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Colin J Worby

Ashlee M Earl

Sarah E Turbett

Margaret Becker

Sowmya R Rao

See next page for additional authors

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Authors
Colin J Worby, Ashlee M Earl, Sarah E Turbett, Margaret Becker, Sowmya R Rao, Elizabeth Oliver, Allison Taylor Walker, Maroya Walters, Paul Kelly, Daniel T Leung, Mark Knouse MD, Stefan H F Hagmann, Edward T Ryan, and Regina C LaRocque

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BRIEF REPORT

Acquisition and Long-term Carriage of Multidrug-Resistant Organisms in US International Travelers

Colin J. Worby,[1] Ashlee M. Earl,[1] Sarah E. Turbett,[2,3,4] Margaret Becker,[4] Sowmya R. Rao,[5,6] Elizabeth Oliver,[2] Allison Taylor Walker,[7] Maroya Walters,[8] Paul Kelly,[9] Daniel T. Leung,[10] Mark Knouse,[11] Stefan H. F. Hagmann,[12] Edward T. Ryan,[2,3,13] and Regina C. LaRocque[2,3]

[1]Infectious Disease and Microbiome Program, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA, [2]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA, [3]Harvard Medical School, Boston, Massachusetts, USA, [4]Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA, [5]Biostatistics Center, Massachusetts General Hospital, Boston, Massachusetts, USA, [6]Department of Global Health, Boston University School of Public Health, Boston, Massachusetts, USA, [7]Division of Global Migration and Quarantine, Travelers' Health Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [8]Division of Healthcare Quality Promotion, Prevention and Response Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [9]Bronx Care Center, New York, New York, USA, [10]University of Utah, Salt Lake City, Utah, USA, [11]Lehigh Valley Medical Center, Allentown, Pennsylvania, USA, [12]Cohen Children's Medical Center, New Hyde Park, New York, USA, and [13]Department of Immunology and Infectious Diseases, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA

We performed prospective screening of stool for multidrug-resistant organisms from 608 US international travelers and identified an acquisition rate of 38% following travel. Carriage rates remained significantly elevated for at least 6 months post-travel. Travel-related diarrhea was a risk factor for acquisition, as well as for long-term carriage upon return.

Keywords. antibiotic resistance; CRE; ESBL; mcr; travelers' health.

Infections caused by multidrug-resistant organisms (MDROs) are a major cause of morbidity and mortality, and the burden continues to increase. The global dissemination of novel resistance mechanisms can be rapid and is facilitated in part by international travel. Many regions are known to be "hotspots" of high MDRO prevalence [1], a phenomenon that may relate to widespread antibiotic use in health care and agriculture [2]. Acquisition of extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-PE) is particularly common among travelers visiting South and Southeast Asia [3–5]. Recent work has also highlighted the risk of acquiring other MDROs of major public health concern during travel, including *mcr*-mediated colistin-resistant Enterobacterales (mcr-E) and carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE) [6, 7].

In addition to the individual-level risk of acquisition, introduction and spread of travel-acquired MDROs may play a role in domestic transmission and outbreaks of these organisms. Household transmission of travel-acquired MDROs is known to occur [3], and prolonged carriage will increase the risk of such community spread. The few studies that have evaluated the duration of MDRO carriage by international travelers indicate that some can remain colonized for up to a year [3, 4]. Understanding the frequency of MDRO acquisition among travelers and the risk factors associated with persistent MDRO colonization can inform strategies for combatting their importation and spread. Here, we present data from a large, ongoing, prospective study of US international travelers, in which subjects were followed for up to a year post-travel to explore factors linked to acquisition and long-term carriage of MDROs. In addition to screening for ESBL-PE, this is the first large study to investigate acquisition and carriage of mcr-E and CP-CRE among travelers.

