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Acquisition of Antibiotic-Resistant Bacteria by U.S. International Travelers

TO THE EDITOR: Antibiotic-resistant bacteria are a global public health threat, and there is geographic variability in the prevalence of antibiotic resistance.[1] Increasing evidence shows that international travelers may asymptomatically acquire antibiotic-resistant bacteria in the gut while abroad and may contribute to the global spread of these organisms.[2,3] Resistance to the polymyxin antibiotic colistin and to antibiotics in the carbapenem class is of particular concern, because these antibiotics are last-resort treatments for highly antibiotic-resistant gram-negative organisms.

We collected stool samples from 412 U.S. travelers before and after international travel. Travelers provided written informed consent, and human-subjects approval was obtained at each of the five participating sites (Massachusetts General Hospital [MGH], Bronx Care Center, University of Utah, Lehigh Valley Medical Center, and Northwell Health). The MGH microbiology laboratory received all the stool samples; the median time between the participants' return from travel and the receipt of the sample was 11 days (interquartile range, 8 to 16). We used validated culture-based protocols to isolate and identify carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE)[4] and *mcr*-mediated colistin-resistant Enterobacterales (MCRE).[5] We performed full antibiotic-susceptibility testing on all isolated CP-CRE and MCRE to identify other resistance phenotypes of interest. We also performed whole-genome sequencing and polymerase-chain-reaction assay for *mcr*-1, *mcr*-2, and *mcr*-3 on the bacterial isolates.

No travelers had CP-CRE or MCRE in the stool before travel. Travel occurred between November 2017 and April 2019; the most common destination countries were India, South Africa, and Peru. We identified 2 travelers (<1%) who had acquired CP-CREs and 20 (5%) who had acquired MCREs (Table 1). A total of 26 phylogenetically distinct resistant organisms (all *Escherichia coli*) were isolated. The most common destinations associated with acquisition of bacteria were Southeast Asia and Peru; 3 travelers to Southeast Asia acquired multiple MCREs. Fourteen of the colonized travelers (64%) reported having had diarrhea on their trip, and 7 (32%) treated themselves with antibiotics that they had brought from home. None were hospitalized or underwent invasive medical procedures while abroad, and none had symptoms associated with the antibiotic-resistant bacteria after their return.

In the two CP-CRE strains that were detected, carbapenem resistance was mediated by the $bla_{\text{NDM-5}}$ gene. International travelers acquired multiple and diverse *mcr* variants. In addition, 6 of the 24 distinct MCREs carried $bla_{\text{CTX-M}}$ genes encoding an extended-spectrum beta-lactamase (ESBL). One traveler to Vietnam acquired two distinct strains with an identical 16-kb transmissible plasmid-borne genetic element containing *mcr*-3.1, as well as genes encoding ESBL ($bla_{\text{CTX-M-55}}$), aminoglycoside resistance (*aac3-IIa*), and fluoroquinolone resistance (*qnrS1*).

Our results highlight the importance of international travel in the acquisition and geographic translocation of antibiotic-resistant bacteria.

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Table 1. Characteristics of Travelers with Highly Antibiotic-Resistant Bacteria.*

