REVIEW

Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin [version 1; referees: 2 approved]

Hattie E. Webb [1], Frederick J. Angulo[2], Sophie A. Granier [3], H. Morgan Scott[4], Guy H. Loneragan[1]

[1]International Center for Food Industry Excellence, Department of Animal and Food Sciences, Texas Tech University, Lubbock, TX, 79409, USA
[2]Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, 30333, USA
[3]Laboratory for Food Safety, Anses, Université Paris-Est, Maisons-Alfort, F-94701, France
[4]Department of Veterinary Pathobiology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, 77843, USA

v1 **First published:** 05 Oct 2017, **6**:1805 (doi: 10.12688/f1000research.12777.1)
Latest published: 05 Oct 2017, **6**:1805 (doi: 10.12688/f1000research.12777.1)

Abstract

Use, overuse, and misuse of antimicrobials contributes to selection and dissemination of bacterial resistance determinants that may be transferred to humans and constitute a global public health concern. Because of the continued emergence and expansion of antimicrobial resistance, combined with the lack of novel antimicrobial agents, efforts are underway to preserve the efficacy of current available life-saving antimicrobials in humans. As a result, uses of medically important antimicrobials in food animal production have generated debate and led to calls to reduce both antimicrobial use and the need for use. This manuscript, commissioned by the World Health Organization (WHO) to help inform the development of the WHO guidelines on the use of medically important antimicrobials in food animals, includes three illustrations of antimicrobial use in food animal production that has contributed to the selection—and subsequent transfer—of resistance determinants from food animals to humans. Herein, antimicrobial use and the epidemiology of bacterial resistance are described for streptothricins, glycopeptides, and colistin. Taken together, these historical and current narratives reinforce the need for actions that will preserve the efficacy of antimicrobials.

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees 1	2
version 1 published 05 Oct 2017	✓ report	✓ report

1 **Wolfgang Witte**, Robert Koch-Institut (RKI), Germany

2 **Séamus Fanning**, University College Dublin, Ireland

Discuss this article

Comments (0)

Corresponding author: Hattie E. Webb (hattie.webb@ttu.edu)

Author roles: Webb HE: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Angulo FJ**: Conceptualization, Writing – Review & Editing; **Granier SA**: Conceptualization, Writing – Review & Editing; **Scott HM**: Conceptualization, Writing – Review & Editing; **Loneragan GH**: Conceptualization, Writing – Review & Editing

Competing interests: GL has accepted consulting fees, honoraria, and reimbursement of travel expenses from Zoetis, Elanco Animal Health, Merck Animal Health, and Bayer.

How to cite this article: Webb HE, Angulo FJ, Granier SA *et al.* **Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin [version 1; referees: 2 approved]** *F1000Research* 2017, **6**:1805 (doi: 10.12688/f1000research.12777.1)

Grant information: This work was commissioned by the WHO. The authors have been given permission to publish this article.

First published: 05 Oct 2017, **6**:1805 (doi: 10.12688/f1000research.12777.1)

Context

Apart from a few molecules, many antimicrobial agents, such as antibiotics, either occur in nature or are derived from natural compounds. Likewise, their corresponding resistance determinants have occurred naturally for millennia. Mounting evidence, however, informs us that decades of global, anthropomorphic antimicrobial overuse has resulted—and is resulting—in the selection and spread of antimicrobial resistant bacteria and their determinants. Much of this antimicrobial use is occurring in food animal production; while some over-selection from this use does not extend to distinctly human pathogens, zoonotic bacteria that can be transmitted from food animals to humans through the food supply and environment may pose an increased risk to humans due to adverse consequences of antimicrobial resistance such as treatment failure. Human deaths attributed to all bacterial resistance are currently estimated to be 700,000 annually[1], and—unless action is taken—this estimate is projected by economists to exceed 10 million by 2050, thereby surpassing cancer[2].

Many organizations have begun to engage in efforts to reduce the potential public-health impact of bacterial resistance associated with the use of antimicrobials in food animals. In particular, the World Health Organization (WHO) has established an Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). This group has been key in producing guidelines on the use of antimicrobials in food-producing animals (hereafter, termed the "guidelines"), the integrated surveillance of antimicrobial resistance, regularly revised lists of critically important antimicrobials for human medicine (CIA List), and supporting capacity building and infrastructure development efforts in the developing world. This review was commissioned in the context of informing the development of the WHO guidelines on use of medically important antimicrobials used in food animals to be published in October, 2017. Therefore, our objective is to provide three specific examples that illustrate selection and subsequent transfer of resistant determinants from food animals to humans. These illustrative examples are streptothricins, glycopeptides, and colistin.

Limitations

Our general knowledge on antimicrobial resistance among bacteria is ever evolving; in particular, the story of colistin resistance is rapidly unfolding. This review was prepared for the WHO AGISAR meeting of October, 2016 (Raleigh, North Carolina, US) at which time the WHO guidelines was being drafted; therefore, the cited literature is considered up to date as of September 15, 2016. The scope of this review paper was centered on the evidence of antimicrobial use (and amount of use) in food animals and the epidemiology of common resistance mechanisms. Routes of antimicrobial administration were not evaluated or discussed within this report, but likely also play a role in antimicrobial resistance determinant selection. Further, dissemination of bacteria and resistance genes are frequently not unidirectional events. As such, we do not discount the importance of other directional routes of transfer (e.g. direct or indirect transfer from human to animal populations); however, the scope of this review was limited to transfer from food-producing animals to humans. The selection and dissemination of antimicrobial resistance is a complex, multifactorial phenomenon. Unfortunately, there is no 'perfect' experiment or controlled environment to demonstrate selection, dissemination, and the subsequent risks imposed through the sharing of resistance determinants among bacterial and host populations, and we acknowledge up front that there remain data gaps.

Streptothricins

Streptothricins are a distinct group of antibiotic compounds isolated from the genus *Streptomyces*[3,4]. The first streptothricin compound (F) was described in 1942[5]. Antibiotic agents of the streptothricin group are composed of varying combinations and proportions of the streptothricin compounds (A, B, C, D, E, F, and X)[6]. More than 70 mixtures of streptothricin compounds have been described and subsequently named, including: streptolin, racemomycin, geomycin, grisein, pleocidin, and nourseothricin; however, the amount of detail available regarding the chemical structure and antibacterial activity of each of the streptothricin antibiotic agents varies greatly. Nonetheless, the streptothricin antibiotic agents are known to be effective against pathogenic fungi and have both bacteriostatic and bactericidal effects on Gram-negative and Gram-positive bacteria through the inhibition of protein synthesis and misreading of genetic information[7–9].

Usage

Nephrotoxicity associated with streptothricin antibiotic agents has prevented clinical use of these agents in human medicine[10,11]. As a result, use of the streptothricin antibiotic agents has been largely limited to plant production and animal husbandry in a select few countries, particularly China and the former German Democratic Republic (GDR; East Germany)[12,13]. The most detailed accounts of streptothricin use and the apparent subsequent dissemination of resistance are available from the GDR. Between 1981 and 1989, nourseothricin—a mixture of streptothricin D and F—was used in the GDR for in-feed growth promotion in the swine industry[5,14]. No data are available about the amounts of streptothricins or nourseothricin produced, distributed, or used in the swine industry during this time. Nourseothricin was not used in animals in the GDR prior to the introduction of its use in swine, and nourseothricin use in the GDR was limited to the swine industry[15]. Furthermore, no use of other streptothricin antibiotic agents in animals or humans has ever been reported in the GDR.

Resistance

It has been reported that, prior to utilization in the GDR swine industry in 1981, acquired nourseothricin resistance in Enterobacteriaceae among animal and human isolates was rare and believed to be solely associated with chromosomal mutations[12,16,17]. Furthermore, when phenotypic resistance was reported, it was never found to be a mobilizable resistance, although the extent of antimicrobial surveillance or screening is not cited and is unknown for that period of time. In 1981, less than one year after the initial use of nourseothricin in the swine industry, a streptothricin-streptomycin-spectinomycin resistance phenotype was observed in *Escherichia coli* isolated from rectal swabs from pigs on multiple farms, "sewage", and from the feces of those in direct contact with the pigs (i.e. farm personnel)[17]. This resistance was found to be mediated by streptothricin-acetyltransferase (*sat*) genes

coding for a nourseothricin-inactivating enzyme, which is carried on a transposon, designated Tn1825[17].

Evidence for transmission

From 1981 to 1983, plasmid-mediated streptothricin resistance was documented in *E. coli* isolated from rectal swabs of pigs being treated with nourseothricin and slurry from their farms in multiple geographical locations within the GDR[14]. Hummel and colleagues also identified streptothricin-resistant *E. coli* in piglets being treated with nourseothricin, the gut flora of persons with direct contact with the pigs (i.e. farm personnel), the gut flora of persons with in-direct contact with the pigs, who had no other connection to the livestock industry (i.e. farm personnel's family members), and among the gut flora of outpatients living in the same region that had no apparent contact with pigs[17,18]. Remarkably, the authors did not observe streptothricin resistance in samples from piglets or humans in regions where nourseothricin was not being used. Further, the prevalence of streptothricin resistance was highest in *E. coli* isolated from piglets (33% of 306) and declined in the following order: isolates from farm personnel (18% of 377), isolates from farm personnel's family members (17% of 334), isolates from outpatients in the region (16% of 266) and isolates from urinary tract infections in outpatients in the region (1% of 28).

Despite discontinuation of nourseothricin use in the GDR swine in 1988, the identification of streptothricin resistance and associated resistance determinants continued and broadened. Streptothricin resistance has now been associated with the *sat*, *stat*, and *nat* genes[19]. In 1992, the first report of streptothricin-resistance *Campylobacter* isolated from pig slurry was published[20,21]. Integrons harboring the gene sequence of these resistance determinants have also been observed in other bacteria (clinical isolates, animal environments, and food-producing animals), including *Salmonella enterica*, *Enterococcus faecium*, *Acinetobacter baumannii*, *Burkholderia cenocepacia*, *Vibrio cholerae, Shigella sonnei,* and *S. flexneri*[12,22–27].

Interestingly, the spread of the streptothricin resistance gene to these other ecological niches and bacterial populations has occurred without direct selection pressure (i.e. use of streptothricins in animals or human medicine)[12]. Importantly, the streptothricin resistance genes are often harbored in integrons with resistance determinants present to other antimicrobial agents, namely determinants coding for resistance to streptomycin, spectinomycin, trimethoprim, or kanamycin[22–25]. It is possible that such co-resistance may have contributed to the early dissemination of streptothricin resistance, but the early epidemiological studies did not report information on use of other antimicrobial agents. Little to no information is provided about the animals and humans from which the isolates were collected. Furthermore, because there were few studies that searched for streptothricin resistance prior to the 1980s, it is not known if streptothricin resistance determinants were present in bacteria before this time. Nonetheless, this illustrative example outlines the published account of the likely emergence and dissemination of plasmid-borne resistance from swine to humans.

Summary

Nourseothricin, a streptothricin antimicrobial agent, was widely used as a growth promoter in the swine industry in the former German Democratic Republic from 1981–1988. In contrast, toxicity prevented use of streptothricin antimicrobial agents in humans. Less than one year after the introduction of nourseothricin in swine, a plasmid-borne streptothricin resistance (*sat*) seemingly emerged in *E. coli* isolated from swine administered nourseothricin. Subsequently, plasmid-borne streptothricin resistance was detected in the gut flora of humans with direct, indirect, and no contact to pig farms, but living in the same regions. Following reports of the plasmid-mediated streptothricin resistance demonstrates an illustrative example of the detection—and apparent emergence—of streptothricin-resistant bacteria in swine as a result of antimicrobial use, and the dissemination of the resistant bacteria and mobile genetic elements conferring resistance to humans.

Glycopeptides

Glycopeptides are a broad-spectrum antimicrobial class, including vancomycin, and its derivatives teicoplanin, telavancin, dalbavancin, oritavancin, and avoparcin[28]. Glycopeptides block cell wall assembly in Gram-positive bacteria by inhibiting peptidoglycan synthesis[28]. Therefore, the clinical importance of the glycopeptide class has been the treatment of infections caused by Gram-positive pathogens. For a large part of the 1980s and 1990s glycopeptides were the drugs of last-resort for multidrug-resistant Gram-positive infections in humans[29].