Participants were recruited from 5 US travel clinics (Table 1) at a pretravel health encounter. A total of 608 travelers (including 19 children; age range, 1–85 years) were enrolled and provided stool samples before travel (median [interquartile range {IQR}], 5 [2–7] days) and upon return (median [IQR], 11 [7–16] days post-travel). Samples were screened for ESBL-PE, mcr-E, and CP-CRE using culture-based protocols followed by phenotypic (ESBL-PE, CP-CRE) or molecular (mcr-E) confirmatory testing as defined by the Clinical Laboratory Standards Institute (CLSI) and Centers for Disease Control and Prevention [8–10]; a traveler was considered colonized with an MDRO if 1 or more of these Enterobacterales organisms were detected. Travelers carrying MDROs upon return provided additional stool samples at 3, 6, and 12 months post-travel. Risk factors for pretravel carriage were assessed using a 2-sided Fisher exact test (binary variables) or a Wilcoxon rank-sum test (continuous variables). Risk factors for acquisition and carriage at subsequent sampling points were assessed similarly, excluding travelers who were colonized pretravel. Logistic regression models were fitted to explore multivariable relationships, and Cox proportional hazards models were used to estimate hazard ratios (HRs) for loss of carriage post-travel.

A total of 40 (6.6%) travelers carried MDROs before travel; all of these samples were positive for ESBL-PE, while 1 was additionally positive for mcr-E. Pretravel carriage was not associated with any reported underlying medical condition, nor with recent international travel (Table 1). Bronx Care enrollees had a significantly higher pretravel carriage rate (15%).

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Correspondence: Colin Worby, PhD, Broad Institute, 415 Main Street, Cambridge, MA 02142 (cworby@broadinstitute.org).

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Table 1. Traveler Characteristics and Risk Factors for Pretravel Carriage and Acquisition of Multidrug-Resistant Organisms

	Pretravel (n = 608)									MDRO Acquisition During Travel (n = 568)								
	No.	Positive		Negative		OR	95% CI		*P*	No.	Yes		No		OR	95% CI		*P*
Age, mean, y		54.6		49.2		—			.07		49.4		49.1		—			.88
Gender (female)	372	26	(7%)	346	(93%)	1.19	*0.58*	*2.52*	.73	346	122	(35%)	224	(65%)	0.73	*0.51*	*1.04*	.08
