Plasmid-mediated colistin resistance (*mcr-1* gene): three months later, the story unfolds

RL Skov [1], DL Monnet [2]
1. Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark
2. Office of Chief Scientist, European Centre for Disease Prevention and Control, Stockholm, Sweden

Correspondence: Robert L. Skov (rsk@ssi.dk)

Citation style for this article:
Skov R, Monnet D. Plasmid-mediated colistin resistance (mcr-1 gene): three months later, the story unfolds. Euro Surveill. 2016;21(9):pii=30155. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.9.30155

Article submitted on 01 March 2016 / accepted on 03 March 2016 / published on 03 March 2016

On 18 November 2015, Liu et al. reported the first description of plasmid-mediated colistin resistance (*mcr-1* gene) in food animals, food and humans in China [1]. In this issue, Kluytmans-van den Bergh et al. report on their finding of the *mcr-1* gene in *Escherichia coli* isolates from three (1.5%) of 196 samples of chicken meat collected at Dutch supermarkets, one in 2009 and two in 2014 [2]. This was done by whole genome sequencing of all *E. coli* isolates and then screening for the presence of the *mcr-1* gene by comparing the assembled sequences with sequence data from two databases. The same study did not find any *mcr-1*-positive isolate among 2,275 extended-spectrum beta-lactamase-positive *Escherichia coli* (screening and clinical isolates) sampled in humans between 2009 and 2015. The exact origin of the sampled chicken meat was not known, with the two samples from 2014 being labelled 'non-Dutch, European'. The fact that the genomes of the two isolates from 2014 differed by only three loci and were from the same lot of chicken meat strongly suggest cross-contamination from a common source.

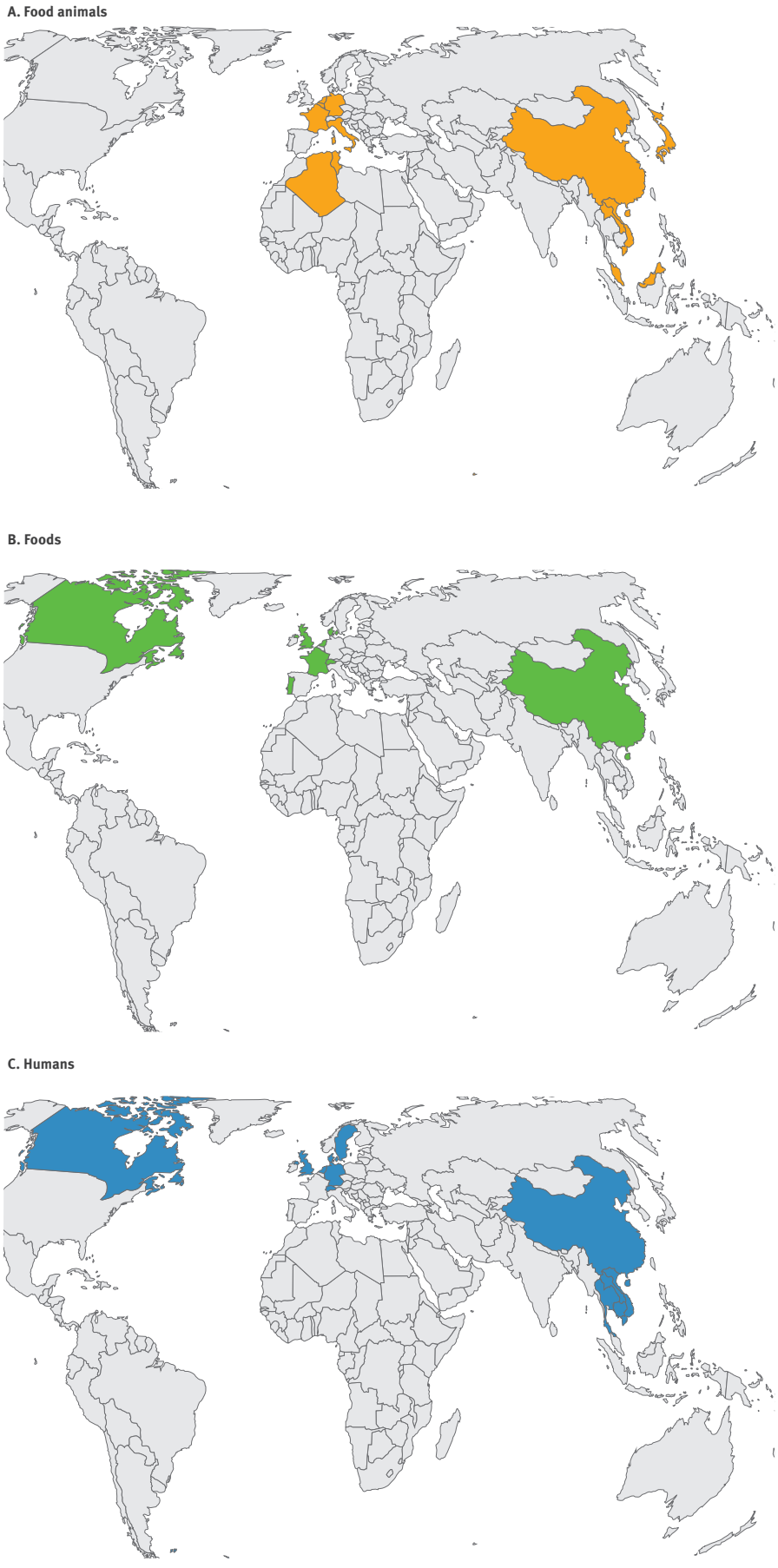
This study adds to the already long list of articles on plasmid-mediated colistin resistance published in this and other journals [3-30] (Figure and Table). Within just three months of the first description, we learned that the *mcr-1* gene (i) had spread to most continents (Figure), (ii) had been found in bacteria isolated from various food animals, from the environment including river water, from various types of meat and vegetables, and from infected patients and asymptomatic human carriers including international travellers, (iii) had been found in various bacterial species, mostly *E. coli*, and on several different plasmids, and (iv) was highly transferrable with in vitro transfer rates as high as 10^{-1}. The fact that we have gained much additional information in such a short time highlights the strength of whole genome sequencing and publicly available sequence databases.

