	55	50	55
Tetracyclines	Tetracycline	73	44	28	62	61	54
	Tigecycline	2	0	0	0	0	0

PL—Poland, GB—United Kingdom, DE—Germany, FR—France, ES—Spain.

EU-monitoring program isolated *E. coli* from healthy broilers across the United Kingdom. The clinical monitoring program is a passive monitoring program. Its aim is the evaluation of AR in bacteria that are isolated from clinical samples of diseased animals to antibiotics of veterinary relevance. Both monitoring programs show high AR rates of *E. coli* to ampicillin and tetracycline. Bywater et al. (2004) and Randall et al. (2011) confirm the higher AR rates to ampicillin and tetracycline in *E. coli* in UK. An analysis of fluoroquinolone resistance in *E. coli* from feces samples of 68 broiler farms detected resistance to ciprofloxacin in 50% of these farms (Taylor et al., 2008).

Germany The Federal Office of Consumer Protection and Food Safety reports on AR monitoring in Germany. Similar to the monitoring programs of the UK, 2 different surveillance systems exist in Germany. The first one (Reports on food safety-zoonoses monitoring) monitors healthy animals and the products thereof. The second system is the GERM Vet Report that contains data about the resistance of animal pathogens. Germany monitors the AR in *E. coli* isolates from intestinal samples of broilers, chicken meat, and diseased animals. Data from all systems show higher resistance rates to ampicillin and sulfamethoxazole than to other antibiotics (German Federal Office of Consumer Protection and Food Safety, 2012a, 2012b, 2014, 2015, 2016). For *E. coli* that were isolated from intestinal samples and retail meat, the resistance rates to ciprofloxacin, nalidixic acid, streptomycin, tetracycline, and trimethoprim are between 40 and 60%. Except for trimethoprim, these antibiotics are not allowed for use in broilers in Germany. However, other representatives of the corresponding antibiotic classes may be used. The resistance rates of *E. coli* from diseased chickens to ciprofloxacin are approximately 7%. It seems that the resistance to ciprofloxacin is lower in diseased animals than in healthy animals, and resistance to cephalosporins is higher in diseased animals than in healthy animals. However, the resistance rates must be measured over longer periods of time to confirm these differences.

France France participates in the EU monitoring of AR in animals and presents data since 2004. The French Agency for Veterinary Medicinal Products (ANSES-ANMV) provides reports on the French surveillance network for AR in pathogenic bacteria of animal origin (RESAPATH). The RESAPATH presents the results of the monitoring of AR in *E. coli* from diseased hens and broilers that are treated by veterinarians as part of their regular clinical services. Additionally, AR data are available from the EU Summary reports (European Food Safety Authority and European Centre for Disease Prevention and Control, 2011, 2012, 2013, 2014, 2015, 2016, 2018).

Tetracyclines and penicillins are approved for use in poultry in France. Due to the availability of the quantitative use of antibiotics in poultry, a comparison between antibiotic use and resistance is possible, as can be seen in Figure 3. The use of penicillins in France was stable over time and resistance level to amoxicillin (40%) was the same in 2006 and 2016, although there was an increase and decrease of resistance rates between 2006 and 2016. The decrease in the use of tetracycline between 2006 and 2016 was accompanied by a decrease of tetracycline-resistance rates in *E. coli* between 2006 and 2016. Thus, less use of tetracyclines may result in less resistance to those antibiotics. This hypothesis needs to be confirmed in other countries, and the availability of quantitative data of antibiotic use allows this comparison. In contrast, the use of polymyxins does not correspond with the resistance rates of colistin. The use of polymyxins is high in France, as it can be seen in Figure 2, but the resistance level to colistin is around 3%. Low colistin resistance levels in *E. coli* can be observed in large poultry-producing European countries. However, it needs to be taken into account that in vitro antimicrobial susceptibility testing for polymyxins is challenging and may be associated with high major errors (Bakthavatchalam et al., 2018). Therefore, no conclusion can be made to the correlation of antibiotic use and resistance to colistin.

Spain The Spanish AR surveillance network “Red de Vigilancia de Resistencias Antibióticas en Bacterias de Origen Veterinario” (VAV) was formed in 1996 (Moreno, 2000). The VAV reported data on AR in *E. coli* that were taken from healthy broilers during the period from 1999 to 2005 (Ministry of Agriculture Fisheries and Food in Spain 2005, 2006). Additionally, AR data are available from the EU Summary reports (European Food Safety Authority and European Centre for Disease Prevention and Control, 2011, 2013, 2015, 2016, 2018).

