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Short Communication

# 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

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ABSTRACT

Since its initial discovery in China in 2015, the plasmid-mediated colistin resistance gene *mcr-1* has been reported in *Escherichia coli* isolated from clinical samples, animals and meat worldwide. In this study, 706 extended-spectrum β-lactamase (ESBL)-producing *E. coli* from 411 persons were detected in a collection of faecal samples from 1000 rural residents in three counties in Shandong Province, China. These isolates were screened for *mcr-1* and phenotypic colistin resistance. The gene was found in 3.5% of the isolates (from 4.9% of persons) from all three counties. All isolates with phenotypic colistin resistance carried *mcr-1*. These data indicate that commensal carriage of ESBL-producing *E. coli* with *mcr-1* among persons in rural China was already present in 2012 and that *mcr-1* was the most important colistin resistance mechanism. Interventions are necessary to minimise further dissemination of *mcr-1*, which would limit the future usefulness of colistin as a last-resort antibiotic.



## 1. Introduction

Antibiotic resistance is considered a threat to global health [1,2]. The increasing prevalence of extended-spectrum β-lactamases (ESBLs) and carbapenemases among clinically important Gram-negative bacteria such as *Escherichia coli* has prompted reliance on other antibiotics, such as colistin, for last-resort use against these difficult-to-treat pathogens [3]. The future usefulness of colistin was challenged in 2015 as the first plasmid-mediated colistin resistance gene (*mcr-1*) was discovered in *E. coli* both from humans and animals in China [4]. Following the discovery, reports emerged of *E. coli* carrying *mcr-1* from many countries worldwide, including isolates from humans, animals and food products [5]. A study on *E. coli* isolated during 2014–2015 from hospitals worldwide found the *mcr-1* gene in >30% of colistin-resistant isolates [6]. Dissemination of *mcr-1* is worrying as it could limit the usefulness of colistin as a last-resort antibiotic and severely affect the possibility of treating infections caused by multidrug-resistant (MDR) Enterobacteriaceae.

The antibiotic resistance situation in China has previously been reported as a major threat to global health [7]. In the initial report on the discovery of *mcr-1* in China, the authors reported a high prevalence of the gene among *E. coli* isolates collected from raw meat (15%) and animals (21%) in 2011–2014, which could be explained by the extensive use of colistin in agriculture [4]. Colistin is not used clinically for humans in China, however sporadic incidences of *E. coli* clinical isolates carrying *mcr-1* from patients in hospitals have been reported [4,8–11]. The prevalence of *mcr-1* appears to be lower in clinical isolates than among isolates from meat and animals. One report on a clinical isolate of *E. coli* with *mcr-1* from a hospital in Guangzhou implicated companion animals as a source of transfer of *mcr-1* to humans [12].

These findings indicate that colonisation of commensal *E. coli* with *mcr-1* among healthy persons might be high in rural

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communities in China, where the transfer from animals to humans is likely taking place.

It is known that commensal carriage of ESBL-producing *E. coli* is high among persons living in rural China. In a study on 1000 individuals in a total of 18 villages in three socioeconomically different counties in Shandong Province, a high and varying level of ESBL-producing Enterobacteriaceae was reported [13]. Overall, 42% of the included persons were ESBL carriers. At county level, the carriage rates were 49%, 45% and 31% in the three counties respectively, and when comparing individual villages the rate varied from 22% to 64%. The aim of the current study was to investigate the prevalence of the plasmid-mediated colistin resistance gene *mcr-1* and phenotypic colistin resistance among ESBL-producing *E. coli* among these isolates.

## 2. Materials and methods

### 2.1. Samples and population

Sampling was carried out during 2012 as described in a previous study [13]. In brief, 1000 participants from 18 villages in three counties (338, 315 and 347 persons participated from each county, respectively) of different socioeconomic status in Shandong Province provided faecal samples with ESwab™ (Copan, Brescia, Italy) and responded to a questionnaire. Questions were asked regarding demographic and socioeconomic factors, living environments and habits, and medical behaviours. ESwab™ were cultured on chromID® ESBL (bioMérieux, Marcy-l'Étoile, France). A total of 706 unique isolates (i.e. different antibiotic susceptibility profiles) of ESBL-producing *E. coli* were found from 411 persons. The *mcr-1* gene was screened for and the minimum inhibitory concentration (MIC) of colistin was determined for these isolates. To our knowledge, the included persons had not previously been treated with colistin.