Another important piece of information is that the *mcr-1* gene has been present, though not detected, for a long time. Shen et al. reported an *mcr-1*-positive isolate from chickens in China dating back to the 1980s [21]. In Europe, the oldest isolate reported so far is an *E. coli* from a diarrhoeic veal calf in France in 2005 [10]. The earliest reported isolate from humans is a *Shigella sonnei* from Vietnam in 2008. Trends are available in one study from China and show that the proportion of *mcr-1*-positive isolates in *E. coli* from chickens has been increasing sharply since 2009 [21]. For most studies, it is impossible to calculate the prevalence of *mcr-1*-positive isolates because detection of the *mcr-1* gene was only performed on colistin-resistant isolates. In France, systematic screening of all isolates from the routine European Union surveillance of antimicrobial resistance in zoonotic commensal bacteria showed that prevalence of the *mcr-1* gene ranged from 0.5% in *E. coli* from pigs to 5.9% in *E. coli* from turkeys in the period 2013 and 2014 [16].

Plasmid-mediated colistin resistance lies at the interface between animal health and human health. Polymyxins, and in particular colistin, have been used, both in human and veterinary medicine, for more than 50 years, although their parenteral usage in humans has been limited because of concerns about nephrotoxicity and neurotoxicity. In veterinary medicine, colistin is widely used, especially for controlling diarrhoeal diseases in pig and poultry production [31]. However, its use varies widely between countries; in Europe, from 0 mg (Finland, Iceland, Norway) to more than 20 mg (Italy, Spain) per kg animal biomass were used in 2013 [32]. Data from other parts of the world are more scarce, however Liu et al. reported that the market value for colistin for veterinary usage increased from USD 8.7 billion (EUR 8.0 billion) in 1992 to a projected USD 43 billion (EUR 39.6 billion) in 2018, with China being the largest user of a projected 12,000 tonnes in 2015 [1]. The Committee for Medicinal Products for Veterinary

Figure

Geographic distribution of the *mcr-1* gene (as of 1st March 2016)



Countries shown in colour have reported at least one isolate with the *mcr-1* gene [1-30].