The fluoroquinolones enrofloxacin and flumequine are allowed for use in poultry in Spain. The monitoring data show that AR to ciprofloxacin in *E. coli* increased from 17% in 2001 to 91% in 2016, and that of nalidixic acid from 60% in 2001 to 88% in 2014. Whether an increased use of the fluoroquinolones may have influenced this increase cannot be evaluated without the presence of quantitative AU data. Tetracycline and the penicillins are also registered for use in Spain. The AR resistance rates to tetracycline and ampicillin are approximately 70%. A decrease of resistance to tetracycline was observed between 1999 and 2016.

OVERARCHING VIEW AND RECOMMENDATIONS

Quantitative AU data for poultry are not available for most large poultry-producing countries. Availability of data for AR in *E. coli* is limited for Brazil. Scientific publications from all regions as well as national monitoring of USA and Europe use different methods for the determination of AR. Harmonized approach in detection of AR is of special importance to provide the global evaluation of data. However, the list of all approved antibiotics for poultry provides valuable qualitative data for all countries, which was combined with AR rates in *E. coli* and presented with the mean of a plot diagram. Data for AR rates from the US were used from the surveillance systems of *E. coli* isolates from retail raw chicken meat, caecal *E. coli* isolates from slaughtered animals, and isolates from processing plants collected as part of HACCP (US Food and Drug Administration, 2018). Additionally, data from the scientific publications on AR in *E. coli* from the US were also included. Data for AR rates in China and Brazil are included in Tables 2 and 3. Data for AR from large European poultry producers were used from European monitoring as well as available data from national resistance monitoring systems in Poland, the UK, Germany, France, and Spain from 2000 to 2017. All used data from national monitoring systems are available in section Supplementary material of this manuscript.

There is a representative amount of AR data from *E. coli* for some antibiotic classes such as aminoglycosides, penicillins, cephalosporins, fenicol, quinolones, fluoroquinolones, sulfonamides, and tetracyclines for all large poultry-producing countries. The resistance rates

of these antibiotics are represented in plot diagrams by dots, as shown in Figures 4 and 5. Each dot on the diagram represents the resistance rate detected during 1 scientific study or a national monitoring program from 2000 to 2017.

Tetracyclines, aminoglycosides, sulfonamides, and penicillins are registered for use in poultry in all countries. The resistance rates in *E. coli* of broiler origin to representatives of these antibiotic classes, e.g., tetracycline, sulfamethoxazole, streptomycin, and ampicillin, are higher than 40% in all countries, with the exception of ampicillin resistance in the US. This outcome indicates that the use of these antibiotics in poultry results in high resistance rates; however, quantitative data on antibiotic use in poultry would be essentially needed for the confirmation. The resistance rates to fluoroquinolones and quinolones are lower in the US in comparison to other large poultry producers where the use of fluoroquinolones is allowed. These findings demonstrate the possibility to produce broilers without fluoroquinolones, which may result out in low resistance rates, but there was no elimination of the occurrence of resistant population.

Colistin, as a representative of the polymyxins, and tylosin, as representative of the macrolides, are both allowed for poultry use in all countries for oral treatment or injection solution, but there is only a limited amount of resistance data available. Due to the detection of plasmid-located colistin resistance genes in some countries, the assessment of resistance rates to this antibiotic would be essential.

There are several classes of antibiotics that are approved for use in poultry, but no *E. coli* AR are available for studied regions. Such classes are as follows: arsenicals, glyco-phospholipids, ionophores, lincosamides, orthosomycins, pleuromutilins, polypeptides, and streptogramins. It is important to note that most of the representatives of these antibiotic classes act against Gram-positive bacteria. However, the prevalence of resistance or resistance determinants in *E. coli* to some of these antibiotics was detected by Heir et al. (2004), Bonnet et al. (2009), Cervantes et al. (1994), and Hummel et al. (1979).

The above outlined evaluation and conclusions from review of AU and AR provide input for the monitoring of antibiotic use in poultry and underlie the need for harmonized global surveillance and detection of the AU and AR.

SUPPLEMENTARY DATA

Supplementary data are available at *Poultry Science* online.

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