### 2.2. DNA extraction and mcr-1 screening

DNA was extracted from pure cultures of *E. coli* using a QIAsymphony DSP Virus/Pathogen Mini Kit (QIAGEN, Hilden, Germany) and QIAsymphony SP instrument (QIAGEN). Samples were stored at –70 °C before subsequent analyses. To detect the *mcr-1* gene, real-time PCR was performed on a CFX-96 System (Bio-Rad Laboratories, Hercules, CA) using the primers described by Liu et al. [4]. PCR products were verified by sequencing (Macrogen, Seoul, South Korea). Clonal relatedness of the *mcr-1*-positive isolates was investigated using poly-trinucleotide $(GTG)_5$-PCR [14].

### 2.3. Antibiotic susceptibility testing and colistin minimum inhibitory concentration determination

The colistin MIC was determined by gradient diffusion with Etest (bioMérieux) for all 706 isolates. The *mcr-1*-positive isolates were further tested for antibiotic susceptibility to cefotaxime, ceftazidime, piperacillin/tazobactam (TZP), fosfomycin and nitrofurantoin by Etest on Mueller–Hinton agar (Oxoid Ltd., Basingstoke, UK) and to cefepime, cefoxitin, aztreonam, ampicillin/sulbactam (SAM), cefoperazone/sulbactam, amoxicillin/clavulanic acid, mecillinam, meropenem, imipenem, amikacin, gentamicin, tobramycin, chloramphenicol, tigecycline, trimethoprim/sulfamethoxazole (SXT), ciprofloxacin and levofloxacin by disk diffusion (Oxoid Ltd.) on Mueller–Hinton agar. Susceptibility breakpoints as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used. Isolates were designated as MDR if they were non-susceptible to antibiotics from at least three different classes.

### 2.4. Statistical analysis

Indications of associations between *mcr-1* carriage in individuals and risk factors were exploratively analysed by $\chi^2$ test. The significance level was set to $\alpha = 0.01$ to compensate for multiple comparisons. All statistical analyses were carried out using Stata/MP 14.1 (StataCorp LP, College Station, TX).

## 3. Results

A total of 706 ESBL-producing *E. coli* isolates from 411 persons were screened for the *mcr-1* gene by real-time PCR, of which 25 isolates (3.5%) from 20 persons (4.9%) were positive for the *mcr-1* gene. The prevalence by person in the three counties was 4.0% ($n = 6/151$), 3.2% ($n = 3/95$) and 6.7% ($n = 11/165$) respectively; the differences were not statistically significant ($P = 0.37$). Data on all participants regarding demographic and socioeconomic factors, living habits, medical behaviour and *mcr-1* prevalence are presented in Table 1. No parameter was significantly associated with *mcr-1* carriage. The colistin MIC was determined for all isolates. All of the isolates carrying *mcr-1* were colistin-resistant, with MICs ranging from 3 mg/L to 6 mg/L (Fig. 1). All isolates that were negative for *mcr-1* were susceptible to colistin, with MICs ranging from 0.125 mg/L to 0.75 mg/L. Data on antibiotic susceptibility to different antibiotic classes for the 25 isolates *mcr-1*-positive are presented in Table 2.

Susceptibility to carbapenems (meropenem and imipenem) was 100%, and susceptibility to TZP and tigecycline was also very high (>90%). All 25 *mcr-1*-positive isolates were MDR. The highest rates of antibiotic resistance were to colistin (100% resistant), cefotaxime (100%), SXT (96%) and SAM (92%). The $(GTG)_5$-patterns differed for 23 of the *mcr-1*-carrying isolates. Two isolates (taken from persons from different villages) had identical $(GTG)_5$-patterns although they differed in susceptibility to gentamicin and tobramycin.