Table a

Characteristics of *mcr-1*-positive isolates from food animals, the environment, food and humans, 1980s–2015 (as of 1st March 2016)

Source	Year	Country	Type of specimen/ animal /infection	Origin/ travelled region	Isolates n (%)	Species	Extended-spectrum beta-lactamase (ESBL)	Carbapenemase	Reference
Food animals	1980s–2014	China	Chickens	[a]	104	*E. coli*	NA	NA	[21]
	2005–2014	France	Veal calves	[a]	106	*E. coli*	CTX-M-1 (n = 7)	No	[10]
	2008–10	Japan	Pigs	[a]	2	*E. coli*	NA	NA	[23]
	2010–2011	Germany	Pigs	[a]	3	*E. coli*	CTX-M-1 (n = 3)	No	[7]
	2010-2015	The Netherlands	Chickens, veal calves, turkeys	[a]	4 (< 1%)	*E. coli*	NA	NA	[5]
	2011	France	Pigs	[a]	1 (< 1%)	*E. coli*	NA	NA	[16]
	2011–12	Belgium	Pigs	[a]	6	*E. coli*	No	No	[13]
	2011–12	Belgium	Veal calves	[a]	7	*E. coli*	No	No	[13]
	2012	Laos	Pigs	[a]	3	*E. coli*	NA	NA	[30]
	2012	China	Pigs	[a]	31 (14%)	*E. coli*	NA	NA	[1]
	2012–13	Japan	Cattle	[a]	4	*E. coli*	CTX-M-27	No	[23]
	2013	Japan	Pigs	[a]	1	*Salmonella* Typhimurium	NA	NA	[23]
	2013	China	Pigs	[a]	68 (25%)	*E. coli*	NA	NA	[1]
	2013	Malaysia	Chickens	[a]	3	*E. coli*	NA	NA	[17]
	2013	Malaysia	Pigs	[a]	1	*E. coli*	NA	NA	[17]
	2013	France	Pigs	[a]	1 (< 1%)	*E. coli*	No	No	[16]
	2013	France	Chickens	[a]	3 (2%)	*E. coli*	No	No	[16]
	2013	France	Chickens (farm)	[a]	1	*Salmonella* 1,4 [5],12:i:-	NA	NA	[26]
	2014	France	Broilers	[a]	4 (2%)	*E. coli*	No	No	[16]
	2014	France	Turkeys	[a]	14 (6%)	*E. coli*	CMY-2	No	[16]
	2014	Italy	Turkeys	[a]	1	*E. coli*	No	No	[4]
	2014	China	Pigs	[a]	67 (21%)	*E. coli*	NA	NA	[1]
	2014	China	Chickens	[a]	1	*E. coli*	CTX-M-65	NDM-9	[27]
	2014–15	Vietnam	Pigs	[a]	9 (38%)	*E. coli*	CTXM-55	No	[14]
	2015	Tunisia	Chickens	France /Tunisia	37 (67%)	*E.coli*	CTX-M-1	NA	[9]
	2015	Algeria	Chickens	[a]	1	*E. coli*	NA	NA	[30]
Environment	2012	Switzerland	River water	[a]	1	*E. coli*	SHV-12	NA	[29]
	2013	Malaysia	Water	[a]	1	*E. coli*	NA	NA	[17]
Food	2009	The Netherlands	Chicken meat	Unknown	1	*E. coli*	CTX-M-1	No	[2]
	2009-2016	The Netherlands	Retail meat (mostly chicken and turkey)	Dutch fresh meat and imported frozen meat	47 (2%)	*E. coli*	NA	NA	[5]
	2010	Canada	Ground beef	Unknown	2	*E. coli*	No	No	[15]
	2011	Portugal	Food product	NA	1	*Salmonella* Typhimurium	CTX-M-32	No	[25]
	2011	China	Chicken meat	[a]	10 (5%)	*E. coli*	NA	NA	[1]
	2011	China	Pork meat	[a]	3 (6%)	*E. coli*	NA	NA	[1]
	2012–2014	Denmark	Chicken meat	Germany	5	*E. coli*	CMY-2, SHV-12	No	[11]
	2012	France	Chicken meat, guinea fowl pie	NA	2	*Salmonella* Paratyphi B	NA	NA	[26]
	2013	France	Pork sausage	NA	1	*Salmonella* Derby	NA	NA	[26]
	2013	China	Chicken meat	[a]	4 (25%)	*E. coli*	NA	NA	[1]
	2013	China	Pork meat	[a]	11 (23%)	*E. coli*	NA	NA	[1]
	2014	China	Chicken meat	[a]	21 (28%)	*E. coli*	NA	NA	[1]
	2014	China	Pork meat	[a]	29 (22%)	*E. coli*	NA	NA	[1]
	2014	The Netherlands	Chicken meat	Europe, non-Dutch (n = 1), origin unknown (n = 1)	2	*E. coli*	SHV-12	No	[2]
	2014	Switzerland	Vegetables	Thailand, Vietnam	2	*E. coli*	CTX-M-55, CTX-M-65	No	[29]
	2012–2015	United Kingdom	Poultry meat	European Union, non-United Kingdom	2	*Salmonella* Paratyphi B var Java	NA	NA	[19]

NA: not available; *E. coli*: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*.