Patient No.	Age	Sex	Trip Duration	Destination	Diarrhea during Trip†	Antibiotic Use during Trip	Type of Antibiotic Resistance	
							Phenotype‡	Resistance Genes§
	yr		*no. of days*					
1	29	Female	14	Thailand	No	No	MCRE	*mcr-3.1, mcr-1.1*
2	68	Female	20	Kenya, Tanzania	Yes	Ciprofloxacin	MCRE	*mcr-1.1*
3	79	Male	19	Vietnam	No	No	MCRE	*mcr-1.1*
4	29¶	Male	19	Thailand, Cambodia, Vietnam	Yes	Azithromycin	ESBL-MCRE (2)	*mcr-3.1*, $bla_{\text{CTX-M-55}}$; *mcr-3.1*, $bla_{\text{CTX-M-55}}$
5	60	Female	10	Vietnam	No	No	MCRE (2)	*mcr-1.1*; *mcr-1.1*
6	59	Female	10	Peru	Yes	Ciprofloxacin	MCRE	*mcr-1.1*
7	55	Female	8	Singapore, Cambodia	No	No	MCRE	*mcr-1.1*
8	34	Male	23	Hong Kong, Vietnam	Yes	No	MCRE	*mcr-1.1*
9	24	Female	45	Japan, Vietnam	Yes	No	MCRE	*mcr-1.1*
10	56	Male	25	Liberia	No	No	MCRE	*mcr-1.1* variant
11	74	Male	18	Peru	Yes	No	ESBL-MCRE	*mcr-1.1*, $bla_{\text{CTX-M-55}}$
12	64	Female	14	Peru	Yes	No	MCRE	*mcr-1.1*
13	66	Male	39	Vietnam, Laos, Cambodia	No	No	MCRE (2); ESBL-MCRE	*mcr-1.1*; *mcr-1.1*; *mcr-1.1*, $bla_{\text{CTX-M-14}}$
14	58	Female	11	Rwanda, Tanzania	No	No	MCRE	*mcr-1.1*
15	64	Male	30	Peru	Yes	No	ESBL-MCRE	*mcr-1.1*, $bla_{\text{CTX-M-55}}$
16	85	Female	8	Nigeria	Yes	Azithromycin	MCRE	*mcr-1.1*
17	27	Male	30	Peru	Yes	No	ESBL-MCRE	*mcr-1.1*, $bla_{\text{CTX-M-55}}$
18	76	Female	9	Peru	No	No	MCRE	*mcr-1.1*
19	55	Female	8	Peru	Yes	Azithromycin	MCRE	*mcr-1*
20	54	Male	8	Peru	Yes	Ciprofloxacin	MCRE	*mcr-1*
21	74	Female	17	Hong Kong, Vietnam, Cambodia, Thailand, Singapore	Yes	Doxycycline	CP-CRE	$bla_{\text{NDM-5}}$, $bla_{\text{CTX-M-15}}$
22	48	Female	9	India	Yes	No	CP-CRE	$bla_{\text{NDM-5}}$, $bla_{\text{CTX-M-15}}$

* CP-CRE denotes carbapenemase-producing carbapenem-resistant Enterobacterales, ESBL extended-spectrum beta-lactamase, and MCRE *mcr*-mediated colistin-resistant Enterobacterales.
† Diarrhea was defined as three or more loose stools in a 24-hour period.
‡ ESBL phenotypes were identified by antibiotic-susceptibility testing and confirmed by disk-diffusion testing with clavulanate inhibition, as recommended by the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. These results are included because ESBL production is a resistance mechanism of high concern. For travelers who had more than one isolate, the number is provided in parentheses.
§ Genes in the same isolate are separated by commas; those in distinct isolates are separated by semicolons.
¶ This traveler was colonized by two distinct isolates, each carrying an identical plasmid-borne multidrug-resistance element containing *mcr-3.1*.

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Metoprolol for the Prevention of Exacerbations of COPD

TO THE EDITOR: The BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) trial by Dransfield and colleagues (Dec. 12 issue)[1] was stopped early because of futility and safety concerns. We write to raise the possibility that early termination of the trial was the cause, rather than the consequence, of these findings.

As a result of stopping early, only approximately half the planned sample size was reached; this diminished power and increased the likelihood of a type II error. Randomization was also ineffective: the percentage of black patients was 8.3 percentage points higher, the percentage of current smokers was 8.5 percentage points higher, and the percentage of patients with visits to the emergency department for exacerbations of chronic obstructive pulmonary disease (COPD) in the previous year was 12.3 percentage points higher in the metoprolol group than in the placebo group. This arouses concern regarding residual confounding from unmeasured covariates in the relationship between the observed increase in severe and very severe exacerbations of COPD and the receipt of metoprolol.

Stratification to ensure a balance of known risk factors for the outcome is one strategy that can be used to minimize residual confounding from ineffective randomization. Although stopping trials early is important to protect participants when there is evidence of harm, careful appraisal of the effect of this decision on the results is warranted.

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TO THE EDITOR: The trial by Dransfield et al. showed a higher risk of severe or very severe exacerbation of COPD with metoprolol than with placebo. Since beta-blockers are a highly heterogeneous class, with considerable within-class differences, including their effects on pulmonary function, the results presented may not have implications for all beta-blockers. For example, an observational study comparing carvedilol with bisoprolol showed that COPD exacerbations were less frequent with bisoprolol than with carvedilol.[1] In a randomized trial involving patients with heart failure and COPD, bisoprolol was associated with improvements in pulmonary function,