Usage

Vancomycin, the first antibiotic of the glycopeptide class, was first described in 1955 and was subsequently approved for human use by the United States (US) Food and Drug Administration (FDA) in 1958[29–31]. The dates of approval and beginnings of human use in European countries are unknown. Renal toxicity and ototoxicity (largely due to impurities in the drug) limited vancomycin use in humans until the early 1980s when multidrug-resistant Gram-positive bacteria began to emerge and purified formulations of vancomycin became available[32,33]. Annual vancomycin usage in humans in the US climbed from 2,000 kg in 1984 to 11,460 kg in 1994[33]. In Europe and Australia, human vancomycin use was more limited[33]; for example, in Australia, an average of 193 kg of vancomycin was used in humans annually between 1991 and 1993[34,35]. France reported 200 kg of vancomycin was used in humans in 1984, increasing to only 1,151 kg in 1994[33]. Annual vancomycin usage in humans in Germany, Italy, United Kingdom (UK), the Netherlands, and Denmark each ranged between 24 to 408 kg in 1994[33,36]. Human use of vancomycin began to decline after 1994 following efforts to promote vancomycin conservation, an attempted to limit dissemination of glycopeptide-resistant bacteria.

Although vancomycin use in humans in Europe was very limited in the 1990s, avoparcin, a glycopeptide antimicrobial, was heavily used in many European countries and Australia as an antimicrobial growth promoter in livestock[34]. Avoparcin use for growth promotion is documented in Europe as early as 1975 and

products containing avoparcin have been registered in Australia since 1978[37–39]; while data supporting heavy use of avoparcin in many European countries are limited, data from Denmark indicate 24,000 kg of active avoparcin were used in swine and broilers in 1994[36]. Austria reported an average of 62,642 kg of avoparcin for animal production use were imported per year from 1992 to 1996[40]. Australia used an annual average of 125,000 kg of avoparcin between 1991 and 1993[34,35]. Avoparcin has never been licensed for use in animals in the US[41]. Following the isolation of glycopeptide-resistant bacteria from food animal products at the retail level, attempts to mitigate the risk of human exposure to glycopeptide-resistant enterococci (GRE) through the food chain led to the ban of avoparcin for growth promotion use in Denmark and Norway in 1995, Germany in 1996, followed by the remaining European Union member states in 1997, and withdraw of avoparcin from the Australian market in 2000[20,38,39,42–46].

Resistance

Transferable glycopeptide resistance in enterococci was first reported in human patients in both France and the UK in 1986, and then in the US in 1987[47–49]. However, it wasn't until the 1990s that considerable attention turned to the evaluation of glycopeptide use and resistance due to differing epidemiological trends between GRE in the US and Europe. In the US in the 1990s, GRE emerged as a significant cause of healthcare-associated infection and colonization in many hospitals—frequently associated with the high use of vancomycin in those hospitals[50–52]. Hospital-associated GRE infections rose at an endemic rate; with the proportion of vancomycin resistant enterococcal blood isolates climbing from little to no resistance in 1989 to 25.9% in 2000[39,53]. In the 1990s in Europe, prevalence rates of GRE in hospitals remained low; however there were reports of GRE in healthy human carriers in the community (e.g. people with no association to a hospital) and sporadic hospital outbreaks[54–56].

Monitoring of antimicrobial resistance to growth promoters was not common practice prior to the mid-1990s[57]. Perhaps as a result, the first detection of GRE isolated from sewage, animals, and healthy humans in the community (i.e. outside of hospitals) were reported in the mid-1990s[39,42,45,56,58–66]. Notably, an association was made between use of avoparcin and the occurrence of GRE in livestock and their environments in Belgium, Denmark, Finland, France, Germany, UK, and the Netherlands—directing a spotlight to food animal production[42,50,51,57,60,61,65,67–74].

The differing epidemiological trends in GRE between the US and Europe led to considerable interest to compare GRE from European farm animals fed avoparcin, hospitalized humans, and non-human sources using various molecular methods[32]. Such investigations provided a great deal of insight about the epidemiology of acquired resistance genotypes associated with glycopeptide resistance, particularly the most globally widespread and prevalent glycopeptide resistance in enterococci, *vanA* resistance. *vanA* is an inducible resistance to vancomycin and often teicoplanin mediated by a complex cluster of resistance genes (*ORF1, ORF2, vanR, vanS, vanH, vanA, vanX, vanY,* and *vanZ*) often carried on a 10,851 bp transposon designated Tn*1546*[67,75–77].

Evidence for transmission

Analysis of GRE with *vanA* resistance revealed a certain level of host-association[51,78–80]. Reports using deoxyribonucleic acid (DNA) sequence typing and phylogenetic analysis for genotyping clustered *vanA Enterococcus faecium* isolates from varying ecological backgrounds into distinct genogroups. Strains collected from pigs and healthy people often clustered together forming a single genotype or cluster. In contrast, isolates collected from poultry and their farmers, veal calves and their farmers, and hospitalized patients from epidemics worldwide each form genetically distinct clusters[78–80]. One of the first insights of genetic relatedness was the observation of a single base change (G8234T) in the *vanX* of Tn*1546*, which was first described by Jensen *et al.*[50,51] The G-variant was associated with isolates collected from poultry and poultry farmers in multiple countries[51,57,68,81]. The T-variant, on the other hand, was predominantly observed in swine isolates from differing countries[51,80]. Interestingly, both G- and T-variants were associated with isolates likely of human origin[51]. In fact, it was observed that all human samples from a Muslim country—a population that likely eats little or no pork—belong to the G-variant associated with poultry, thus further suggesting GRE transmission may occur between food animals and humans[51].

Further investigation of *vanA* mechanism by Willems *et al.*[80], revealed amplified fragment length polymorphism (ALFP) genotyping clustered a bank of 255 *E. faecium* isolates from various ecological niches and geographic locations into four genogroups (designated A–D). All isolates collected from pigs and 76% of isolates collected from healthy people clustered to form Genogroup A. Almost all isolates collected from poultry (95%) and 50% of isolates from poultry farmers clustered to form Genogroup B, and Genogroup D contained 70% of isolates collected from veal calves and their farmers. Further, 84% of isolates collected from hospitalized patients from epidemics in the UK, US, and Australia formed a genetically distinct cluster from the healthy humans and animal genogroups, which the authors designated Genogroup C[80]. Similar findings have been demonstrated using various other genotypic methods[39,72,78,79,82–84].

The VanA gene cluster is now one of many described genotypic determinants encoding glycopeptide resistance, and the early genotypic studies described herein only evidence the likely dissemination of a single glycopeptide resistance determinant from animals to healthy people. Further, the differing epidemiological trends between the US and Europe detail two situations that consequently led to the selection of glycopeptide resistance determinants in distinct ecological niches—one in hospitalized patients and the other in healthy humans and animals. Nonetheless, the genetic characterization of the VanA gene cluster provides an illustrative example of the dissemination of glycopeptide resistance from animals to humans following selection, due to use of avoparcin for growth promotion.

Summary

Avoparcin appears to have been widely used in food animals, particularly in chickens and pigs, in parts of Europe, since before

the mid 1970s. Vancomycin use in humans, in contrast, was very limited in Europe until the late 1990s. It appears likely that the use of avoparcin in food animals selected for the emergence and dissemination of a resistance gene cluster (VanA), which was increasingly identified in animals and healthy people. Molecular subtyping of the VanA gene cluster has identified variants that are more likely to be associated with certain food animal species. Subsequently, GRE were transmitted and found to colonize healthy humans, presumably via the food chain. Therefore, evaluation of the VanA gene cluster variants provides an illustrative example of the emergence and selection of a genetic resistance determinant as a consequence of antimicrobial use in food animals, and subsequent dissemination of the resistant bacteria to humans.

Colistin

Polymyxin E (herein simply referred to as colistin) is a cationic, multicomponent lipopeptide antimicrobial agent of the polymyxin family that was first discovered in 1949 and isolated in 1950[85]. Polymyxins are effective against Gram-negative bacilli through their affinity to bind to the negatively charged lipopolysaccharide (LPS) of the cell outer membrane[86]. This binding, more specifically to the anionic lipid A of the LPS, leads to disruption of the cell membrane integrity, ultimately leading to leakage induced cell death[86–88]. Two forms of the colistin compound are available for clinical use: colistin sulfate (colistin S) and the pro-drug, colistimethate sodium (colistin methanesulfonate sodium, colistin sulfomethate sodium, colistin M).

Usage

The US FDA first approved colistin for human use in 1962—in the form of colistin sulfate; this first approval was for ear drops[89]. The FDA subsequently approved a product for injection—in the form of colistimethate sodium—for human use in 1970[90]. No US data are available on the quantities of colistin used in humans, although use in the US is thought to have been very low as parenteral use in human medicine quickly fell out of favor due to initial reports of nephro- and neurotoxicity[90–96]. More recently, colistin has reemerged as an antimicrobial of interest as a last-resort treatment option for life threatening human infections of multidrug-resistant Gram-negative bacteria, particularly *Pseudomonas aeruginosa, Acinetobacter baumannii* strains, and carbapenem-resistant Enterobacteriaceae[97–102]. Approval dates for human use of colistin products in member states of the EU are not clear; however, it is believed that human use began in the 1960s. More recent estimates of polymyxin consumption in humans are available in the EU/European Economic Area[103]. A sum of 0.8 tonnes of active polymyxin ingredients—including colistin and polymyxin B—were consumed by humans in 22 European countries in 2012[104]. In 2014, polymyxin consumption in humans in Europe was 0.012 defined daily doses (DDD) per 1,000 inhabitants—a 50% increase since the 0.008 DDD per 1,000 inhabitants was reported in 2010[105]. Countries reporting highest use of polymyxin in humans include Greece, Italy, and Slovakia (0.095, 0.025, and 0.025 defined daily doses per 1,000 inhabitants, respectively)[105].

In animals, the extent of colistin sales and use is largely unknown outside of the EU[106–109]. In the US, one colistin product, in the form of an injectable colistimethate sodium, was approved for use in chickens in 1998[110]; however its marketing status is unclear. In Canada, colistin is not approved for veterinary medicine; however, a loophole in regulation leaves opportunity for "own-use importation," meaning farmers may import—and use—unlicensed, non-prescription antimicrobials in their animals[111]. As such, use in swine production has been explored under the veterinarian's liability (dose, withdrawal period)[112,113]. In the EU, colistin-containing products for use in animals are authorized[114], though marketing authorization is on a national level and little historical information is available. It is believed that colistin has been used in food animals in the EU since the 1950s[103]. Colistin is chiefly administered as an oral group treatment in food-producing species to alleviate and prevent Gram-negative infections of the gastrointestinal tract[107]. Such use is predominantly reported in pigs, poultry, cattle, sheep, goats, and rabbits; however, colistin is also used in laying hens and milk-producing cattle, sheep, and goats[106,107]. To date, no data are available that would allow comparison among uses in differing animal species on a European level.

Colistin is also reported to be used in food animal production in Asia, although publically available data are scarce. In China, approximately 90% of the 17.5 million tonnes of colistin produced in 2014 were reportedly consumed by the domestic agriculture industry[108]. If so, China likely represents the largest colistin producer and consumer in the world. In comparison, a sum of 545.2 tonnes of active polymyxin ingredients—including colistin and polymyxin B—were consumed by food-producing animals, primarily in poultry and swine, in 22 European countries in 2012[104]. In 2013, polymyxins were estimated to be the fifth most commonly sold antimicrobial class (7%) for food-producing animals across the EU[107]. Reported consumption of colistin in animals varied greatly, ranging from <0.2 tonnes in Slovenia, Sweden, Ireland, and Luxembourg to >100 tonnes in Germany, Italy, and Spain[104]. In another report, annual colistin use in animals in Europe ranged between 0 mg (Finland, Iceland, and Norway) to more than 20 mg (Italy and Spain) per kg of animal biomass[115].

Use of colistin for growth promotion in China was banned effective November 1, 2016—which was expected to decrease colistin use in food animal production in China by an estimated 8,000 tonnes[116]. In March 2015, the European Commission adopted a Decision restricting indications, target species, duration of treatment, and added prudent use warnings to products administered orally to animals that contain colistin as the sole active ingredient[117]. Evidently, such conversations have continued, as the European Commission recently implemented a Directive to withdraw marketing authorizations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally[118]. The European Medicines Agency issued a recommendation advising colistin to be used solely as a second line treatment in animals and for

sales to be minimized EU-wide[103]. In Canada, the "own-use importation" loophole has been acknowledged and regulation changes have been proposed that would prohibit such practices[119].