[a] Same as reporting country.

Table b

Characteristics of *mcr-1*-positive isolates from food animals, the environment, food and humans, 1980s–2015 (as of 1st March 2016)

Source	Year	Country	Type of specimen/ animal /infection	Origin/ travelled region	Isolates n (%)	Species	Extended-spectrum beta-lactamase (ESBL)	Carbapenemase	Reference
Humans	2008	Vietnam	Dysentery	Vietnam	1	*Shigella sonnei*	NA	NA	[24]
	Before 2010	China	Faecal carriage	[a]	27 (7%)	NA	NA	NA	[12,20]
	2011	Canada	Gastrostomy tube	Egypt (previous healthcare)	1	*E. coli*	NA	OXA-48	[15]
	2011	The Netherlands	Bloodstream infection	[a]	1 (0.08%)	*E. coli*	NA	NA	[5]
	2012–2013	The Netherlands	Faecal carriage	China (n = 2), South America (n = 2), Tunisia, South-East Asia	6	*E. coli*	CTX-M-1, CTX-M-14, CTX-M-15, CTX-M-55 (2), CTX-M-65	No	[3]
	NA	Sweden	Faecal carriage	Asia	2	*E. coli*	NA	NA	[8]
	2012	Thailand	Faecal carriage	[a]	2	*E. coli*	NA	NA	[30]
	2012	Laos	Faecal carriage	[a]	6	*E. coli*	NA	NA	[30]
	2012	Cambodia	Faecal carriage	[a]	1	*E. coli*	CTX-M-55	No	[22]
	2012–2015	United Kingdom	Salmonellosis	Asia (n = 2)	8	*Salmonella* Typhimurium	No	No	[19]
	2012–2015	United Kingdom	Salmonellosis	Asia	1	*Salmonella* Paratyphi B var Java	No	No	[19]
	2012–2015	United Kingdom	Salmonellosis	[a]	1	*Salmonella* Virchow	No	No	[19]
	2012–2015	United Kingdom	NA	NA	3	*E. coli*	CTX-M-type	No	[19]
	2014	Germany	Wound infection (foot)	NA	1	*E. coli*	No	KPC-2	[7]
	2014	China	Inpatient	[a]	13 (1%)	*E. coli*	NA	NA	[1]
	2014–2015	China	Bloodstream infection	[a]	2	*E. coli*	CTX-M-1	No	[6]
	2015	Denmark	Bloodstream infection	[a]	1	*E. coli*	CTX-M-55, CMY-2	No	[11]
	2015	Switzerland	Urinary tract infection	NA	1	*E. coli*	No	VIM	[18]
	2015	China	Inpatient	[a]	3 (< 1%)	K. *pneumoniae*	NA	NA	[1]
	2015	China	Surgical site infection, peritoneal fluid	[a]	2	K. *pneumoniae*	CTX-M-1	NDM-5	[6]
	2015	China	Faecal carriage (children)	[a]	5 (2%)	*E. coli*	CTX-M-15	No	[28]

NA: not available; *E. coli*: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*.

[a] Same as reporting country.

Use (CVMP) of the European Medicines Agency (EMA) reviewed all veterinary medicinal products containing colistin oral use and recommended variations to the terms of their marketing authorisations, for example that the indication is restricted to enteric infections caused by non-invasive *E. coli* susceptible to colistin and that presence of the disease in the herd should be established before metaphylactic treatment [33]. This opinion of the CVMP was converted into a Decision by the European Commission on 16 March 2015 [34], and a similar review is currently being performed for combination products containing colistin. In addition, in view of the recent developments with plasmid-mediated colistin resistance and at the request of the European Commission, the Antimicrobial Advice ad hoc Expert Group of the EMA is currently working on an update of its 2013 advice on the "use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health" [35].