## 4. Discussion

In this study, we report a carriage rate of 4.9% for ESBL-producing commensal *E. coli* with *mcr-1* among non-hospitalised individuals living in rural areas in Shandong Province in 2012. *Escherichia coli* positive for *mcr-1* isolated from humans has previously been reported in clinical settings in China [4,8–11]. One percent of inpatients at two hospitals in Guangdong and Zhejiang Provinces have been reported to carry *E. coli* positive for *mcr-1* [4]. Other publications have shown the incidence of *mcr-1* among *E. coli* isolated from faecal samples at hospitals; 6.3% for diarrhoeal patients at hospitals in Shenzen City [9] and 2.1% among hospitalised children [10]. Although the prevalence in the studies on clinical isolates cannot be directly compared owing to sampling differences, the prevalence among clinical isolates appears to be somewhat lower than the colonisation data presented in the current study.

Use of colistin in farming in China is extensive and the prevalence of *E. coli* with *mcr-1* in farming animals and meat has been consistently reported as high. Between 2011 and 2014, 15% of *E. coli* isolated from retail meat from Guangzhou and 21% from animals from Guangdong, Guangxi, Hunan and Jiangxi were positive for *mcr-1* [4]. One study reported an annual prevalence of *mcr-1* among *E. coli* isolated from chicken in eight provinces in China and showed an increase in prevalence from 5.2% in 2009 to 30.0% in 2014 and also found the gene in an isolate from chicken from the 1980s [15]. These data indicate that *mcr-1* likely was selected for in animal farming and later transferred to humans, a process that is likely still ongoing. As such, the increasing prevalence reported also implies that the colonisation prevalence of 4.9% in 2012 reported in the current study is likely much higher today.

There is currently a lack of consensus on how to preferably determine colistin MICs. Polymyxins adhere to plastics, which lowers

**Table 1**
Demographic and socioeconomic factors, living habits and medical behaviours among individuals with extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* in this study and the number of these individuals carrying an *mcr-1*-positive ESBL-producing *E. coli*.

| | Total | *mcr-1* + | *P*-value [a] |
|---|---|---|---|
| Demographic and socioeconomic factors | | | |
| Residence | | | |
| County A | 151 | 6 | 0.37 |
| County B | 95 | 3 | |
| County C | 165 | 11 | |
| Sex | | | |
| Male | 192 | 11 | 0.45 |
| Female | 219 | 9 | |
| Age | | | |
| <7 years | 99 | 4 | 0.89 |
| 7–15 years | 105 | 5 | |
| 16–60 years | 112 | 5 | |
| >60 years | 95 | 6 | |
| Educational level | | | |
| Pre-school | 92 | 4 | 0.78 |
| 1–5 years | 150 | 6 | |
| >5 years | 87 | 6 | |
| Illiterate | 82 | 4 | |
| Annual household income | | | |
| <10 000 Yuan | 147 | 9 | 0.43 |
| 10 000–30 000 Yuan | 159 | 5 | |
| >30 000 Yuan | 105 | 6 | |
| Living habits | | | |
| Vegetarian diet | | | |
| Non-vegetarian | 372 | 19 | 0.48 |
| Vegetarian | 39 | 1 | |
| Raw vegetable consumption | | | |
| Does not usually eat raw vegetables | 291 | 14 | 0.94 |
| Usually eats raw vegetables | 120 | 6 | |
| Water source | | | |
| Tap water | 221 | 8 | 0.46 |
| Private well | 142 | 10 | |
| Shared well | 40 | 2 | |
| Other | 8 | 0 | |
| Unboiled water consumption | | | |
| Does not usually drink unboiled water | 380 | 19 | 0.66 |
| Usually drinks unboiled water | 31 | 1 | |
| Pets in the house | | | |
| No | 347 | 18 | 0.48 |
| Yes | 64 | 2 | |
| Commercial farm nearby village | | | |
| No | 120 | 10 | 0.036 |
| Yes | 291 | 10 | |
| Medical behaviour | | | |
| History of hospitalisation | | | |
| Has never been hospitalised | 235 | 15 | 0.099 |
| Has been hospitalised | 176 | 5 | |
| History of hospitalisation in 2012 | | | |
| No | 370 | 19 | 0.45 |
| Yes | 41 | 1 | |
| Chronic disease | | | |
| No | 287 | 15 | 0.61 |
| Yes | 124 | 5 | |
| No gastritis | 111 | 4 | 0.48 |
| Gastritis | 13 | 1 | |
| Bronchitis | | | |
| No | 394 | 19 | 0.84 |
| Yes | 17 | 1 | |
| Diabetes | | | |
| No | 397 | 18 | 0.096 |
| Yes | 14 | 2 | |
| Intravenous injection in 2012 | | | |
| No | 218 | 12 | 0.52 |
| Yes | 193 | 8 | |
| Has used antibiotics | | | |
| No | 64 | 4 | 0.58 |
| Yes | 347 | 16 | |
| Fulfils antibiotic prescription | | | |
| No | 295 | 17 | 0.18 |
| Yes | 116 | 3 | |
| Uses more than one antibiotic for one disease | | | |
| No | 252 | 10 | 0.74 |
| Yes | 83 | 4 | |
| Self-adjusts the antibiotic dose | | | |
| No | 315 | 14 | 0.78 |
| Yes | 30 | 1 | |
| Ends antibiotic treatment when symptoms stop | | | |
| No | 81 | 3 | 0.64 |
| Yes | 262 | 13 | |