Resistance

Despite widespread and continuous veterinary use, data gaps persist around colistin resistance. Lack of agreement on standardized *in vitro* screening methods and interpretation criteria has complicated and hindered phenotypic surveillance efforts[86,120–123]. This dilemma is largely a consequence of two important colistin characteristics: a large molecule size—which reduces its rate of diffusion into media—and its affinity to adhere to plastics—which are commonly used in phenotypic methods[86,123]. Until recently, colistin resistance was believed to be extremely rare; however, surveillance efforts were minimal. In fact, mandatory EU monitoring for colistin resistance in *Salmonella* and *E. coli* only began in 2014[124,125]. Even so, many member states have reported technical difficulties in using the only recommended screening method (i.e., broth dilution)[103].

Before November 2015, described phenotypic colistin resistance was associated with chromosomal mutations, which, at least in theory, would be limited to vertical (clonal) dissemination[86,126]. However, this previous belief was proven too narrow by the description of a novel, conjugable plasmid-mediated gene conferring colistin resistance[108]. The gene, designated mobile colistin resistance, or *mcr-1*, was described in *E. coli* and *Klebsiella pneumoniae* isolated from human clinical isolates, retail meat, and food animals in China, between 2011 and 2014[108]. The discovery prompted an immediate worldwide response with screening via genomic data mining exercises or else a combination of phenotypic and polymerase chain reaction (PCR)-based methods[127–133]. It has now been retrospectively identified with 100% homology in other members of the Enterobacteriaceae family isolated from human, animal, food, and environmental samples and from multiple continents[133–140].

Evidence for transmission

In humans, the earliest identified *mcr-1* was found in a *Shigella sonnei* isolate arising from a hospitalized child with diarrhea in Vietnam in 2008[141]. Bacteria harboring *mcr-1* have also been reported in isolates from humans (both infected patients and asymptomatic human carriers) in Canada[142,143], China[108,136,144–154], Denmark[106,140], Ecuador[155], Egypt[156], France[130,157], Germany[137,158,159], Hong Kong[159,160], India[161,162], Italy[159,163–165], Laos[130], Malaysia[159,166], Netherlands[131,167–170], Norway[171], Poland[159,172], Portugal[173], Russia[159], Saudi Arabia[174], Singapore[175,176], South Africa[177,178], Spain[159,179], Sweden[180,181], Switzerland[182–185], Taiwan[186], Thailand[130,187], United Arab Emirates[174], UK[188], US[159,189–191], Venezuela[192], and Vietnam[141,193]. Bacteria harboring the *mcr-1* gene sequence have likewise been documented from food samples on multiple continents[108,129,136,138,140,142,168,173,185,186,188,194–199], suggesting this may be an important route of dissemination from animals to humans.

To date, the earliest identified *mcr-1*-positive isolates are three *E. coli* isolates collected from chickens in China during the 1980s[200]. Interestingly, *mcr-1* has not been detected in isolates arising during the two subsequent decades; however, the reported proportion of *mcr-1*-positive isolates in China begins increasing in 2009[200]. Furthermore, in Europe the earliest *mcr-1*-positive isolate was identified as an *E. coli* originating from a diarrheic veal calf in France in 2005[132]. Observations of *mcr-1* in bacteria isolated from food-producing animals, their products, or environments now includes: pigs (Belgium[128,201], Brazil[202], China[203,204], France[127], Germany[137,205,206], Japan[133,207], Laos[130], Malaysia[136,138,166], Spain[208], Taiwan[186], Venezuela[192], Vietnam[209,210], UK[211], US[212]), poultry (Algeria[130,213], Brazil[202,214,215], China[216–218], Denmark[199], Egypt[218], France[127], Germany[205], Italy[106,219], Malaysia[136,138,166], Netherlands[169], South Africa[220,221], Spain[208], Taiwan[186], Tunisia[185], Vietnam[193,209]), and cattle (Belgium[128], Denmark[199], Egypt[222], France[127,132,223], Germany[205], Japan[133], Netherlands[169]).

Widespread reports of *mcr-1* shortly after its initial characterization indicate the gene was likely being disseminated in an uncharacterized state, and thereby undetected rather than not being present, for a long period of time. The gene has evidently been widely disseminated geographically, as well as across multiple bacterial species of differing origins. Thus far, *mcr-1* has mostly been reported in *E. coli*, although *mcr-1*-positive *Citrobacter*[224,225], *Klebsiella*[108,157,175,224], *Shigella*[141], *Enterobacter*[144,160,176,224], and *Salmonella*[129,135,136,173,188,195,208,211,217] spp. have also been documented. Furthermore, *mcr-1* has been observed in bacteria from wild animals and water samples, indicating the resistance determinant has also disseminated into the environment[194,224,226–230].

Retrospective screening for colistin-resistant bacteria may be limited by the availability of historical isolates and their genomic data. Further, lack of standardized phenotypic screening methods and the delay in genotypic description have likely lead to the underestimation of colistin resistance; nonetheless, the identification and description of the gene has opened the door for screening via genotypic methods. Nevertheless, resistance is still believed to be rare, particularly in humans and in some regions of the world. The initial paper reported the *mcr-1* gene sequence in 1.4% of 902 *E. coli* and 0.7% of 420 *Klebsiella pneumoniae* clinical isolates in China; however, prevalence among *E. coli* isolates originating from pigs and retail meats in China were surprisingly higher: 20.6% of 804 isolates from pigs at slaughter collected between 2012–14 and 14.9% of 523 isolates from retail meats (chicken and pork) collected between 2011–2014[108]. Still, in the US the *mcr-1* gene sequence is rare. It was detected in one *E. coli* isolate out of 949 animal intestine samples screened and was not detected in more than 44,000 *Salmonella* and 9,000 *E. coli* and *Shigella* isolates from the National Antimicrobial Resistance Monitoring System (NARMS) and National Center for Biotechnology Information (NCBI) genomic database[212]. In many reports to date, phenotypic screening is frequently performed prior to genotypic screening. For example, in France, Perrin-Guyomard and colleagues report *mcr-1* in 0.3% of 590 isolates from healthy pigs in 2011–13, 1.8% of 227 isolates from broilers in 2014, and 5.9% of 239 isolates from turkeys in 2014[127]; importantly, screening for *mcr-1* was performed only on isolates with a colistin minimum inhibitory concentration > 2 mg/L. Some

limitations are inevitable with this approach, as it implies a level of dependency on the much-debated breakpoints and phenotypic methods.

The technological response afforded by genomics-based methods is also not without limitations, especially by not detecting variants of *mcr-1*. In fact, on July 7, 2016, the first account of *mcr-2*, a seemingly distinct gene also conferring colistin resistance was described in *E. coli* isolated from calves and piglets in Belgium[231]. This *mcr-2* appeared to be more prevalent than *mcr-1* among colistin-resistant *E. coli* of porcine origin[231]. Then, on July 11, 2016, the first functional variant of *mcr-1*, designated *mcr-1.2*, was reported in *K. pneumoniae* isolated from a surveillance rectal swab of a child in Italy[232]. Since this report was prepared, a number of other *mcr* variants have been reported, some of which also appear to have been disseminating globally prior to characterization[233–235]. While some of these genes may also contribute towards evidencing selection—and subsequent dissemination—of the colistin resistance determinant from food animals to humans, the focus of this report was the initial epidemiology of colistin resistance (i.e. *mcr-1*). Very likely, there remain additional yet-to-be-characterized mechanisms of colistin resistance. Much more work is needed to explore other mechanisms of resistance and to fully comprehend the overall prevalence of colistin resistance determinants and their phenotypic characteristics.

Summary

Colistin has been widely used in food animals—particularly poultry and swine—in areas of Europe and Asia for decades, perhaps since the early 1980s or earlier. In contrast, colistin use in humans has been extremely limited, at least until recently. It appears highly probable that the use of colistin in food animals has selected for a novel resistance gene (*mcr-1*), identified as far back as the mid-1980s in chickens in China, which has become increasingly identified in isolates from food animals in many regions of the world since its discovery in 2015. This novel resistance gene has more recently been identified among isolates from humans; however, to date *mcr-1* has been more frequently associated with food animal and meat isolates compared to human isolates. Prevalence of *mcr-1* in animal samples—and to some degree in human samples—appears to be proportional to its use in animals. These chains of events, despite the data gaps, provide an illustrative example of the emergence, selection, and widespread dissemination of a resistance gene as a consequence of antimicrobial use in food animals, and subsequent transfer of bacteria harboring that resistant gene to humans.

Conclusions

In this review, we have focused on three illustrative examples (i.e. streptothricins, glycopeptides, and colistin) of selection—and subsequent transfer of antimicrobial resistance determinants from food animals to humans. The use of antimicrobials in food animal production contributes to the selection and dissemination of antimicrobial resistance determinants that may reach human populations. However, this review is only part of the picture if taken in a One Health perspective. Its objectives do not encompass the impact of other industries (i.e. environment, human, companion animals, etc.) that also contribute to selection of antimicrobial resistance and it's consequences on each health sector. To tackle the problem of selection and dissemination of antimicrobial resistance in a true One Health perspective, there is need to fully investigate the role of each of those industries. Nevertheless, the three examples we have described serve to illustrate that use of antimicrobials in food animals can result in antimicrobial resistance that can be transmitted to humans. Therefore, these illustrative examples support the need for actions, such as the proposed WHO Guidelines on use of medically important antimicrobials in food animals, to mitigate the risk of adverse human health consequences resulting from the use of antimicrobial agents in food animals.

Competing interests

GL has accepted consulting fees, honoraria, and reimbursement of travel expenses from Zoetis, Elanco Animal Health, Merck Animal Health, and Bayer.

Grant information

This work was commissioned by the WHO. The authors have been given permission to publish this article.

Acknowledgements

We appreciate Yves Millemann and Gérard Moulin for providing their expertise concerning antimicrobials and their use. Also, we would like to thank John M. Conly, Peter Collignon, and Scott McEwen for their critical eye and feedback during the preparation of this review. We would like to acknowledge the WHO Secretariat, Yuki Minato, and the Coordinator of the WHO AGISAR, Awa Aidara-Kane.

References

1. O'Neill J: **Review on AMR. Antimicrobial resistance: tackling a crisis for the health and wealth of nations.** London: HM Government and the Wellcome Trust, 2014.
Reference Source

2. O'Neill J: **Tackling drug-resistant infections globally: final report and recommendations.** London: HM Government and the Wellcome Trust, 2016.
Reference Source

3. Ji Z, Wang M, Zhang J, *et al.*: **Two new members of streptothricin class antibiotics from *Streptomyces qinlingensis* sp. nov.** *J Antibiot (Tokyo).* 2007; **60**(12): 739–44.
PubMed Abstract | Publisher Full Text

4. Taniyama H, Sawada Y, Kitagawa T: **Characterization of racemomycins.** *Chem Pharm Bull.* 1971; **19**(8): 1627–34.
Publisher Full Text

5. Waksman SA, Woodruff HB: **Streptothricin, a New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria.** *Exp Biol Med.* 1942; **49**(2): 207–10.
Publisher Full Text

6. Weinstein MJ, Wagman GH: **Journal of Chromatography Library, Antibiotics: isolation, separation and purification.** Amsterdam, Oxford, New York: Elsevier; 1978; **15**.
Reference Source

7. Umezawa H, Hayano S, Ogata Y: **Classification of antibiotic strains of streptomyces and their antibiotic substances on the basis of their antibacterial spectra.** *Jpn Med J (Natl Inst Health Jpn).* 1948; **1**(6): 504–11.
Publisher Full Text

8. Haupt I, Hübener R, Thrum H: **Streptothricin F, an inhibitor of protein synthesis with miscoding activity.** *J Antibiot (Tokyo).* 1978; **31**(11): 1137–42.
PubMed Abstract | Publisher Full Text

9. Haupt I, Jonák J, Rychlík I, *et al.*: **Action of streptothricin F on ribosomal functions.** *J Antibiot (Tokyo).* 1980; **33**(6): 636–41.
PubMed Abstract | Publisher Full Text

10. van Hoek A, Mevius D, Guerra B, *et al.*: **Acquired antibiotic resistance genes: an overview.** *Front Microbiol.* 2011; **2**: 203.
PubMed Abstract | Publisher Full Text | Free Full Text

11. Kim BT, Lee JY, Lee YY, *et al.*: ***N*-methylstreptothricin D--a new streptothricin-group antibiotic from a *Streptomyces* spp.** *J Antibiot (Tokyo).* 1994; **47**(11): 1333–6.
PubMed Abstract | Publisher Full Text

12. Tschäpe H: **The spread of plasmids as a function of bacterial adaptability.** *FEMS Microbiol Ecol.* 1994; **15**(1–2): 23–31.
Publisher Full Text

13. Li J, Guo Z, Huang W, *et al.*: **Mining of a streptothricin gene cluster from *Streptomyces* sp. TP-A0356 genome via heterologous expression.** *Sci China Life Sci.* 2013; **56**(7): 619–27.
PubMed Abstract | Publisher Full Text

