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Updated Prevalence of *mcr*-Like Genes among *Escherichia coli* and *Klebsiella pneumoniae* in the SENTRY Program and Characterization of *mcr-1.11* Variant

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Increased prevalence of infections caused by Gram-negative pathogens that are multidrug resistant has prompted the reconsideration of polymyxins as therapeutic options. Resistance to polymyxins is due to mutations in the lipid A synthesis (1) that can be caused by the acquisition of *mcr* (2). Genes *mcr-1* through *mcr-8* (3, 4) and multiple subtypes have been reported to encode proteins that share 30 to 70% amino acid identity.

We previously reported the prevalence of *mcr-1* among *Escherichia coli* and *Klebsiella pneumoniae* isolates collected worldwide during 2014 and 2015 by the SENTRY Program (5). As an ongoing effort, colistin-resistant *E. coli* and *K. pneumoniae* clinical isolates collected in 2016 were screened for the presence of *mcr*, and a new *mcr-1* variant was characterized.

Among 11,493 *E. coli* and *K. pneumoniae* isolates tested, 199 (1.7%) were resistant to colistin per EUCAST criteria (6) and considered non-wild type by the CLSI (7) epidemiological cutoff value. Isolates displaying colistin MIC values of ≥4 mg/liter (resistant/non-wild type) were screened for the *mcr-1* and *mcr-2* genes by PCR. All isolates carrying *mcr* were submitted to whole-genome sequencing.

A total of 12 isolates were *mcr-1* positive, including 10 *E. coli* isolates (2 in the United States, 3 [clonal] in Venezuela, 3 in Peru, 1 in Colombia, and 1 in Poland) and 2 *K. pneumoniae* isolates (1 each in Spain and Italy) (Table 1) recovered from invasive infections (Table 1). Colistin MIC values ranged from 4 to >8 mg/liter. No isolate yielded positive results for *mcr-2*.

One *E. coli* isolate from Peru (sequence type 95 [ST95]) carried *mcr-1* displaying an insertion of valine in amino acid position 6 and was designated *mcr-1.11*. This isolate showed susceptible phenotypes to β-lactams, aminoglycosides, tigecycline, and trimethoprim-sulfamethoxazole but resistance to tetracycline and quinolones (Table 1). The *mcr-1.11* gene was located on a 63-kb IncI2 plasmid carrying no other resistance genes (GenBank accession number KY853650). Two genetically unrelated *E. coli* isolates (ST7954 and ST1485) from the same hospital that carried *mcr-1* displayed the same plasmid structure (Table 1; Fig. 1).

The *mcr-1.11* gene cloned in an *E. coli* background exhibited colistin and polymyxin B MIC results (2 to 8 mg/liter) similar to those of *mcr-1* (2 to 4 mg/liter). The *mcr-1.11* gene likely emerged via spontaneous mutation within a plasmid structure that is endemic to the medical center in Peru, as seems common among *mcr*-like genes (1).

Unlike the vast majority of reports of *mcr*-like genes from animal-based sources, our results show a global prevalence of colistin resistance and *mcr-1* among isolates collected from important human infections. Similar to the 2014 to 2015 survey, isolates carrying *mcr-1* were identified in only 0.1% of the isolates tested; however, this study emphasizes its worldwide dissemination. Furthermore, our results and others (8, 9)

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TABLE 1 Characteristics of *mcr-1*-producing isolates

