

Epidemiological Alert

Enterobacteriaceae with plasmid-mediated transferable colistin resistance, public health implications in the Americas

10 June 2016

Due to the detection in several countries in the Region of the Americas of plasmid-mediated colistin resistance mechanism encoded by the *mcr-1* gene, isolated from animals and humans, the Pan American Health Organization / World Health Organization (PAHO / WHO) urges Member States to implement and maintain the capability to detect, prevent and control transmission of colistin resistance *mcr-1* microorganisms. PAHO / WHO also calls on Member States to take measures leading to prohibiting the use of these antimicrobials for prophylaxis and as growth promoters in animals destined for human consumption.

Situation summary

In November 2015, the detection of a plasmid-mediated colistin resistance mechanism, related to the *mcr-1* (**Mobile Colistin Resistance**) gene that produces an enzyme responsible for bacterial resistance to this antibiotic treatment, was reported. Colistin is a last line antibiotic used for treatment of multidrug-resistant infections. This *mcr-1* gene is in a plasmid, allowing bacteria to easily spread the resistance to other bacteria.¹

Until this discovery, it had been known that resistance to polymyxin, in which colistin is included, occurred by chromosomal mutations and the horizontal transfer of genes conferring resistance has not been reported.

The identification of this gene occurred through a retrospective study of prevalence *mcr-1* gene in *E. coli* and *K. pneumoniae* strains collected between April 2011 and November 2014 in China. The study identified *mcr-1* carriage in *E. coli* isolates collected from 78 (15%) out of 523 samples of raw meat; 166 (21%) out of 804 animal samples; and 16 (1%) out of 1,322 samples from inpatients with infection.

Other countries later reported similar retrospective findings. The *mcr-1* gene was detected in databases and collections of bacterial strains from all continents. Samples of bacteria such as *E. coli* and *Salmonella*, with plasmid mediated colistin resistance, were isolated from various sources: humans (isolates from the community), pigs, and poultry meat.^{2, 3, 4}

Colistin Resistance (or polymyxin β)

Colistin belongs to the polymyxin family, broad spectrum antibiotic discovered in the 1940s to treat gram-negative infections. After several years of clinical use, its popularity declined because of its nephrotoxicity and neurotoxicity.

In recent years, the antibiotic has reemerged as a last line treatment option for organisms resistant to multiple antibiotics, including carbapenems, such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* responsible for high morbidity and mortality health care associated infections.

Until a few years ago colistin resistance had been rare and mostly chromosomally mediated, and involved mutations in genes leading to modification in the lipopolysaccharide, the colistin site of action.^{2, 3}

Suggested citation: Pan American Health Organization / World Health Organization. Epidemiological Alert: Enterobacteriaceae with plasmid-mediated transferable colistin resistance, public health implications in the Americas, 10 June 2016. Washington, D.C.: PAHO/WHO; 2016

Situation in the Americas

Between November 2012 and November 2013, a retrospective study detected *mcr-1* gene in 6 of 9 isolates of *E. coli* producing extended-spectrum β -lactamase (ESBL) that were resistant to colistin; the samples were collected from Dutch travelers within one and two weeks following their return to the Netherlands. The isolates correspond to 6 travelers, two of whom visited Peru and Bolivia, two whom visited China, one that visited Tunisia, and one that visited Thailand, Vietnam, Laos and Cambodia in Southeast Asia. The duration of travel was between 8 and 40 days, with an average of 21.3 days.³

In December 2015, the Public Health Agency of Canada reported colistin-resistant *mcr-1 E. coli* in Canada in samples previously collected for special research projects. One sample was isolated from a 62 year-old patient and two were isolated from samples of ground beef for retail; they were collected in 2010.⁵ These findings have not yet been published in peer review journals.

In April 2016, researchers from Brazil reported colistin-resistant *mcr-1 E. coli* isolated from food and animal samples.⁶ The same report indicated the isolation of *mcr-1* gene carrier *E. coli* in a sample of human origin from Ecuador, the sequence is registered in the GenBank® (access number: KU886144.1).