14. Tschäpe H, Tietze E, Prager R, *et al.*: **Occurrence in Water and Waste Water of *E. coli* and Coliform Bacteria Carrying R – Plasmids Part 3: Plasmids Encoding Gentamicin, Trimethoprim or Streptothricin Resistance.** *Acta Hydroch Hydrob.* 1986; **14**(2): 167–74.
Publisher Full Text

15. Aarestrup FM: **Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals.** *Int J Antimicrob Agents.* 1999; **12**(4): 279–85.
PubMed Abstract | Publisher Full Text

16. Witte W, Heier H, Klare I, *et al.*: **[The development of antibiotic resistance of coliform bacteria in connection with the nutritional use of nourseothricin in swine].** *Arch Exp Veterinarmed.* 1984; **38**(6): 807–15.
PubMed Abstract

17. Tschäpe H, Tietze E, Prager R, *et al.*: **Plasmid-borne streptothricin resistance in gram-negative bacteria.** *Plasmid.* 1984; **12**(3): 189–96.
PubMed Abstract | Publisher Full Text

18. Hummel R, Tschäpe H, Witte W: **Spread of plasmid-mediated nourseothricin resistance due to antibiotic use in animal husbandry.** *J Basic Microbiol.* 1986; **26**(8): 461–6.
PubMed Abstract | Publisher Full Text

19. Krügel H, Fiedler G, Smith C, *et al.*: **Sequence and transcriptional analysis of the nourseothricin acetyltransferase-encoding gene *nat1* from *Streptomyces noursei*.** *Gene.* 1993; **127**(1): 127–31.
PubMed Abstract | Publisher Full Text

20. Sundsfjord A, Simonsen GS, Courvalin P: **Human infections caused by glycopeptide-resistant *Enterococcus* spp: are they a zoonosis?** *Clin Microbiol Infect.* 2001; **7**(Suppl 4): 16–33.
PubMed Abstract | Publisher Full Text

21. Böttcher I, Jacob J: **The occurrence of high-level streptothricin resistance in thermotolerant campylobacters isolated from the slurry of swine and the environment.** *Zentralbl Bakteriol.* 1992; **277**(4): 467–73.
PubMed Abstract | Publisher Full Text

22. Werner G, Hildebrandt B, Witte W: **Aminoglycoside-streptothricin resistance gene cluster *aadE-sat4-aphA-3* disseminated among multiresistant isolates of *Enterococcus faecium*.** *Antimicrob Agents Chemother.* 2001; **45**(11): 3267–9.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Ramírez MS, Quiroga C, Centrón D: **Novel rearrangement of a class 2 integron in two non-epidemiologically related isolates of *Acinetobacter baumannii*.** *Antimicrob Agents Chemother.* 2005; **49**(12): 5179–81.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Ramírez MS, Vargas LJ, Cagnoni V, *et al.*: **Class 2 integron with a novel cassette array in a *Burkholderia cenocepacia* isolate.** *Antimicrob Agents Chemother.* 2005; **49**(10): 4418–20.
PubMed Abstract | Publisher Full Text | Free Full Text

25. Ploy MC, Denis F, Courvalin P, *et al.*: **Molecular Characterization of Integrons in *Acinetobacter baumannii*: Description of a Hybrid Class 2 Integron.** *Antimicrob Agents Chemother.* 2000; **44**(10): 2684–8.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Ahmed AM, Kawaguchi F, Shimamoto T: **Class 2 integrons in *Vibrio cholerae*.** *J Med Microbiol.* 2006; **55**(Pt 5): 643–4.
PubMed Abstract | Publisher Full Text

27. Pan JC, Ye R, Meng DM, *et al.*: **Molecular characteristics of class 1 and class 2 integrons and their relationships to antibiotic resistance in clinical isolates of *Shigella sonnei* and *Shigella flexneri*.** *J Antimicrob Chemother.* 2006; **58**(2): 288–96.
PubMed Abstract | Publisher Full Text

28. Walsh C, Wencewicz T: **Antibiotics: challenges, mechanisms, opportunities**. ASM Press; 2016.
Publisher Full Text

29. Levine DP: **Vancomycin: a history.** *Clin Infect Dis.* 2006; **42**(Suppl 1): S5–12.
PubMed Abstract | Publisher Full Text

30. Anderson R, Higgins HJ, Pettinga C: **Symposium: how a drug is born.** *Cinci J Med.* 1961; **42**: 49–60.

31. McCormick MH, McGuire JM, Pittenger GE, *et al.*: **Vancomycin, a new antibiotic. I. Chemical and biologic properties.** *Antibiot Annu.* 1955–1956; **3**: 606–11.
PubMed Abstract

32. Leclercq R, Courvalin P: **Resistance to glycopeptides in enterococci.** *Clin Infect Dis.* 1997; **24**(4): 545–54.
Reference Source

33. Kirst HA, Thompson DG, Nicas TI: **Historical yearly usage of vancomycin.** *Antimicrob Agents Chemother.* 1998; **42**(5): 1303–4.
PubMed Abstract | Free Full Text

34. Collignon PJ: **Vancomycin-resistant enterococci and use of avoparcin in animal feed: is there a link?** *Med J Aust.* 1999; **171**(3): 144–6.
PubMed Abstract

35. Turnidge J, Howard R: **Australia's antibiotic burden.** *Microbiology Australia.* 1996; **17**(11).

36. Wegener HC: **Historical yearly usage of glycopeptides for animals and humans: the American-European paradox revisited.** *Antimicrob Agents Chemother.* 1998; **42**(11): 3049.
PubMed Abstract | Free Full Text

37. Witte W, Klare I: **Glycopeptide-resistant *Enterococcus faecium* outside hospitals: a commentary.** *Microb Drug Resist.* 1995; **1**(3): 259–63.
PubMed Abstract | Publisher Full Text

38. National Registration Authority for Agricultural and Veterinary Chemicals (NRA): **The special review of avoparcin.** Canberra, Australia. 2001.
Reference Source

39. Bonten MJ, Willems R, Weinstein RA: **Vancomycin-resistant enterococci: why are they here, and where do they come from?** *Lancet Infect Dis.* 2001; **1**(5): 314–25.
PubMed Abstract | Publisher Full Text

40. Witte W: **Medical consequences of antibiotic use in agriculture.** *Science.* 1998; **279**(5353): 996–7.
PubMed Abstract | Publisher Full Text

41. McDonald LC, Kuehnert MJ, Tenover FC, *et al.*: **Vancomycin-resistant enterococci outside the health-care setting: prevalence, sources, and public health implications.** *Emerg Infect Dis.* 1997; **3**(3): 311–7.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Bates J, Jordens JZ, Griffiths DT: **Farm animals as a putative reservoir for vancomycin-resistant enterococcal infection in man.** *J Antimicrob Chemother.* 1994; **34**(4): 507–14.
PubMed Abstract | Publisher Full Text

43. Kühn I, Iversen A, Finn M, *et al.*: **Occurrence and relatedness of vancomycin-resistant enterococci in animals, humans, and the environment in different European regions.** *Appl Environ Microbiol.* 2005; **71**(9): 5383–90.
PubMed Abstract | Publisher Full Text | Free Full Text

44. Aarestrup FM: **Characterization of glycopeptide-resistant *Enterococcus faecium* (GRE) from broilers and pigs in Denmark: genetic evidence that persistence of GRE in pig herds is associated with coselection by resistance to macrolides.** *J Clin Microbiol.* 2000; **38**(7): 2774–7.
PubMed Abstract | Free Full Text

45. van den Braak N, van Belkum A, van Keulen M, *et al.*: **Molecular characterization of vancomycin-resistant enterococci from hospitalized patients and poultry products in The Netherlands.** *J Clin Microbiol.* 1998; **36**(7): 1927–32.
PubMed Abstract | Free Full Text

46. Klein G, Pack A, Reuter G: **Antibiotic resistance patterns of enterococci and occurrence of vancomycin-resistant enterococci in raw minced beef and pork in Germany.** *Appl Environ Microbiol.* 1998; **64**(5): 1825–30.
PubMed Abstract | Free Full Text

47. Uttley AH, Collins CH, Naidoo J, *et al.*: **Vancomycin-resistant enterococci.** *Lancet.* 1988; **331**(8575–6): 57–8.
PubMed Abstract | Publisher Full Text

48. Leclercq R, Derlot E, Duval J, *et al.*: **Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*.** *N Engl J Med.* 1988; **319**(3): 157–61.
PubMed Abstract | Publisher Full Text

49. Sahm DF, Kissinger J, Gilmore MS, *et al.*: ***In vitro* susceptibility studies of vancomycin-resistant *Enterococcus faecalis*.** *Antimicrob Agents Chemother.* 1989; **33**(9): 1588–91.
PubMed Abstract | Publisher Full Text | Free Full Text

50. Jensen LB, Ahrens P, Dons L, *et al.*: **Molecular analysis of Tn*1546* in *Enterococcus faecium* isolated from animals and humans.** *J Clin Microbiol.* 1998; **36**(2): 437–42.
PubMed Abstract | Free Full Text

51. Jensen LB: **Differences in the occurrence of two base pair variants of Tn*1546* from vancomycin-resistant enterococci from humans, pigs, and poultry.** *Antimicrob Agents Chemother.* 1998; **42**(9): 2463–4.
PubMed Abstract | Free Full Text

52. Centers for Disease Control and Prevention (CDC): **Nosocomial enterococci resistant to vancomycin--United States, 1989–1993.** *MMWR Morb Mortal Wkly Rep.* 1993; **42**(30): 597.
PubMed Abstract

53. Gerberding J, Gaynes R, Horan T, *et al.*: **National nosocomial infections surveillance (NNIS) system report, data summary from January 1992-April 2000, issued June 2000.** *Am J Infect Control.* 2000; **28**(6): 429–48.
PubMed Abstract | Publisher Full Text

54. Van den Bogaard AE, Mertens P, London NH, *et al.*: **High prevalence of colonization with vancomycin- and pristinamycin-resistant enterococci in healthy humans and pigs in The Netherlands: is the addition of antibiotics to animal feeds to blame?** *J Antimicrob Chemother.* 1997; **40**(3): 454–6.
PubMed Abstract | Publisher Full Text

55. Gambarotto K, Ploy MC, Turlure P, *et al.*: **Prevalence of vancomycin-resistant enterococci in fecal samples from hospitalized patients and nonhospitalized controls in a cattle-rearing area of France.** *J Clin Microbiol.* 2000; **38**(2): 620–4.
PubMed Abstract | Free Full Text

56. Endtz HP, van den Braak N, van Belkum A, *et al.*: **Fecal carriage of vancomycin-resistant enterococci in hospitalized patients and those living in the community in The Netherlands.** *J Clin Microbiol.* 1997; **35**(12): 3026–31.
PubMed Abstract | Free Full Text

57. Wegener HC, Aarestrup FM, Jensen LB, *et al.*: **Use of antimicrobial growth promoters in food animals and *Enterococcus faecium* resistance to therapeutic antimicrobial drugs in Europe.** *Emerg Infect Dis.* 1999; **5**(3): 329–35.
PubMed Abstract | Publisher Full Text | Free Full Text

58. Jordens JZ, Bates J, Griffiths DT: **Faecal carriage and nosocomial spread of vancomycin-resistant *Enterococcus faecium*.** *J Antimicrob Chemother.* 1994; **34**(4): 515–28.
PubMed Abstract | Publisher Full Text

59. Torres C, Reguera JA, Sanmartin MJ, *et al.*: **vanA-Mediated vancomycin-resistant *Enterococcus* spp. in sewage.** *J Antimicrob Chemother.* 1994; **33**(3): 553–61.
PubMed Abstract | Publisher Full Text

60. Aarestrup FM: **Occurrence of glycopeptide resistance among *Enterococcus faecium* isolates from conventional and ecological poultry farms.** *Microb Drug Resist.* 1995; **1**(3): 255–7.
PubMed Abstract | Publisher Full Text

61. Klare I, Heier H, Claus H, *et al.*: **vanA-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry.** *FEMS Microbiol Lett.* 1995; **125**(2–3): 165–71.
PubMed Abstract | Publisher Full Text

62. van Belkum A, van den Braak N, Thomassen R, *et al.*: **Vancomycin-resistant enterococci in cats and dogs.** *Lancet.* 1996; **348**(9033): 1038–9.
PubMed Abstract | Publisher Full Text