In human medicine, colistin is increasingly used parenterally for the treatment of patients infected with highly resistant bacteria such as carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter* spp. for which other treatment options are limited. In addition it is used topically by inhalation, especially in cystic fibrosis patients, as well as part of the regimen for selective decontamination of the digestive tract and of the oropharynx. As a result, consumption of polymyxins, mainly colistin, in European healthcare increased by 50% between 2010 and 2014, although with wide variation in the consumption rate depending on the country [36]. In some European countries, this has resulted in increasing percentages of isolates and outbreaks of *Enterobacteriaceae*, mainly *Klebsiella pneumoniae*, that

are resistant to both carbapenems and colistin, the latter because of chromosomal point mutations [37,38].

In 2012, consumption of polymyxins, mainly colistin, was on average more than 600 times higher in food animals than in humans for those 19 Member States in the European Union and European Economic Area that reported complete data both for food animals and for humans and after controlling for biomass (analysis of data from the first joint report by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Agency (EFSA) and EMA on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals [39], data not shown). The fact that plasmid-mediated colistin resistance originated from animals combined with the much larger use of colistin in animals than in humans, has contributed to the perception that the problem needs to be tackled first in veterinary medicine. As documented by Kluytmans-van den Bergh et al., *mcr-1*-positive isolates have so far only been found sporadically in humans in Europe [2]. This could be due to absence of selection in a non-favourable environment as indicated by the fact that all travellers that were tested positive for *mcr-1* upon return were negative after one month [3]. However, the presence of plasmid-mediated colistin resistance in foods and asymptomatic human carriers combined with increasing colistin use in European hospitals may be a game changer. In addition, *mcr-1*-positive isolates often carry multiple resistance genes, including genes encoding for an extended-spectrum beta-lactamase or a carbapenemase (Table), and may thus be selected by usage of most antibiotics. Ultimately, if index cases are not detected early and proper control measures are not implemented, Europe may face hospital outbreaks of infections for which there will be little, and possibly no, antibiotic treatment options.

Hospitals must be aware of this new threat to patient safety and may want to consider a few practicable and proportionate preparedness options. Clinical microbiology laboratories should consider testing for colistin susceptibility more frequently, within their available resources, for example in situations involving multidrug-resistant Gram-negative bacteria, isolates from patients that receive or have received colistin, or isolates from patients transferred from or recently hospitalised in a foreign country. It should be noted that disk diffusion is not a reliable test for colistin susceptibility, which should rather be assessed by a method measuring the minimum inhibitory concentration [40]. Enhanced infection control precautions, including patient isolation, should be considered already at the suspicion of colistin resistance and not await confirmation from a reference laboratory. Finally, measures aiming at strengthening infection prevention and control (hospital hygiene) as well as a more prudent use of antibiotics are essential to prevent and control antimicrobial resistance in general, and should be considered for plasmid-mediated colistin resistance.

There is no doubt that more information will surface in the coming months. In the meantime, increased awareness and preparedness may prevent spread of *mcr-1*-positive *Enterobacteriaceae* in hospitals and other healthcare settings in Europe and elsewhere.

Conflict of interest

None declared.

Authors' contributions

RSK and DLM both compiled the data and wrote the manuscript.