Organism and country	MLST[a]	Infection type[b]	MIC (mg/liter) for[c]:												Other resistance genes
			CST	CAZ	CRO	FEP	TZP	IPM	CIP	GEN	TOB	TET	TGC	SXT	
Escherichia coli															
Colombia	131	BSI	8 (R)	0.12 (S)	≤0.06 (S)	≤0.12 (S)	2 (S)	0.25 (S)	≤0.03 (S)	1 (S)	1 (S)	2 (S)	0.12 (S)	>4 (R)	*ant(3′)-Ia*, *dfrA1*
Peru[d]	95	BSI	4 (R)	0.12 (S)	≤0.06 (S)	≤0.12 (S)	1 (S)	≤0.12 (S)	>4 (R)	1 (S)	1 (S)	>16 (R)	0.12 (S)	1 (S)	*ant(3′)-Ia*, *aph(6)-Ia*, *aph(6)-Id*, bla_{TEM-1}, *dfrA1*, *fosA*, *qnrB19*, *sul2*, *tet*(A)
Peru	7954	SSSI	4 (R)	0.12 (S)	≤0.06 (S)	≤0.12 (S)	2 (S)	≤0.12 (S)	>4 (R)	>8 (R)	4 (S)	>16 (R)	0.25 (S)	>4 (R)	*aac(3)-IIa*, *aph(3′)-Ia*, *aph(6)-Ia*, *catA1*, *dfrA12*, *sul1*, *sul2*, bla_{TEM-1}, *tet*(A)
Peru	1485	SSSI	4 (R)	>8 (R)	>8 (R)	>16 (R)	2 (S)	≤0.12 (S)	1 (S)	1 (S)	1 (S)	>16 (R)	0.12 (S)	>4 (R)	$bla_{CTX-M-55}$, *sul2*, *tet*(A)
Poland	410	UTI	4 (R)	8 (R)	>8 (R)	8 (R)	1 (S)	≤0.12 (S)	>4 (R)	1 (S)	0.5 (S)	>16 (R)	0.5 (S)	>4 (R)	*aadA2*, *aph(6)-Ia*, $bla_{CTX-M-15}$, bla_{TEM-1}, *dfrA12*, *sul1*
USA	58	BSI	4 (R)	0.25 (S)	>8 (R)	2 (S)	2 (S)	≤0.12 (S)	0.06 (S)	1 (S)	1 (S)	>16 (R)	0.25 (S)	>4 (R)	*aadA2*, *ant(3′)-Ia*, $bla_{CTX-M-14}$, bla_{TEM-1}, *cmlA1*, *dfrA12*, *floR*, *sul2*, *sul3*, *tet*(A)
USA	1148	UTI	4 (R)	>8 (R)	>8 (R)	2 (S)	2 (S)	≤0.12 (S)	>4 (R)	0.25 (S)	0.5 (S)	>16 (R)	0.12 (S)	>4 (R)	*aadA2*, *aph(3′)-Ia*, bla_{SHV-12}, bla_{TEM-1}, *dfrA12*, *qnrB19*, *sul3*
Venezuela[e]	744	BSI	4 (R)	2 (S)	>8 (R)	4 (R)	1 (S)	≤0.12 (S)	>4 (R)	0.5 (S)	1 (S)	>16 (R)	0.25 (S)	>4 (R)	*aadA5*, *ant(3′)-Ia*, *aph(3′)-Ia*, *aph(3′)-IIa*, *aph(6)-Ia*, *aph(6)-Id*, $bla_{CTX-M-65}$, bla_{TEM-1}, *lnu(G)*, *catA1*, *cmlA1*, *floR*, *sul3*, *tetB*, *dfrA12*, *dfrA17*
Venezuela[e]	744	SSSI	4 (R)	1 (S)	>8 (R)	2 (S)	1 (S)	≤0.12 (S)	>4 (R)	0.25 (S)	0.5 (S)	>16 (R)	0.12 (S)	>4 (R)	*aadA5*, *ant(3′)-Ia*, *aph(3′)-Ia*, *aph(3′)-IIa*, *aph(6)-Ia*, *aph(6)-Id*, $bla_{CTX-M-65}$, bla_{TEM-1}, *lnu(G)*, *catA1*, *cmlA1*, *floR*, *sul3*, *tetB*, *dfrA12*, *dfrA17*
Venezuela[e]	744	PIHP	8 (R)	0.12 (S)	≤0.06 (S)	≤0.12 (S)	2 (S)	≤0.12 (S)	4 (R)	0.5 (S)	0.5 (S)	>16 (R)	0.25 (S)	>4 (R)	*ant(3′)-Ia*, *aph(3′)-Ia*, *aph(3′)-IIa*, *aph(6)-Ia*, *aph(6)-Id*, bla_{TEM-1}, *lnu(G)*, *catA1*, *cmlA1*, *floR*, *sul3*, *tetB*, *dfrA12*
Klebsiella pneumoniae															
Italy	219	UTI	>8 (R)	>8 (R)	>8 (R)	>16 (R)	4 (S)	0.25 (S)	1 (S)	0.5 (S)	1 (S)	>16 (R)	0.5 (S)	>4 (R)	*aadA2*, *aph(3′)-Ia*, *aph(6)-Ia-like*, *aph(6)-Id*, $bla_{CTX-M-15}$, bla_{SHV-1}, *dfrA12*, *mph(A)*, *oqxA10*, *oqxB5*, *qnrS1*, *sul1*, *sul2*, *tet*(A)
Spain	806	BSI	>8 (R)	0.12 (S)	≤0.06 (S)	≤0.12 (S)	2 (S)	≤0.12 (S)	≤0.03 (S)	0.25 (S)	0.25 (S)	4 (S)	0.5 (S)	≤0.5 (S)	*aph(6)-Ia*, *aph(6)-Id*, bla_{SHV-1}, *fosA*

[a]MLST, multilocus sequence type.

[b]BSI, bloodstream infection; SSSI, skin and skin structure infection; UTI, urinary tract infection; PIHP, pneumonia in hospital patient.

[c]CST, colistin; CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime; TZP, piperacillin-tazobactam; IPM, imipenem; CIP, ciprofloxacin; GEN, gentamicin; TOB, tobramycin; TET, tetracycline; TGC, tigecycline; SXT, trimethoprim-sulfamethoxazole; ND, not determined; R, resistant per CLSI/EUCAST criteria; S, susceptible per CLSI/EUCAST criteria.