63. Stobberingh E, van den Bogaard A, London N, *et al.*: **Enterococci with glycopeptide resistance in turkeys, turkey farmers, turkey slaughterers, and (sub)urban residents in the south of The Netherlands: evidence for transmission of vancomycin resistance from animals to humans?** *Antimicrob Agents Chemother.* 1999; **43**(9): 2215–21.
PubMed Abstract | Free Full Text

64. van Den Bogaard A, London N, Stobberingh EE: **Antimicrobial resistance in pig faecal samples from the Netherlands (five abattoirs) and Sweden.** *J Antimicrob Chemother.* 2000; **45**(5): 663–71.
PubMed Abstract | Publisher Full Text

65. Klare I, Heier H, Claus H, *et al.*: ***Enterococcus faecium* strains with *vanA*-mediated high-level glycopeptide resistance isolated from animal foodstuffs and fecal samples of humans in the community.** *Microb Drug Resist.* 1995; **1**(3): 265–72.
PubMed Abstract | Publisher Full Text

66. Van der Auwera P, Pensart N, Korten V, *et al.*: **Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci.** *J Infect Dis.* 1996; **173**(5): 1129–36.
PubMed Abstract | Publisher Full Text

67. Woodford N: **Epidemiology of the genetic elements responsible for acquired glycopeptide resistance in enterococci.** *Microb Drug Resist.* 2001; **7**(3): 229–36.
PubMed Abstract | Publisher Full Text

68. Borgen K, Simonsen GS, Sundsfjord A, *et al.*: **Continuing high prevalence of VanA-type vancomycin-resistant enterococci on Norwegian poultry farms three years after avoparcin was banned.** *J Appl Microbiol.* 2000; **89**(3): 478–85.
PubMed Abstract | Publisher Full Text

69. Yoshimura H, Ishimaru M, Endoh YS, *et al.*: **Isolation of glycopeptide-resistant enterococci from chicken in Japan.** *Antimicrob Agents Chemother.* 1998; **42**(12): 3333.
PubMed Abstract | Free Full Text

70. Kruse H, Johansen BK, Rørvik LM, *et al.*: **The use of avoparcin as a growth promoter and the occurrence of vancomycin-resistant *Enterococcus* species in Norwegian poultry and swine production.** *Microb Drug Resist.* 1999; **5**(2): 135–9.
PubMed Abstract | Publisher Full Text

71. Bager F, Madsen M, Christensen J, *et al.*: **Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant *Enterococcus faecium* on Danish poultry and pig farms.** *Prev Vet Med.* 1997; **31**(1–2): 95–112.
PubMed Abstract | Publisher Full Text

72. Coque TM, Tomayko JF, Ricke SC, *et al.*: **Vancomycin-resistant enterococci from nosocomial, community, and animal sources in the United States.** *Antimicrob Agents Chemother.* 1996; **40**(11): 2605–9.
PubMed Abstract | Free Full Text

73. Devriese LA, Ieven M, Goossens H, *et al.*: **Presence of vancomycin-resistant enterococci in farm and pet animals.** *Antimicrob Agents Chemother.* 1996; **40**(10): 2285–7.
PubMed Abstract | Free Full Text

74. Aarestrup FM, Ahrens P, Madsen M, *et al.*: **Glycopeptide susceptibility among Danish *Enterococcus faecium* and *Enterococcus faecalis* isolates of animal and human origin and PCR identification of genes within the VanA cluster.** *Antimicrob Agents Chemother.* 1996; **40**(8): 1938–40.
PubMed Abstract | Free Full Text

75. Woodford N: **Glycopeptide-resistant enterococci: a decade of experience.** *J Med Microbiol.* 1998; **47**(10): 849–62.
PubMed Abstract | Publisher Full Text

76. Woodford N, Johnson AP, Morrison D, *et al.*: **Current perspectives on glycopeptide resistance.** *Clin Microbiol Rev.* 1995; **8**(4): 585–615.
PubMed Abstract | Free Full Text

77. Arthur M, Molinas C, Depardieu F, *et al.*: **Characterization of Tn1546, a Tn3-related transposon conferring glycopeptide resistance by synthesis of depsipeptide peptidoglycan precursors in Enterococcus faecium BM4147.** *J Bacteriol.* 1993; **175**(1): 117–27.
PubMed Abstract | Publisher Full Text | Free Full Text

78. Willems RJ, Hanage WP, Bessen DE, *et al.*: **Population biology of Gram-positive pathogens: high-risk clones for dissemination of antibiotic resistance.** *FEMS Microbiol Rev.* 2011; **35**(5): 872–900.
PubMed Abstract | Publisher Full Text | Free Full Text

79. Willems RJ, Top J, van Den Braak N, *et al.*: **Host specificity of vancomycin-resistant *Enterococcus faecium*.** *J Infect Dis.* 2000; **182**(3): 816–23.
PubMed Abstract | Publisher Full Text

80. Willems RJ, Top J, van den Braak N, *et al.*: **Molecular diversity and evolutionary relationships of Tn*1546*-like elements in enterococci from humans and animals.** *Antimicrob Agents Chemother.* 1999; **43**(3): 483–91.
PubMed Abstract | Free Full Text

81. Darini AL, Palepou MF, Woodford N: **Nucleotide sequence of IS*1542*, an insertion sequence identified within VanA glycopeptide resistance elements of enterococci.** *FEMS Microbiol Lett.* 1999; **173**(2): 341–6.
PubMed Abstract | Publisher Full Text

82. Van der Steen LF, Bonten MJ, Van Kregten E, *et al.*: **[Vancomycin-resistant *Enterococcus faecium* outbreak in a nephrology ward].** *Ned Tijdschr Geneeskd.* 2000; **144**(53): 2568–71.
PubMed Abstract

83. Routsi C, Platsouka E, Konstantinidis K, *et al.*: **Clinical and molecular surveillance of glycopeptide-resistant *Enterococcus faecium* (GREF) isolates in a Greek ICU**. *Intensive Care Medicine.* Springer-Verlag; 2001; S151–S.
Reference Source

84. Arthur M, Reynolds P, Courvalin P: **Glycopeptide resistance in enterococci.** *Trends Microbiol.* 1996; **4**(10): 401–7.
PubMed Abstract | Publisher Full Text

85. Koyama Y, Kurosasa A, Tsuchiya A, *et al.*: **A new antibiotic 'colistin' produced by spore-forming soil bacteria.** *Journal of Antibiotics.* 1950; **3**: 457–8.

86. Landman D, Georgescu C, Martin DA, *et al.*: **Polymyxins revisited.** *Clin Microbiol Rev.* 2008; **21**(3): 449–65.
PubMed Abstract | Publisher Full Text | Free Full Text

87. Schindler M, Osborn MJ: **Interaction of divalent cations and polymyxin B with lipopolysaccharide.** *Biochemistry.* 1979; **18**(20): 4425–30.
PubMed Abstract | Publisher Full Text

88. Falagas ME, Kasiakou SK: **Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections.** *Clin Infect Dis.* 2005; **40**(9): 1333–41.
PubMed Abstract | Publisher Full Text

89. U.S. Food and Drug Administration (FDA): **Coly-Mycin® S Otic with Neomycin and Hydrocortisone.** In: Center for Drug Evaluation and Research, editor. 1962.

90. U.S. Food and Drug Administration (FDA): **Coly-Mycin® M Parenteral.** In: Center for Drug Evaluation and Research, editor. 1970.

91. Cox CE, Harrison LH: **Intravenous sodium colistimethate therapy of urinary-tract infections: pharmacological and bacteriological studies.** *Antimicrob Agents Chemother (Bethesda).* 1970; **10**: 296–302.
PubMed Abstract

92. Edgar WM, Dickinson KM: **A trial of colistin methane sulfonate in urinary infection with *Pseudomonas pyocyanea*.** *Lancet.* 1962; **7259**: 739–40.

93. Koch-Weser J, Sidel VW, Federman EB, *et al.*: **Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy.** *Ann Intern Med.* 1970; **72**(6): 857–68.
PubMed Abstract | Publisher Full Text

94. McMillan M, Price TM, MacLaren DM, *et al.*: ***Pseudomonas pyocyanea* infection treated with colistin methane sulphonate.** *Lancet.* 1962; **2**(7259): 737–9.
PubMed Abstract | Publisher Full Text

95. Falagas ME, Kasiakou SK: **Toxicity of polymyxins: a systematic review of the**

evidence from old and recent studies. *Crit Care.* 2006; **10**(1): R27.
PubMed Abstract | Publisher Full Text | Free Full Text

96. Fekety FR Jr, Norman PS, Cluff LE: **The treatment of gram-negative bacillary infections with colistin. The toxicity and efficacy of large doses in forty-eight patients.** *Ann Intern Med.* 1962; **57**(2 Part 1): 214–29.
PubMed Abstract | Publisher Full Text

97. Levin AS, Barone AA, Penço J, *et al.*: **Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.** *Clin Infect Dis.* 1999; **28**(5): 1008–11.
PubMed Abstract | Publisher Full Text

98. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, *et al.*: **Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP.** *Clin Infect Dis.* 2003; **36**(9): 1111–8.
PubMed Abstract | Publisher Full Text

99. Linden PK, Kusne S, Coley K, *et al.*: **Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*.** *Clin Infect Dis.* 2003; **37**(11): e154–e60.
PubMed Abstract | Publisher Full Text

100. Samra Z, Ofir O, Lishtzinsky Y, *et al.*: **Outbreak of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-3 in a tertiary medical centre in Israel.** *Int J Antimicrob Agents.* 2007; **30**(6): 525–9.
PubMed Abstract | Publisher Full Text

101. Souli M, Galani I, Antoniadou A, *et al.*: **An outbreak of infection due to beta-Lactamase *Klebsiella pneumoniae* Carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes.** *Clin Infect Dis.* 2010; **50**(3): 364–73.
PubMed Abstract | Publisher Full Text

102. Markou N, Apostolakos H, Koumoudiou C, *et al.*: **Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients.** *Crit Care.* 2003; **7**(5): R78–83.
PubMed Abstract | Publisher Full Text | Free Full Text

103. European Medicines Agency (EMA): **Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health**. In: Committee for Medicinal Products for Veterinary use (CVMP), Committee for Medicinal Products for Human Use (CHMP), editors. London; 2016.
Reference Source

104. European Centers for Disease Control and Prevention (ECDC), European Food Safety Authority (EFSA), European Food Safety Authority (EFSA): **ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and foodproducing animals.** *European Food Safety Authority (EFSA) Journal.* 2015; **13**(1): 4006.
Publisher Full Text

105. European Centers for Disease Control and Prevention (ECDC): **Summary of the latest data on antibiotic consumption in the European Union Antibiotic consumption in Europe**. Stockholm, 2015.
Reference Source

106. European Medicines Agency (EMA): **Use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health**. 2016.

107. Catry B, Cavaleri M, Baptiste K, *et al.*: **Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health.** *Int J Antimicrob Agents.* 2015; **46**(3): 297–306.
PubMed Abstract | Publisher Full Text

108. Liu YY, Wang Y, Walsh TR, *et al.*: **Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study.** *Lancet Infect Dis.* 2015; **16**(2): 161–8.
PubMed Abstract | Publisher Full Text

109. U.S. Food and Drug Administration (FDA): **2014 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals.** 2015.
Reference Source

110. U.S. Food and Drug Administration: **NADA 141-069 FIRST GUARD STERILE POWDER - original approval**. 1998.
Reference Source

111. Spring Reports of the Auditor General of Canada: **Report 1—Antimicrobial Resistance**. 2015.
Reference Source

112. Rhouma M, Beaudry F, Thériault W, *et al.*: ***In vivo* therapeutic efficacy and pharmacokinetics of colistin sulfate in an experimental model of enterotoxigenic *Escherichia coli* infection in weaned pigs.** *Vet Res.* 2016; **47**(1): 58.
PubMed Abstract | Publisher Full Text | Free Full Text

113. Rhouma M, Beaudry F, Thériault W, *et al.*: **Gastric stability and oral bioavailability of colistin sulfate in pigs challenged or not with *Escherichia coli* O149: F4 (K88).** *Res Vet Sci.* 2015; **102**: 173–81.
PubMed Abstract | Publisher Full Text

114. European Commission Decision: **Summary of European Union decisions on marketing authorisations in respect of medicinal products from 1 March 2010 to 30 June 2010.** *Official Journal of the European Union.* 2010; **C 258/32**(24.9.2010): Annex II.