References

1. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, 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. 2016;16(2):161-8. DOI: 10.1016/S1473-3099(15)00424-7 PMID: 26603172
2. Kluytmans–van den Bergh M, Huizinga P, Bonten M, Bos M, De Bruyne K, Friedrich A, 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. DOI: 10.2807/1560-7917.ES.2016.21.9.30149
3. Arcilla MS, van Hattem JM, Matamoros S, Melles DC, Penders J, de Jong MD, et al. Dissemination of the mcr-1 colistin resistance gene. Lancet Infect Dis. 2016;16(2):147-9. DOI: 10.1016/S1473-3099(15)00541-1 PMID: 26711361
4. Battisti A. Antibiotic resistance – Italy: colistin, MCR-1, E. coli, turkeys 2014. ProMEDmail 20160113.3933461 (12 January 2016).Available from: http://www.promedmail.org/post/3933461
5. Bonten MJ. [Antimicrobial resistance: is it really all going wrong now?]. Ned Tijdschr Geneeskd. 2015;160(0):D81. Dutch. PMID: 26860752
6. Du H, Chen L, Tang YW, Kreiswirth BN. Emergence of the mcr-1 colistin resistance gene in carbapenem-resistant Enterobacteriaceae.Lancet Infect Dis. 2016;16(3):287-8. DOI: 10.1016/S1473-3099(16)00056-6 PMID: 26842776
7. Falgenhauer L, Waezsada SE, Yao Y, Imirzalioglu C, Käsbohrer A, Roesler U, 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. DOI: 10.1016/S1473-3099(16)00009-8 PMID: 26774242
8. Bakterie resistent mot sista behandlingsalternativet funnen. [Bacteria resistant to the last treatment option found]. Press release. Stockholm: Folkhälsomyndigheten; 10 February 2016. Swedish. Available from: http://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2016/februari/bakterie-resistent-mot-sista-behandlingsalternativet-funnen/
9. Grami R, Mansour W, Mehri W, Bouallègue O, Boujaâfar N, Madec J, 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. DOI: 10.2807/1560-7917.ES.2016.21.8.30144
10. Haenni M, Poirel L, Kieffer N, Châtre P, Saras E, Métayer V, et al. Co-occurrence of extended spectrum β lactamase and MCR-1 encoding genes on plasmids. Lancet Infect Dis. 2016;16(3):281-2. DOI: 10.1016/S1473-3099(16)00007-4 PMID: 26774244
11. Hasman H, Hammerum AM, Hansen F, Hendriksen RS, Olesen B, Agersø Y, 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):30085. DOI: 10.2807/1560-7917.ES.2015.20.49.30085 PMID: 26676364
12. Hu Y, Liu F, Lin IY, Gao GF, Zhu B. Dissemination of the mcr-1 colistin resistance gene.Lancet Infect Dis. 2016;16(2):146-7. DOI: 10.1016/S1473-3099(15)00533-2 PMID: 26711359