[a] The significance level was set to $\alpha = 0.01$ to compensate for multiple comparisons.

**Table 2**
Antibiotic susceptibility data for 25 isolates of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* carrying the *mcr-1* colistin resistance gene.

| Antibiotic | % Susceptible | % Resistant |
|---|---|---|
| Colistin | 0 | 100 |
| Cefotaxime | 0 | 100 |
| Ceftazidime | 16 | 68 |
| Cefepime | 8 | 68 |
| Cefoxitin | 84 | 16 |
| Ampicillin/sulbactam | 8 | 92 |
| Cefoperazone/sulbactam | 64 | 8 |
| Amoxicillin/clavulanic acid | 20 | 28 |
| Piperacillin/tazobactam | 96 | 4 |
| Mecillinam | 88 | 4 |
| Aztreonam | 8 | 80 |
| Meropenem | 100 | 0 |
| Imipenem | 100 | 0 |
| Fosfomycin | 36 | 64 |
| Amikacin | 68 | 32 |
| Gentamicin | 44 | 56 |
| Tobramycin | 36 | 60 |
| Chloramphenicol | 16 | 84 |
| Tigecycline | 96 | 0 |
| Trimethoprim/sulfamethoxazole | 4 | 96 |
| Ciprofloxacin | 20 | 80 |
| Levofloxacin | 16 | 56 |
| Nitrofurantoin | 16 | 40 |

the active amount of substance in broth microdilution assays. Furthermore, polymyxins diffuse poorly in agar, which has raised concerns about the validity of disk and gradient diffusion methods [16]. Despite these worries regarding the validity of gradient diffusion methods, the current study showed that gradient diffusion methodology was able to differentiate between *E. coli* isolates carrying *mcr-1* and isolates without the gene. This indicates that gradient diffusion methodology might be useful in screening for *E. coli* isolates with *mcr-1*. All isolates with the colistin-resistant phenotype in this study carried *mcr-1*, indicating that the gene is the predominant resistance determinant for colistin resistance in this setting. This is supported by the report by Shen et al. [15] in which it was shown that a rising prevalence of *E. coli* with the colistin-resistant phenotype co-occurred with a rising prevalence of *E. coli* carrying *mcr-1* in chicken in China. In another report based on clinical isolates from the SENTRY study, it was shown that the prevalence of *mcr-1* was >30% in clinical isolates of colistin-resistant *E. coli* worldwide [6], which further indicates the importance of this resistance mechanism in *E. coli*.