Underlying medical conditions	450	31	(7%)	419	(93%)	1.18	*0.53*	*2.90*	.85	419	154	(37%)	265	(63%)	0.79	*0.53*	*1.19*	.24
Enrollment site									—									.001
MGH, Boston, MA	373	20	(5%)	353	(95%)	—				353	127	(36%)	226	(64%)	—			
Bronx Care, New York, NY[a]	81	12	(15%)	69	(85%)	3.06	*1.30*	*6.93*	.01	69	38	(55%)	31	(45%)	2.18	*1.26*	*3.81*	.004
University of Utah Hospital, Salt Lake City, UT[a]	58	2	(3%)	56	(97%)	0.63	*0.07*	*2.72*	.75	56	28	(50%)	28	(50%)	1.78	*0.97*	*3.27*	.05
Northwell Health, New York, NY[a]	34	2	(6%)	32	(94%)	1.10	*0.12*	*4.89*	.70	32	8	(25%)	24	(75%)	0.59	*0.22*	*1.42*	.25
Lehigh Valley Medical Center, PA[a]	62	4	(6%)	58	(94%)	1.22	*0.29*	*3.82*	.76	58	16	(28%)	42	(72%)	0.68	*0.34*	*1.30*	.24
In the year before enrollment:																		
International travel	302	19	(6%)	283	(94%)	0.73	*0.35*	*1.57*	.38	283	103	(36%)	180	(64%)	0.84	*0.56*	*1.26*	.37
Antibiotic use	156	11	(7%)	145	(93%)	0.99	*0.42*	*2.16*	1.00	145	50	(34%)	95	(66%)	0.81	*0.52*	*1.24*	.35
Hospitalization	35	2	(6%)	33	(94%)	0.80	*0.09*	*3.38*	1.00	33	7	(21%)	26	(79%)	0.42	*0.15*	*1.02*	.04
Regularly taking:																		
Proton pump inhibitor/H2 blocker	75	6	(8%)	69	(92%)	1.28	*0.42*	*3.23*	.62	69	25	(36%)	44	(64%)	0.91	*0.52*	*1.57*	.79
Bismuth	7	0	(0%)	7	(100%)	0.00	*0.00*	*10.10*	1.00	7	4	(57%)	3	(43%)	2.18	*0.36*	*15.00*	.44
Other antacid	42	2	(5%)	40	(95%)	0.70	*0.08*	*2.87*	1.00	40	17	(43%)	23	(58%)	1.21	*0.59*	*2.44*	.61
During travel:																		
Travel duration, median, d											14		13		—			.37
VFR										39	23	(59%)	16	(41%)	2.48	*1.22*	*5.16*	.01
Leisure										407	144	(35%)	263	(65%)	0.66	*0.44*	*0.97*	.03
Business										59	24	(41%)	35	(59%)	1.12	*0.62*	*2.01*	.67
Street food										155	66	(43%)	89	(57%)	1.29	*0.87*	*1.90*	.21
Undercooked meat										45	10	(22%)	35	(78%)	0.44	*0.19*	*0.93*	.02
Unfiltered tapwater										122	47	(39%)	75	(61%)	1.02	*0.66*	*1.56*	1
Unwashed fruit										285	101	(35%)	184	(65%)	0.79	*0.55*	*1.13*	.2
Uncooked vegetables										291	113	(39%)	178	(61%)	1.06	*0.74*	*1.50*	.8
Dined in family home										202	86	(43%)	116	(57%)	1.33	*0.92*	*1.92*	.13
Diarrhea										185	89	(48%)	96	(52%)	1.87	*1.29*	*2.74*	<.001
Malarone										274	105	(38%)	169	(62%)	1.01	*0.71*	*1.44*	1
Doxycycline										6	3	(50%)	3	(50%)	1.62	*0.22*	*12.25*	.68
Any antibiotics										82	43	(52%)	39	(48%)	2.00	*1.21*	*3.30*	.004