115. European Medicines Agency (EMA): **Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013**. *Fifth ESVAC report.* ESVAC: European Surveillance of Veterinary Antimicrobial Consumption. 2015.
Reference Source

116. Walsh TR, Wu Y: **China bans colistin as a feed additive for animals.** *Lancet Infect Dis.* 2016; **16**(10): 1102–3.
PubMed Abstract | Publisher Full Text

117. European Commission: **COMMISSION IMPLEMENTING DECISION of 16.3.2015 concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for all veterinary medicinal products containing "Colistin" to be administered orally**. 2015.
Reference Source

118. European Commission: **COMMISSION IMPLEMENTING DECISION of 14.7.2016 concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for all veterinary medicinal products containing "colistin" in combination with other antimicrobial substances to be administered orally**. C(2016) 4708 final.
Reference Source

119. Canada Go: **Regulations Amending the Food and Drug Regulations (Veterinary Drugs — Antimicrobial Resistance).** *Canada Gazette.* 2016; **150**(27).
Reference Source

120. Tan TY, Ng LS: **Comparison of three standardized disc susceptibility testing methods for colistin.** *J Antimicrob Chemother.* 2006; **58**(4): 864–7.
PubMed Abstract | Publisher Full Text

121. Lo-Ten-Foe JR, de Smet AM, Diederen BM, *et al.*: **Comparative evaluation of the VITEK 2, disk diffusion, etest, broth microdilution, and agar dilution susceptibility testing methods for colistin in clinical isolates, including heteroresistant *Enterobacter cloacae* and *Acinetobacter baumannii* strains.** *Antimicrob Agents Chemother.* 2007; **51**(10): 3726–30.
PubMed Abstract | Publisher Full Text | Free Full Text

122. Tan TY, Ng SY: **Comparison of Etest, Vitek and agar dilution for susceptibility testing of colistin.** *Clin Microbiol Infect.* 2007; **13**(5): 541–4.
PubMed Abstract | Publisher Full Text

123. Hindler JA, Humphries RM: **Colistin MIC variability by method for contemporary clinical isolates of multidrug-resistant Gram-negative bacilli.** *J Clin Microbiol.* 2013; **51**(6): 1678–84.
PubMed Abstract | Publisher Full Text | Free Full Text

124. European Parliament, Council of the European Union: **COMMISSION IMPLEMENTING DECISION 2013/652/EU of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria.** *Off J Eur Union.* (L 303/26). 2013.
Reference Source

125. European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC): **The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014.** *EFSA J.* 2016; **14**(2): 4380.
Publisher Full Text

126. Callens B, Persoons D, Maes D, *et al.*: **Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds.** *Prev Vet Med.* 2012; **106**(1): 53–62.
PubMed Abstract | Publisher Full Text

127. Perrin-Guyomard A, Bruneau M, Houée P, *et al.*: **Prevalence of *mcr-1* in commensal *Escherichia coli* from French livestock, 2007 to 2014.** *Euro Surveill.* 2016; **21**(6).
PubMed Abstract | Publisher Full Text

128. Malhotra-Kumar S, Xavier BB, Das AJ, *et al.*: **Colistin resistance gene *mcr-1* harboured on a multidrug resistant plasmid.** *Lancet Infect Dis.* 2016; **16**(3): 283–4.
PubMed Abstract | Publisher Full Text

129. Webb HE, Granier SA, Marault M, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(2): 144–5.
PubMed Abstract | Publisher Full Text

130. Olaitan AO, Chabou S, Okdah L, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(2): 147.
PubMed Abstract | Publisher Full Text

131. Arcilla MS, van Hattemb JM, Matamorosb S, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(2): 147–9.
PubMed Abstract | Publisher Full Text

132. Haenni M, Poirel L, Kieffer N, *et al.*: **Co-occurrence of extended spectrum β lactamase and MCR-1 encoding genes on plasmids.** *Lancet Infect Dis.* 2016; **16**(3): 281–2.
PubMed Abstract | Publisher Full Text

133. Suzuki S, Ohnishi M, Kawanishi M, *et al.*: **Investigation of a plasmid genome database for colistin-resistance gene *mcr-1*.** *Lancet Infect Dis.* 2016; **16**(3): 284–5.
PubMed Abstract | Publisher Full Text

134. Public Health England (PHE): **First detection of plasmid-mediated colistin resistance (*mcr-1* gene) in food and human isolates in England and Wales (Serial number 2015/090)**. 2015.

135. Tse H, Yuen KY: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(2): 145–6.
PubMed Abstract | Publisher Full Text

136. Hu Y, Liu F, Lin IY, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(2): 146–7.
PubMed Abstract | Publisher Full Text

137. Falgenhauer L, Waezsada SE, Yao Y, *et al.*: **Colistin resistance gene *mcr-1* in extended-spectrum β-lactamase-producing and carbapenemase-producing**

Gram-negative bacteria in Germany. *Lancet Infect Dis.* 2016; **16**(3): 282–3.
PubMed Abstract | Publisher Full Text

138. Petrillo M, Angers-Loustau A, Kreysa J: **Possible genetic events producing colistin resistance gene *mcr-1*.** *Lancet Infect Dis.* 2016; **16**(3): 280.
PubMed Abstract | Publisher Full Text

139. Stoesser N, Mathers AJ, Moore CE, *et al.*: **Colistin resistance gene *mcr-1* and pHNSHP45 plasmid in human isolates of *Escherichia coli* and *Klebsiella pneumoniae*.** *Lancet Infect Dis.* 2016; **16**(3): 285–6.
PubMed Abstract | Publisher Full Text

140. Hasman H, Hammerum A, Hansen F, *et al.*: **Detection of *mcr-1* encoding plasmid-mediated colistin-resistant *Escherichia coli* isolates from human bloodstream infection and imported chicken meat, Denmark 2015.** *Euro Surveill.* 2015; **20**(49).
PubMed Abstract | Publisher Full Text

141. Pham Thanh D, Thanh Tuyen H, Nguyen Thi Nguyen T, *et al.*: **Inducible colistin resistance via a disrupted plasmid-borne *mcr-1* gene in a 2008 Vietnamese *Shigella sonnei* isolate.** *J Antimicrob Chemother.* 2016; **71**(8): 2314–7.
PubMed Abstract | Publisher Full Text | Free Full Text

142. Mulvey MR, Mataseje LF, Robertson J, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(3): 289–90.
PubMed Abstract | Publisher Full Text

143. Payne M, Croxen MA, Lee TD, *et al.*: ***mcr-1*-Positive Colistin-Resistant *Escherichia coli* in Traveler Returning to Canada from China.** *Emerg Infect Dis.* 2016; **22**(9): 1673–5.
PubMed Abstract | Publisher Full Text | Free Full Text

144. Zeng KJ, Doi Y, Patil S, *et al.*: **Emergence of the plasmid-mediated *mcr-1* gene in colistin-resistant *Enterobacter aerogenes* and *Enterobacter cloacae*.** *Antimicrob Agents Chemother.* 2016; **60**(6): 3862–3.
PubMed Abstract | Publisher Full Text | Free Full Text

145. Bi Z, Berglund B, Sun Q, *et al.*: **Prevalence of the *mcr-1* colistin resistance gene in extended-spectrum β-lactamase-producing *Escherichia coli* from human faecal samples collected in 2012 in rural villages in Shandong Province, China.** *Int J Antimicrob Agents.* 2017; **49**(4): 493–7.
PubMed Abstract | Publisher Full Text

146. Li A, Yang Y, Miao M, *et al.*: **Complete Sequences of *mcr-1*-Harboring Plasmids from Extended-Spectrum-β-Lactamase- and Carbapenemase-Producing *Enterobacteriaceae*.** *Antimicrob Agents Chemother.* 2016; **60**(7): 4351–4.
PubMed Abstract | Publisher Full Text | Free Full Text

147. Zhang R, Huang Y, Chan EW, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(3): 291–2.
PubMed Abstract | Publisher Full Text

148. Zhang XF, Doi Y, Huang X, *et al.*: **Possible Transmission of *mcr-1*-Harboring *Escherichia coli* between Companion Animals and Human.** *Emerg Infect Dis.* 2016; **22**(9): 1679–81.
PubMed Abstract | Publisher Full Text | Free Full Text

149. Zheng B, Dong H, Xu H, *et al.*: **Coexistence of MCR-1 and NDM-1 in Clinical *Escherichia coli* Isolates.** *Clin Infect Dis.* 2016; **63**(10): 1393–5.
PubMed Abstract | Publisher Full Text

150. Ye H, Li Y, Li Z, *et al.*: **Diversified *mcr-1*-Harbouring Plasmid Reservoirs Confer Resistance to Colistin in Human Gut Microbiota.** *mBio.* 2016; **7**(2): e00177–16.
PubMed Abstract | Publisher Full Text | Free Full Text

151. Ruppé E, Le Chatelier E, Pons N, *et al.*: **Dissemination of the *mcr-1* colistin resistance gene.** *Lancet Infect Dis.* 2016; **16**(3): 290–1.
PubMed Abstract | Publisher Full Text

152. He QW, Xu XH, Lan FJ, *et al.*: **Molecular characteristic of *mcr-1* producing *Escherichia coli* in a Chinese university hospital.** *Ann Clin Microbiol Antimicrob.* 2017; **16**(1): 32.
PubMed Abstract | Publisher Full Text | Free Full Text

153. Du H, Chen L, Tang YW, *et al.*: **Emergence of the *mcr-1* colistin resistance gene in carbapenem-resistant Enterobacteriaceae.** *Lancet Infect Dis.* 2016; **16**(3): 287–8.
PubMed Abstract | Publisher Full Text

154. Yu H, Qu F, Shan B, *et al.*: **Detection of the *mcr-1* Colistin Resistance Gene in Carbapenem-Resistant *Enterobacteriaceae* from Different Hospitals in China.** *Antimicrob Agents Chemother.* 2016; **60**(8): 5033–5.
PubMed Abstract | Publisher Full Text | Free Full Text

155. Ortega-Paredes D, Barba P, Zurita J: **Colistin-resistant *Escherichia coli* clinical isolate harbouring the *mcr-1* gene in Ecuador.** *Epidemiol Infect.* 2016; **144**(14): 2967–2970.
PubMed Abstract | Publisher Full Text

156. Elnahriry SS, Khalifa HO, Soliman AM, *et al.*: **Emergence of Plasmid-Mediated Colistin Resistance Gene *mcr-1* in a Clinical *Escherichia coli* Isolate from Egypt.** *Antimicrob Agents Chemother.* 2016; **60**(5): 3249–50.
PubMed Abstract | Publisher Full Text | Free Full Text

157. Caspar Y, Maillet M, Pavese P, *et al.*: ***mcr-1* Colistin Resistance in ESBL-Producing *Klebsiella pneumoniae*, France.** *Emerg Infect Dis.* 2017; **23**(5): 874–876.
PubMed Abstract | Publisher Full Text | Free Full Text

158. Fritzenwanker M, Imirzalioglu C, Gentil K, *et al.*: **Incidental detection of a urinary *Escherichia coli* isolate harbouring *mcr-1* of a patient with no history of colistin treatment.** *Clin Microbiol Infect.* 2016; **22**(11): 954–955.
PubMed Abstract | Publisher Full Text

159. Castanheira M, Griffin MA, Deshpande LM, *et al.*: **Detection of *mcr-1* among *Escherichia coli* Clinical Isolates Collected Worldwide as Part of the SENTRY Antimicrobial Surveillance Program in 2014 and 2015.** *Antimicrob Agents Chemother.* 2016; **60**(9): 5623–4.
PubMed Abstract | Publisher Full Text | Free Full Text

160. Wong SC, Tse H, Chen JH, *et al.*: **Colistin-Resistant *Enterobacteriaceae* Carrying the *mcr-1* Gene among Patients in Hong Kong.** *Emerg Infect Dis.* 2016; **22**(9): 1667–9.
PubMed Abstract | Publisher Full Text | Free Full Text

161. Kumar M, Saha S, Subudhi E: **More Furious Than Ever: *Escherichia coli*-Acquired Co-resistance Toward Colistin and Carbapenems.** *Clin Infect Dis.* 2016; **63**(9): 1267–68.
PubMed Abstract | Publisher Full Text

162. Bernasconi OJ, Kuenzli E, Pires J, *et al.*: **Travelers can import colistin-resistant *Enterobacteriaceae*, including those possessing the plasmid-mediated *mcr-1* gene.** *Antimicrob Agents Chemother.* 2016; **60**(8): 5080–4.
PubMed Abstract | Publisher Full Text | Free Full Text

163. Giufrè M, Monaco M, Accogli M, *et al.*: **Emergence of the colistin resistance *mcr-1* determinant in commensal *Escherichia coli* from residents of long-term-care facilities in Italy.** *J Antimicrob Chemother.* 2016; **71**(8): 2329–31.
PubMed Abstract | Publisher Full Text