In May 2016, the Latin American Antimicrobial Resistance Surveillance Network (RELAVRA) Regional Reference Laboratory and the "Dr. Carlos G. Malbrán" Antimicrobial Service of INEI-ANLIS of Buenos Aires, Argentina, confirmed the detection of colistin-resistant *mcr-1 E. coli*.⁷ The strains were isolated from 9 inpatients from six different hospitals in Argentina, whose samples were collected between January 2008 and January 2016. The different *mcr-1* gene carrier isolates had no genetic relationship to each other and the resistance detected was transferable plasmid-mediated type. This demonstrates the resistance is capable of moving from one bacterium to another, spreading antibiotic resistance among bacterial species. Additionally, the detection of the *mcr-1* gene in invasive infections indicates the potential for dissemination in hospital settings.

Additionally, in May 2016, Colombia reported the detection of *mcr-1* gene in three isolates of *Salmonella enterica* serovar Typhimurium of patients from Antioquia, Bogotá, and Boyacá, and an *E. coli* isolate in a patient from Santander. The discovery was made as part of a retrospective study of isolates obtained from 2014 to May 2016.

In June 2016, the United States Centers for Disease Control and Prevention (CDC) reported to PAHO/WHO of the first identification of colistin-resistant *mcr-1 E. coli* in a person in the U.S. This detection was made by Multidrug-resistant Organism Repository and Surveillance Network (MRSN) at the Walter Reed Army Institute of Research.⁸ In addition, the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (HHS) are searching for colistin-resistant bacteria in food, animals, retail meats, and people and they have found colistin-resistant *E. coli* in a single sample from a pig intestine. The *E. coli* was resistant to ampicillin, streptomycin, sulfisoxazole, and tetracycline.⁹

To date, there have been no reports of outbreaks or deaths caused by colistin-resistance *mcr-1* microorganisms. However, the risk of spread to other more virulent strains or hyper epidemic clones through transferable plasmid mechanisms cannot be discarded.

Recommendations

In light of the findings, PAHO / WHO recommends Member States implement and strengthen surveillance and epidemiological investigation to detect the presence of plasmid-mediated colistin resistance microorganisms to implement appropriate prevention and control measures. Due to the use of colistin in veterinary medicine, PAHO/WHO encourages Member States to implement integrated animal-human surveillance, as well as to coordinate actions between human and animal health sectors to prevent and control the spread of microorganisms with transferable colistin resistance.

Epidemiological surveillance and investigation

The key actions in relation to epidemiological surveillance and investigation are the following:

- Increase the participation of national public health laboratories in surveillance activities for early detection of outbreaks, in order to provide adequate early antimicrobial treatment of patients and implement prevention and control measures.
- In Enterobacteriaceae isolated from patients with suspected multidrug resistance or decreased sensitivity to colistin, it is recommended to test for colistin antimicrobial susceptibility.
- Ensure analysis and molecular characterization of microorganisms with phenotypic resistance to colistin, in order to investigate the presence of *mcr-1* gene. In cases of suspected polymyxin resistance through *mcr-1*, it is recommended to send the strain to a national or regional reference laboratory for confirmation and molecular typing.
- Use the regional protocol for detecting *mcr-1*.
- Report immediately to the local infection control authorities, as well as the national level competent public health authorities, the detection of microorganisms with a resistance mechanism due to the *mcr-1* gene.
- Disseminate information received and provide recommendations to alert health care workers and decision makers at all levels.
- Strengthen monitoring of polymyxin use and resistance in food production for human consumption.

Laboratory detection

Laboratories participating in RELAVRA have the tools for phenotypic detection of colistin resistance. Molecular typing can be performed at either national reference laboratories in the Americas or samples may be sent to the Regional Reference Laboratory for analysis and molecular characterization.

The role of laboratories in both the detection and containment of resistant pathogens is key. Upon detection of the resistance mechanism, prompt notification to the competent authorities and decision makers at the health facility and national level is important to ensure other hospitals are alerted.

Colistin use in veterinary medicine

Due to colistin toxicity, it is infrequently used in human health care. In recent years, it was used as a reserve antibiotic to treat infections caused by bacteria resistant to carbapenems. However, polymyxins are used in veterinary medicine, specifically in farm animals, to prevent infection and promote growth.¹⁰ For this reason, it is important that the surveillance of *mcr-1* spread is not limited to human medicine but include the field of veterinary medicine.

Polymyxin use in animal husbandry has favored the emergence of colistin resistant plasmid. It is urgent that the use of this antibiotic be limited to treating clinically affected animals and be prohibited from use as a prophylaxis under the principle of responsible antimicrobial use.

References

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