Susceptibilities to antibiotics other than colistin were investigated for the 25 *mcr-1*-positive isolates. Although all isolates were MDR, they were also all susceptible to the carbapenems meropenem and imipenem, which are the drugs of choice for treatment of infections with ESBL-producing Enterobacteriaceae. Carbapenem-resistant *E. coli* with *mcr-1* have, however, been sporadically reported in China. One study reported on several carbapenem-resistant clinical isolates with *mcr-1* from different hospitals in China that carried the carbapenemase gene $bla_{NDM-5}$ [11] whereas another study reported on an isolate from a sample taken in 2014 from chicken meat in Guangzhou that produced the carbapenemase NDM-9 [17]. Co-carriage of *mcr-1* and $bla_{NDM-1}$ in two clinical isolates of *E. coli* from two different hospitals in China has also been reported [18]. Caution should be exercised when treating ESBL-producing *E. coli* with carbapenems to prevent the emergence and dissemination of such colistin- and carbapenem-resistant strains. The prevalence of carbapenem resistance in *Klebsiella pneumoniae* and *Acinetobacter baumannii* has increased in China in recent years [19,20], which emphasises the need for prudent antibiotic stewardship for *E. coli* as well.

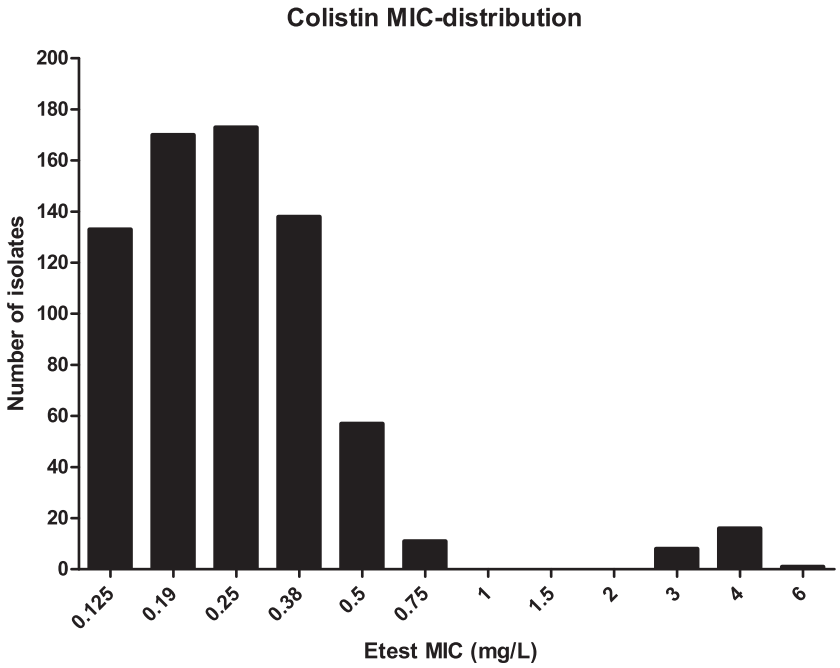


**Fig. 1.** Minimum inhibitory concentrations (MICs) of colistin for 706 isolates of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* determined by gradient diffusion. All isolates for which the colistin MIC was ≥3 mg/L carried the *mcr-1* gene.

## 5. Conclusions

The data presented in this and previous studies indicate that the prevalence of *mcr-1* among ESBL-producing *E. coli* colonising humans in rural China is already high and could be increasing. A high colonisation rate of colistin-resistant ESBL-producing *E. coli* could increase the risk of infection with this difficult-to-treat pathogen and facilitate dissemination of *mcr-1* to other strains. Even more worrying is the potential for these strains to acquire resistance to carbapenems. The indications that *mcr-1* is the predominant colistin resistance mechanism in *E. coli* emphasises the need for controlling the spread of this gene. Chinese policy-makers have become aware of the serious threat that antibiotic resistance poses to humans and animals as well as its healthcare system. Health information systems with surveillance should include monitoring of the epidemiology and prevalence of *mcr-1* among *E. coli* in order to use this information as evidence for policies with strategies for interventions to prevent further dissemination of this antibiotic resistance gene.

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