164. Cannatelli A, Giani T, Antonelli A, *et al.*: **First detection of the *mcr-1* colistin resistance gene in *Escherichia coli* in Italy.** *Antimicrob Agents Chemother.* 2016; **60**(5): 3257–8.
PubMed Abstract | Publisher Full Text | Free Full Text

165. Corbella M, Mariani B, Ferrari C, *et al.*: **Three cases of *mcr-1*-positive colistin-resistant *Escherichia coli* bloodstream infections in Italy, August 2016 to January 2017.** *Euro Surveill.* 2017; **22**(16): pii: 30517.
PubMed Abstract | Publisher Full Text | Free Full Text

166. Yu CY, Ang GY, Chin PS, *et al.*: **Emergence of *mcr-1*-mediated colistin resistance in *Escherichia coli* in Malaysia.** *Int J Antimicrob Agents.* 2016; **47**(6): 504–5.
PubMed Abstract | Publisher Full Text

167. Terveer EM, Nijhuis RHT, Crobach MJT, *et al.*: **Prevalence of colistin resistance gene (*mcr-1*) containing *Enterobacteriaceae* in feces of patients attending a tertiary care hospital and detection of a *mcr-1* containing, colistin susceptible *E. coli*.** *PLoS One.* 2017; **12**(6): e0178598.
PubMed Abstract | Publisher Full Text | Free Full Text

168. Nijhuis RH, Veldman KT, Schelfaut J, *et al.*: **Detection of the plasmid-mediated colistin-resistance gene *mcr-1* in clinical isolates and stool specimens obtained from hospitalized patients using a newly developed real-time PCR assay.** *J Antimicrob Chemother.* 2016; **71**(8): 2344–6.
PubMed Abstract | Publisher Full Text

169. Bonten MJ: **[Antimicrobial resistance: is it really all going wrong now?].** *Ned Tijdschr Geneeskd.* 2016; **160**: D81.
PubMed Abstract

170. von Wintersdorff CJ, Wolffs PF, van Niekerk JM, *et al.*: **Detection of the plasmid-mediated colistin-resistance gene *mcr-1* in faecal metagenomes of Dutch travellers.** *J Antimicrob Chemother.* 2016; **71**(12): 3416–9.
PubMed Abstract | Publisher Full Text

171. Solheim M, Bohlin J, Ulstad CR, *et al.*: **Plasmid-mediated colistin-resistant *Escherichia coli* detected from 2014 in Norway.** *Int J Antimicrob Agents.* 2016; **48**(2): 227–8.
PubMed Abstract | Publisher Full Text

172. Izdebski R, Baraniak A, Bojarska K, *et al.*: **Mobile MCR-1-associated resistance to colistin in Poland.** *J Antimicrob Chemother.* 2016; **71**(8): 2331–3.
PubMed Abstract | Publisher Full Text

173. Campos J, Cristino L, Peixe L, *et al.*: **MCR-1 in multidrug-resistant and copper-tolerant clinically relevant Salmonella 1,4,[5],12:i:- and S. Rissen clones in Portugal, 2011 to 2015.** *Euro Surveill.* 2016; **21**(26).
PubMed Abstract | Publisher Full Text

174. Sonnevend Á, Ghazawi A, Alqahtani M, *et al.*: **Plasmid-mediated colistin resistance in *Escherichia coli* from the Arabian Peninsula.** *Int J Infect Dis.* 2016; **50**: 85–90.
PubMed Abstract | Publisher Full Text

175. Teo JW, Chew KL, Lin RT: **Transmissible colistin resistance encoded by *mcr-1* detected in clinical Enterobacteriaceae isolates in Singapore.** *Emerg Microbes Infect.* 2016; **5**(8): e87.
PubMed Abstract | Publisher Full Text | Free Full Text

176. Teo JQ, Ong RT, Xia E, *et al.*: ***mcr-1* in Multidrug-Resistant bla_{KPC-2}-Producing Clinical *Enterobacteriaceae* Isolates in Singapore.** *Antimicrob Agents Chemother.* 2016; **60**(10): 6435–7.
PubMed Abstract | Publisher Full Text | Free Full Text

177. Coetzee J, Corcoran C, Prentice E, *et al.*: **Emergence of plasmid-mediated colistin resistance (MCR-1) among *Escherichia coli* isolated from South African patients.** *S Afr Med J.* 2016; **106**(5): 35–6.
PubMed Abstract | Publisher Full Text

178. Poirel L, Kieffer N, Brink A, *et al.*: **Genetic Features of MCR-1-Producing Colistin-Resistant *Escherichia coli* Isolates in South Africa.** *Antimicrob Agents Chemother.* 2016; **60**(7): 4394–7.
PubMed Abstract | Publisher Full Text | Free Full Text

179. Prim N, Rivera A, Rodríguez-Navarro J, *et al.*: **Characteristics of *Escherichia coli* isolates harbouring *mcr-1* and epidemiological data of the patients, Barcelona, 2012–15.** *Blood.* 2016; **27**: 12.

180. Folkhalsomyndigheten: **Bakterie resistent mot sista behandlingsalternativet funnen**. [Bacteria resistant to the last treatment option found]. 2016; (accessed

March 18 2016).
Reference Source

181. Vading M, Kabir MH, Kalin M, *et al.*: **Frequent acquisition of low-virulence strains of ESBL-producing *Escherichia coli* in travellers.** *J Antimicrob Chemother.* 2016; **71**(12): 3548–55.
PubMed Abstract | Publisher Full Text

182. Poirel L, Kieffer N, Liassine N, *et al.*: **Plasmid-mediated carbapenem and colistin resistance in a clinical isolate of *Escherichia coli.*** *Lancet Infect Dis.* 2016; **16**(3): 281.
PubMed Abstract | Publisher Full Text

183. Liassine N, Assouvie L, Descombes MC, *et al.*: **Very low prevalence of MCR-1/MCR-2 plasmid-mediated colistin resistance in urinary tract *Enterobacteriaceae* in Switzerland.** *Int J Infect Dis.* 2016; **51**: 4–5.
PubMed Abstract | Publisher Full Text

184. Nordmann P, Lienhard R, Kieffer N, *et al.*: **Plasmid-Mediated Colistin-Resistant *Escherichia coli* in Bacteremia in Switzerland.** *Clin Infect Dis.* 2016; **62**(10): 1322–3.
PubMed Abstract | Publisher Full Text

185. Grami R, Mansour W, Mehri W, *et al.*: **Impact of food animal trade on the spread of *mcr-1*-mediated colistin resistance, Tunisia, July 2015.** *Euro Surveill.* 2016; **21**(8): 30144.
PubMed Abstract | Publisher Full Text

186. Kuo SC, Huang WC, Wang HY, *et al.*: **Colistin resistance gene *mcr-1* in *Escherichia coli* isolates from humans and retail meats, Taiwan.** *J Antimicrob Chemother.* 2016; **71**(8): 2327–9.
PubMed Abstract | Publisher Full Text

187. Paveenkittiporn W, Kerdsin A, Chokngam S, *et al.*: **Emergence of plasmid-mediated colistin resistance and New Delhi metallo-β-lactamase genes in extensively drug-resistant *Escherichia coli* isolated from a patient in Thailand.** *Diagn Microbiol Infect Dis.* 2017; **87**(2): 157–9.
PubMed Abstract | Publisher Full Text

188. Doumith M, Godbole G, Ashton P, *et al.*: **Detection of the plasmid-mediated *mcr-1* gene conferring colistin resistance in human and food isolates of *Salmonella enterica* and *Escherichia coli* in England and Wales.** *J Antimicrob Chemother.* 2016; **71**(8): 2300–5.
PubMed Abstract | Publisher Full Text

189. McGann P, Snesrud E, Maybank R, *et al.*: ***Escherichia coli* Harboring *mcr-1* and bla_{CTX-M} on a Novel IncF Plasmid: First report of *mcr-1* in the United States.** *Antimicrob Agents Chemother.* 2016; **60**(7): 4420–1.
PubMed Abstract | Publisher Full Text | Free Full Text

190. Mediavilla JR, Patrawalla A, Chen L, *et al.*: **Colistin- and Carbapenem-Resistant *Escherichia coli* Harboring *mcr-1* and bla_{NDM-5}, Causing a Complicated Urinary Tract Infection in a Patient from the United States.** *mBio.* 2016; **7**(4): pii: e01191-16.
PubMed Abstract | Publisher Full Text | Free Full Text

191. Vasquez AM, Montero N, Laughlin M, *et al.*: **Investigation of *Escherichia coli* Harboring the *mcr-1* Resistance Gene - Connecticut, 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; **65**(36): 979–80.
PubMed Abstract | Publisher Full Text

192. Delgado-Blas JF, Ovejero CM, Patiño L, *et al.*: **Coexistence of *mcr-1* and bla_{NDM-1} in *Escherichia coli* from Venezuela.** *Antimicrob Agents Chemother.* 2016; **60**(10): 6356–8.
PubMed Abstract | Publisher Full Text | Free Full Text

193. Trung NV, Matamoros S, Carrique-Mas JJ, *et al.*: **Zoonotic Transmission of *mcr-1* Colistin Resistance Gene from Small-Scale Poultry Farms, Vietnam.** *Emerg Infect Dis.* 2017; **23**(3): 529–532.
PubMed Abstract | Publisher Full Text | Free Full Text

194. Zurfuh K, Poirel L, Nordmann P, *et al.*: **Occurrence of the Plasmid-Borne *mcr-1* Colistin Resistance Gene in Extended-Spectrum-β-Lactamase-Producing Enterobacteriaceae in River Water and Imported Vegetable Samples in Switzerland.** *Antimicrob Agents Chemother.* 2016; **60**(4): 2594–5.
PubMed Abstract | Publisher Full Text | Free Full Text

195. Figueiredo R, Card RM, Nunez J, *et al.*: **Detection of an *mcr-1*-encoding plasmid mediating colistin resistance in *Salmonella enterica* from retail meat in Portugal.** *J Antimicrob Chemother.* 2016; **71**(8): 2338–40.
PubMed Abstract | Publisher Full Text

196. Kluytmans-van den Bergh MF, Huizinga P, Bonten MJ, *et al.*: **Presence of *mcr-1*-positive *Enterobacteriaceae* in retail chicken meat but not in humans in the Netherlands since 2009.** *Euro Surveill.* 2016; **21**(9): 30149.
PubMed Abstract | Publisher Full Text

197. Yao X, Doi Y, Zeng L, *et al.*: **Carbapenem-resistant and colistin-resistant *Escherichia coli* co-producing NDM-9 and MCR-1.** *Lancet Infect Dis.* 2016; **16**(3): 288–9.
PubMed Abstract | Publisher Full Text

198. Zogg AL, Zurfluh K, Nüesch-Inderbinen M, *et al.*: **Characteristics of ESBL-producing Enterobacteriaceae and Methicillinresistant *Staphylococcus aureus* (MRSA) isolated from Swiss and imported raw poultry meat collected at retail level.** *Schweiz Arch Tierheilkd.* 2016; **158**(6): 451–6.
PubMed Abstract | Publisher Full Text

199. Veldman K, van Essen-Zandbergen A, Rapallini M, *et al.*: **Location of colistin resistance gene *mcr-1* in Enterobacteriaceae from livestock and meat.** *J Antimicrob Chemother.* 2016; **71**(8): 2340–2.
PubMed Abstract | Publisher Full Text

200. Shen Z, Wang Y, Shen Y, *et al.*: **Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals.** *Lancet Infect Dis.* 2016; **16**(3): 293.
PubMed Abstract | Publisher Full Text

201. Xavier BB, Lammens C, Butaye P, *et al.*: **Complete sequence of an IncFII plasmid harbouring the colistin resistance gene *mcr-1* isolated from Belgian pig farms.** *J Antimicrob Chemother.* 2016; **71**(8): 2342–4.
PubMed Abstract | Publisher Full Text

202. Fernandes MR, Moura Q, Sartori L, *et al.*: **Silent dissemination of colistin-resistant *Escherichia coli* in South America could contribute to the global spread of the *mcr-1* gene.** *Euro Surveill.* 2016; **21**(17).
PubMed Abstract | Publisher Full Text

203. Bai L, Hurley D, Li J, *et al.*: **Characterisation of multidrug-resistant Shiga toxin-producing *Escherichia coli* cultured from pigs in China: co-occurrence of extended-spectrum β-lactamase- and *mcr-1*-encoding genes on plasmids.** *Int J Antimicrob Agents.* 2016; **48**(4): 445–8.
PubMed Abstract | Publisher Full Text