13. Malhotra-Kumar S, Xavier BB, Das AJ, Lammens C, Butaye P, Goossens H. Colistin resistance gene mcr-1 harboured on a multidrug resistant plasmid.Lancet Infect Dis. 2016;16(3):283-4. DOI: 10.1016/S1473-3099(16)00012-8 PMID: 26774247
14. Malhotra-Kumar S, Xavier BB, Das AJ, Lammens C, Hoang HT, Pham NT, et al. Colistin-resistant Escherichia coli harbouring mcr-1 isolated from food animals in Hanoi, Vietnam. Lancet Infect Dis. 2016;16(3):286-7. DOI: 10.1016/S1473-3099(16)00014-1 PMID: 26774248
15. Mulvey MR, Mataseje LF, Robertson J, Nash JHE, Boerlin P, Toye B, et al. Dissemination of the mcr-1 colistin resistance gene. Lancet Infect Dis. 2016;16(3):289-90.
16. Perrin-Guyomard A, Bruneau M, Houée P, Deleurme K, Legrandois P, Poirier C, et.al. Prevalence of mcr-1 in commensal Escherichia coli from French livestock, 2007 to 2014. Euro Surveill. 2016; 11;21(6):pii=30135. doi: DOI: 10.2807/1560-7917.ES.2016.21.6.30135 .
17. Petrillo M, Angers-Loustau A, Kreysa J. Possible genetic events producing colistin resistance gene mcr-1.Lancet Infect Dis. 2016;16(3):280-1. DOI: 10.1016/S1473-3099(16)00005-0 PMID: 26774240
18. Poirel L, Kieffer N, Liassine N, Thanh D, Nordmann P. Plasmid-mediated carbapenem and colistin resistance in a clinical isolate of Escherichia coli.Lancet Infect Dis. 2016;16(3):281. DOI: 10.1016/S1473-3099(16)00006-2 PMID: 26774246
19. 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). London: PHE; 2015.
20. Ruppé E, Le Chatelier E, Pons N, Andremont A, Dusko Ehrlich S. Dissemination of the mcr-1 colistin resistance gene.Lancet Infect Dis. 2016;16(3):290-1. DOI: 10.1016/S1473-3099(16)00066-9
21. Shen Z, Wang Y, Shen Y, Shen J, Wu C. Early emergence of mcr-1 in Escherichia coli from food-producing animals.Lancet Infect Dis. 2016;16(3):293. DOI: 10.1016/S1473-3099(16)00061-X
22. Stoesser N, Mathers AJ, Moore CE, Day NP, Crook DW. 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. DOI: 10.1016/S1473-3099(16)00010-4 PMID: 26774239
23. Suzuki S, Ohnishi M, Kawanishi M, Akiba M, Kuroda M. Investigation of a plasmid genome database for colistin-resistance gene mcr-1.Lancet Infect Dis. 2016;16(3):284-5. DOI: 10.1016/S1473-3099(16)00008-6 PMID: 26774245
24. Thanh DP, Tuyen HT, Nguyen TN, The HC, Wick RR, Thwaites G, et al. Inducible colistin resistance via a disrupted plasmid-borne mcr-1 gene in a 2008 Vietnamese Shigella sonnei isolate. bioRxiv 2016 (preprint first posted online, Feb. 18, 2016). doi: http://dx.doi.org/DOI: 10.1101/039925
25. Tse H, Yuen KY. Dissemination of the mcr-1 colistin resistance gene.Lancet Infect Dis. 2016;16(2):145-6. DOI: 10.1016/S1473-3099(15)00532-0 PMID: 26711362
26. Webb HE, Granier SA, Marault M, Millemann Y, den Bakker HC, Nightingale KK, et al. Dissemination of the mcr-1 colistin resistance gene. Lancet Infect Dis. 2016;16(2):144-5. DOI: 10.1016/S1473-3099(15)00538-1 PMID: 26711363
27. Yao X, Doi Y, Zeng L, Lv L, Liu JH. Carbapenem-resistant and colistin-resistant Escherichia coli co-producing NDM-9 and MCR-1.Lancet Infect Dis. 2016;16(3):288-9. DOI: 10.1016/S1473-3099(16)00057-8 PMID: 26842777
28. Zhang R, Huang Y, Chan EW, Zhou H, Chen S. Dissemination of the mcr-1 colistin resistance gene.Lancet Infect Dis. 2016;16(3):291-2. DOI: 10.1016/S1473-3099(16)00062-1
29. Zurfuh K, Poirel L, Nordmann P, Nüesch-Inderbinen M, Hächler H, Stephan R. Occurrence of the plasmid-borne mcr-1 colistin resistance gene in ESBL-producing Enterobacteriaceae in river water and imported vegetable samples in Switzerland. Antimicrob Agents Chemother. 2016 Feb 16. pii: AAC.00066-16.
30. Olaitan AO, Chabou S, Okdah L, Morand S, Rolain JM. Dissemination of the mcr-1 colistin resistance gene. Lancet Infect Dis. 2016;16(2):147. DOI: 10.1016/S1473-3099(15)00540-X PMID: 26711360
31. Kempf I, Fleury MA, Drider D, Bruneau M, Sanders P, Chauvin C, et al. What do we know about resistance to colistin in Enterobacteriaceae in avian and pig production in Europe? Int J Antimicrob Agents. 2013;42(5):379-83. DOI: 10.1016/j.ijantimicag.2013.06.012 PMID: 24076115
32. European Medicines Agency (EMA). Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013. Fifth ESVAC report ESVAC. EMA/387934/2015. London: EMA; 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/10/WC500195687.pdf
33. Committee for Medicinal Products for Veterinary Use (CVMP). Annexes to the opinion following an Article 35 referral for veterinary medicinal products containing colistin to be administered orally. London: EMA; 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Colistin_oral_35/WC500185447.pdf
34. Committee for Medicinal Products for Veterinary Use (CVMP). Opinion following an Article 35 referral for veterinary medicinal products containing colistin to be administered orally. London: EMA; 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Colistin_oral_35/WC500185448.pdf
35. European Medicines Agency (EMA). Recommendations on the use of antibiotics in animals. London: EMA. [Accessed March 1, 2016]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000639.jsp&mid=WC0b01ac058080a585
36. European Centre for Disease Prevention and Control (ECDC). Summary of the latest data on antibiotic consumption in the European Union. ESAC-Net data. November 2015. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/eaad/antibiotics-news/Documents/antimicrobial-consumption-ESAC-Net-summary-2015.pdf
37. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2014.pdf
38. Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, et al. Colistin resistance superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014. Euro Surveill. 2014;19(42):20939. DOI: 10.2807/1560-7917.ES2014.19.42.20939 PMID: 25358041
39. European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA). 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 food-producing animals. Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. Stockholm/Parma/London: ECDC/EFSA/EMA; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-JIACRA-report.pdf
40. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0. EUCAST; 2016.. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf

License and copyright