[d]*E. coli* harboring *mcr-1.11*.

[e]*E. coli* isolates from Venezuela were clonal and displayed identical resistance gene profiles.

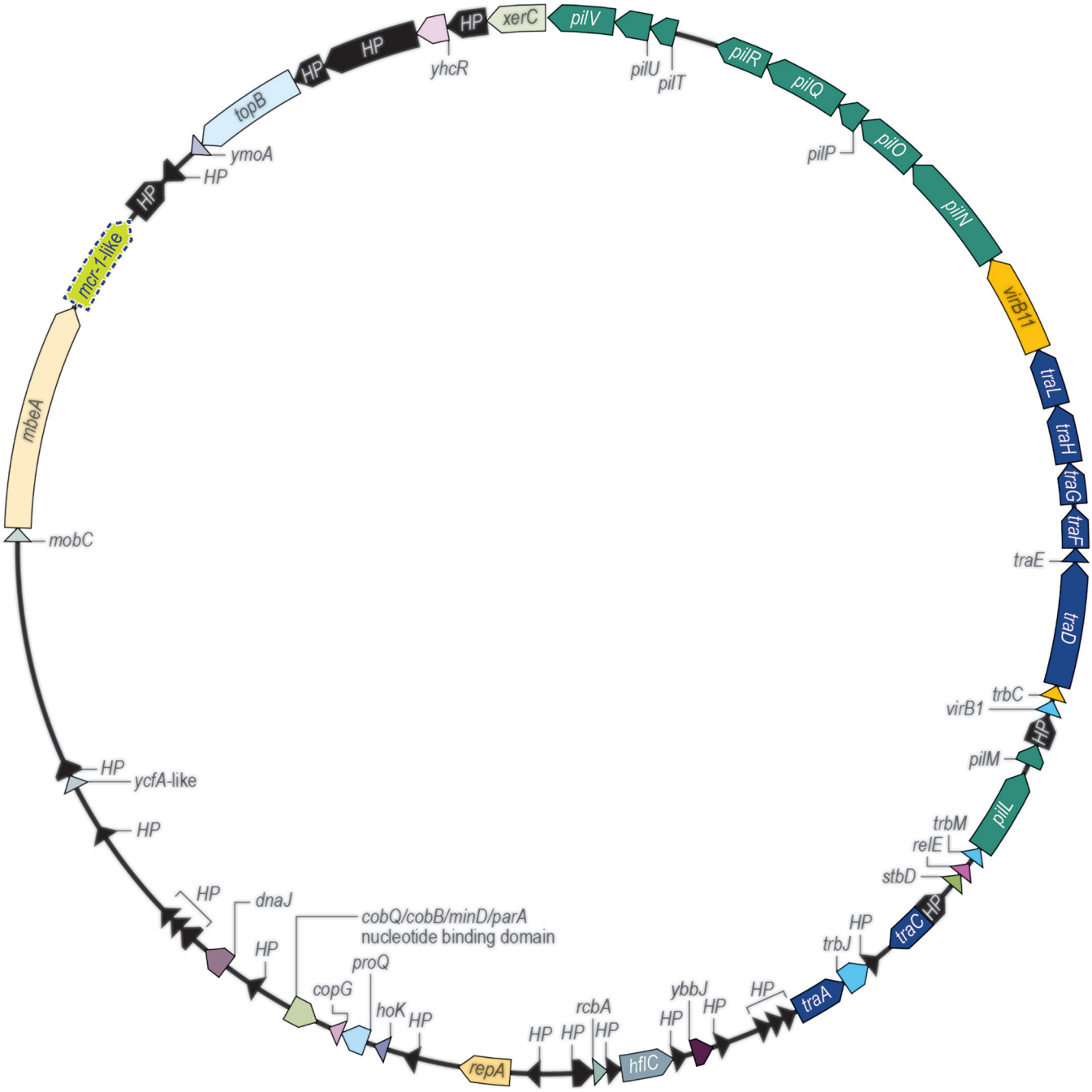

FIG 1 Schematic representation of IncI2 plasmids carrying *mcr-1*-like genes detected among *E. coli* isolates from a Peruvian medical center.

suggest that these genes are prone to mutations as they spread, as was observed in the isolates from Peru.

A much higher prevalence of *mcr*-like genes from specific geographic locations (1, 10, 11) accompanied by the first report of *mcr-1* in *Pseudomonas aeruginosa* (12) located on a chromosome demonstrate the ability of this gene to disseminate. Continued monitoring of *mcr* genes is warranted, but the development of global policies that might decrease the use of agents important to treat human infections or agents known to coselect for these resistance genes (13) seems prudent.

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We have no speakers' bureau or stock options to declare.

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