204. Li Z, Tan C, Lin J, *et al.*: **Diversified variants of the *mcr-1*-carrying plasmid reservoir in the swine lung microbiota.** *Sci China Life Sci.* 2016; **59**(9): 971–3.
PubMed Abstract | Publisher Full Text

205. Irrgang A, Roschanski N, Tenhagen BA, *et al.*: **Prevalence of *mcr-1* in *E. coli* from Livestock and Food in Germany, 2010–2015.** *PLoS One.* 2016; **11**(7): e0159863.
PubMed Abstract | Publisher Full Text | Free Full Text

206. Roschanski N, Falgenhauer L, Grobbel M, *et al.*: **Retrospective survey of *mcr-1* and *mcr-2* in German pig-fattening farms, 2011–2012.** *Int J Antimicrob Agents.* 2017; **50**(2): 266–71.
PubMed Abstract | Publisher Full Text

207. Kusumoto M, Ogura Y, Gotoh Y, *et al.*: **Colistin-Resistant *mcr-1*-Positive Pathogenic *Escherichia coli* in Swine, Japan, 2007–2014.** *Emerg Infect Dis.* 2016; **22**(7): 1315–7.
PubMed Abstract | Publisher Full Text | Free Full Text

208. Quesada A, Ugarte-Ruiz M, Iglesias MR, *et al.*: **Detection of plasmid mediated colistin resistance (*MCR-1*) in *Escherichia coli* and *Salmonella enterica* isolated from poultry and swine in Spain.** *Res Vet Sci.* 2016; **105**: 134–5.
PubMed Abstract | Publisher Full Text

209. Nguyen NT, Nguyen HM, Nguyen CV, *et al.*: **Use of Colistin and Other Critical Antimicrobials on Pig and Chicken Farms in Southern Vietnam and Its Association with Resistance in Commensal *Escherichia coli* Bacteria.** *Appl Environ Microbiol.* 2016; **82**(13): 3727–35.
PubMed Abstract | Publisher Full Text | Free Full Text

210. Malhotra-Kumar S, Xavier BB, Das AJ, *et al.*: **Colistin-resistant *Escherichia coli* harbouring *mcr-1* isolated from food animals in Hanoi, Vietnam.** *Lancet Infect Dis.* 2016; **16**(3): 286–7.
PubMed Abstract | Publisher Full Text

211. Anjum MF, Duggett NA, AbuOun M, *et al.*: **Colistin resistance in *Salmonella* and *Escherichia coli* isolates from a pig farm in Great Britain.** *J Antimicrob Chemother.* 2016; **71**(8): 2306–13.
PubMed Abstract | Publisher Full Text

212. United States Department of Health and Human Services (HHS): **Proactive efforts by U.S. federal agencies enable early detection of new antibiotic resistance**. 2016.
Reference Source

213. Chabou S, Leangapichart T, Okdah L, *et al.*: **Real-time quantitative PCR assay with Taqman(®) probe for rapid detection of MCR-1 plasmid-mediated colistin resistance.** *New Microbes New Infect.* 2016; **13**: 71–4.
PubMed Abstract | Publisher Full Text | Free Full Text

214. Lentz SA, de Lima-Morales D, Cuppertino VM, *et al.*: **Letter to the editor: *Escherichia coli* harbouring *mcr-1* gene isolated from poultry not exposed to polymyxins in Brazil.** *Euro Surveill.* 2016; **21**(26).
PubMed Abstract | Publisher Full Text

215. Monte DF, Fernandes MR, Cerdeira L, *et al.*: **Draft Genome Sequences of Colistin-Resistant MCR-1-Producing *Escherichia coli* ST1850 and ST74 Strains Isolated from Commercial Chicken Meat.** *Genome Announc.* 2017; **5**(20): pii: e00329-17.
PubMed Abstract | Publisher Full Text | Free Full Text

216. Sun J, Li XP, Yang RS, *et al.*: **Complete Nucleotide Sequence of an IncI2 Plasmid Coharboring $bla_{CTX-M-55}$ and *mcr-1*.** *Antimicrob Agents Chemother.* 2016; **60**(8): 5014–7.
PubMed Abstract | Publisher Full Text | Free Full Text

217. Yang YQ, Zhang AY, Ma SZ, *et al.*: **Co-occurrence of *mcr-1* and ESBL on a single plasmid in *Salmonella enterica.*** *J Antimicrob Chemother.* 2016; **71**(8): 2336–8.
PubMed Abstract | Publisher Full Text

218. Lima Barbieri N, Nielsen DW, Wannemuehler Y, *et al.*: ***mcr-1* identified in Avian Pathogenic *Escherichia coli* (APEC).** *PLoS One.* 2017; **12**(3): e0172997.
PubMed Abstract | Publisher Full Text | Free Full Text

219. Battisti A: **Antibiotic resistance - Italy: colistin, MCR-1, *E. coli,* turkeys, 2014**. 2016; (accessed September 10 2016).
Reference Source

220. Keeton C: **Mutant superbug threat to SA poultry**. 2016; (accessed March 25 2016).
Reference Source

221. Perreten V, Strauss C, Collaud A, *et al.*: **Colistin Resistance Gene *mcr-1* in Avian-**

Pathogenic *Escherichia coli* in South Africa. *Antimicrob Agents Chemother.* 2016; **60**(7): 4414–5.
PubMed Abstract | Publisher Full Text | Free Full Text

222. Khalifa HO, Ahmed AM, Oreiby AF, *et al.*: **Characterisation of the plasmid-mediated colistin resistance gene *mcr-1* in *Escherichia coli* isolated from animals in Egypt.** *Int J Antimicrob Agents.* 2016; **47**(5): 413–4.
PubMed Abstract | Publisher Full Text

223. Brennan E, Martins M, McCusker MP, *et al.*: **Multidrug-Resistant *Escherichia coli* in Bovine Animals, Europe.** *Emerg Infect Dis.* 2016; **22**(9): 1650–2.
PubMed Abstract | Publisher Full Text | Free Full Text

224. Zhou HW, Zhang T, Ma JH, *et al.*: **Occurrence of Plasmid- and Chromosome-Carried *mcr-1* in Waterborne *Enterobacteriaceae* in China.** *Antimicrob Agents Chemother.* 2017; **61**(8): pii: e00017-17.
PubMed Abstract | Publisher Full Text | Free Full Text

225. Sennati S, Di Pilato V, Riccobono E, *et al.*: ***Citrobacter braakii* carrying plasmid-borne *mcr-1* colistin resistance gene from ready-to-eat food from a market in the Chaco region of Bolivia.** *J Antimicrob Chemother.* 2017; **72**(7): 2127–9.
PubMed Abstract | Publisher Full Text

226. Sellera FP, Fernandes MR, Sartori L, *et al.*: ***Escherichia coli* carrying IncX4 plasmid-mediated *mcr-1* and *bla*CTX-M genes in infected migratory Magellanic penguins (*Spheniscus magellanicus*).** *J Antimicrob Chemother.* 2017; **72**(4): 1255–6.
PubMed Abstract | Publisher Full Text

227. Liakopoulos A, Mevius DJ, Olsen B, *et al.*: **The colistin resistance *mcr-1* gene is going wild.** *J Antimicrob Chemother.* 2016; **71**(8): 2335–6.
PubMed Abstract | Publisher Full Text

228. Mohsin M, Raza S, Roschanski N, *et al.*: **First description of plasmid-mediated colistin-resistant extended-spectrum β-lactamase-producing *Escherichia coli* in a wild migratory bird from Asia.** *Int J Antimicrob Agents.* 2016; **48**(4): 463–4.
PubMed Abstract | Publisher Full Text

229. Ruzauskas M, Vaskeviciute L: **Detection of the *mcr-1* gene in *Escherichia coli* prevalent in the migratory bird species *Larus argentatus*.** *J Antimicrob Chemother.* 2016; **71**(8): 2333–4.
PubMed Abstract | Publisher Full Text

230. Yang D, Qiu Z, Shen Z, *et al.*: **The Occurrence of the Colistin Resistance Gene *mcr-1* in the Haihe River (China).** *Int J Environ Res Public Health.* 2017; **14**(6): pii: E576.
PubMed Abstract | Publisher Full Text | Free Full Text

231. Xavier B, Lammens C, Ruhal R, *et al.*: **Identification of *mcr-2* in colistin-resistant *E. coli* isolates not harbouring *mcr-1*.** *Eurosurveillance.* 2016; **21**(27).

232. Di Pilato V, Arena F, Tascini C, *et al.*: ***mcr-1.2*, a New *mcr* Variant Carried on a Transferable Plasmid from a Colistin-Resistant KPC Carbapenemase-Producing *Klebsiella pneumoniae* Strain of Sequence Type 512.** *Antimicrob Agents Chemother.* 2016; **60**(9): 5612–5.
PubMed Abstract | Publisher Full Text | Free Full Text

233. Yin W, Li H, Shen Y, *et al.*: **Novel Plasmid-Mediated Colistin Resistance Gene *mcr-3* in *Escherichia coli*.** *mBio.* 2017; **8**(3): pii: e00543-17.
PubMed Abstract | Publisher Full Text | Free Full Text

234. Carattoli A, Villa L, Feudi C, *et al.*: **Novel plasmid-mediated colistin resistance *mcr-4* gene in *Salmonella* and *Escherichia coli*, Italy 2013, Spain and Belgium, 2015 to 2016.** *Euro Surveill.* 2017; **22**(31): pii: 30589.
PubMed Abstract | Publisher Full Text | Free Full Text

235. Borowiak M, Fischer J, Hammerl JA, *et al.*: **Identification of a novel transposon-associated phosphoethanolamine transferase gene, *mcr-5*, conferring colistin resistance in *d*-tartrate fermenting *Salmonella enterica* subsp. *enterica* serovar Paratyphi B.** *J Antimicrob Chemother.* 2017; dkx327.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Referee Status: ✔ ✔

Version 1

Referee Report 14 November 2017

doi:10.5256/f1000research.13843.r27472

✔ **Séamus Fanning**
UCD-Centre for Food Safety, Science Centre South, University College Dublin, Dublin, Ireland

In this review, Illustrative examples of probable transfer of resistance determinants from food animals to humans: strepothricins, glycopeptides and coilstin, these authors provide a timely update on this important topic of interest to veterinary public health. The three selected antimicrobial agents highlighted are described so as to provide the reader with a background on their uses; the emergence of resistance to these compounds and possible routes of dissemination. Two of the three examples provided (streptothricin- and glycopeptide-resistance) are historical in nature, whilst the colistin-resistant chapter is more recent. The selection of these topics clearly demonstrated the consequences of antimicrobial compound usage and the subsequent response from bacteria of importance to animal- and human-health.

The manuscript is well designed and clearly written, as presented. It is scientifically sound. The topic is of immediate interest and would serve as a very useful and comprehensive review of our current understanding of this subject. In places the authors highlight some of the limitations in current approaches to the study of some of these resistance mechanisms, particularly in regard to colistin.

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Molecular mechanism of antimicrobial resistance, dissemination of resistance determinants, WGS characterisation of AMR genotypes

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 03 November 2017

doi:10.5256/f1000research.13843.r27473

Wolfgang Witte
Robert Koch-Institut (RKI), Wernigerode, Germany

Manuscript “Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin” describes evidence for antibiotic resistance gene transfer from bacteria colonizing / infecting livestock to bacteria colonizing / infecting humans by means of three examples: streptothricine-resistance and glycopeptide resistance as historical examples, and *mcr* mediated resistance to colistin as an important recent example. Altogether this review is well written and based on a very careful literature research together with a balanced selection of the really relevant publications. Above all the comprehensive and condensed presentation of studies on colistin resistance is impressing.

A few points will need attention:

- A short discussion on the consequences of the ban of avoparcin as growth promoter would be of interest (e.g. significant reduction of gastrointestinal colonization of healthy humans in the community, Klare et al., 1999). It should also be mentioned that despite this ban several European countries faced an increase of VRE among isolates from blood cultures (EARSnet) since 2004. The question whether the ban was of little significance for the VRE situation in human medicine or whether it could have come much more worse in case of a continuing existing van gene pool in the community cannot be answered in retrospect.

- For the chapter on colistin resistance I suggest to mention that the extent to which *mcr* contributes to colistin resistance in clinical isolates cannot exactly be assessed so far, and that there are cases of acquisition of *mcr* by carbapenemase producing *K.pneumoniae* (Newton-Food et al., 2017). Furthermore, the emergence of *E.coli* harbouring *mcr*-1 and bla_{KPC-2} after meropenem and colistin therapy is of interest (Tacao et al., 2017).

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Molecular epidemiology of antibiotic resistance, studies on transmission of antibiotic resistant bacteria and their resistance genes at the interface between livestock and humans

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.