For binary outcomes, a 2-sided Fisher exact test was applied; continuous variables were compared using the Wilcoxon rank-sum test. Variance across enrollment sites was assessed using a chi-square test; this was not performed for baseline carriage rates due to low numbers.

Abbreviations: MGH, Massachusetts General Hospital; OR, odds ratio; VFR, returning to region of origin of self or family to a low- or low–middle-income country to visit friends and relatives.

[a]Individual enrollment sites were compared with MGH using a 2-sided Fisher exact test. Missing responses are excluded from analyses.

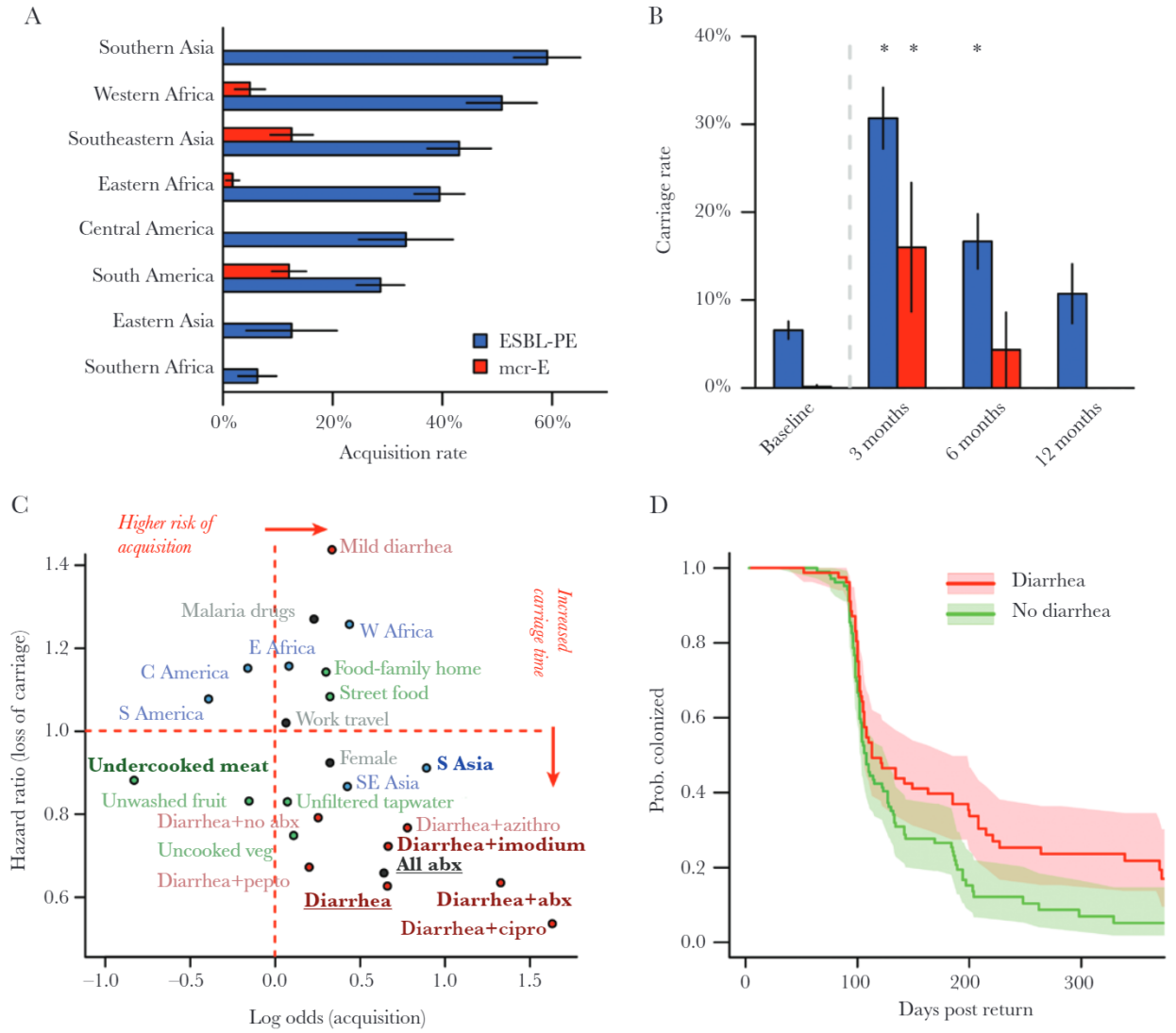

Figure 1. A, Acquisition rates for ESBL-PE and mcr-E across all regions with >10 travelers. Standard errors are shown as lines. MDROs are considered travel-acquired if detected in the post-travel stool sample but not in the pretravel sample. B, MDRO carriage rates at 3, 6, and 12 months post-travel for travelers who acquired MDROs abroad, compared with pretravel carriage rates across all travelers (baseline). Significance was based on 2-sided Fisher exact tests. C, Univariate risk factors for MDRO acquisition and long-term carriage, including travel destinations (blue), travel behavior (green), and diarrhea (red). Significant acquisition risk factors ($P < .05$) are in bold; significant carriage length factors are underlined. Travel to East Asia and Southern Africa is associated with a significantly reduced risk of acquisition, but falls outside the range of this plot. D, Kaplan-Meier survival curves for carriage among travelers who acquired MDROs, partitioned on those reporting diarrhea during travel. Events are right-censored when travelers carried MDROs at their most recent observation time (*$P < .0005$). Abbreviations: abx, antibiotics; azithro, azithromycin; cipro, ciprofloxacin; ESBL-PE, extended-spectrum beta-lactamase-producing Enterobacterales; MDROs, multidrug-resistant organisms; pepto, bismuth subsalicylate, eg, Pepto Bismol.

Of the 568 travelers testing negative for MDROs pretravel, 217 (38%) had at least 1 MDRO detected upon return (97% of which were *Escherichia coli*), suggesting travel-associated acquisition. The highest rates of MDRO acquisition were among travelers to South Asia (39/66; 59%) and Southeast Asia (34/72; 47%) (Figure 1A). Trip duration was not associated with risk of acquisition (Table 1). Acquisition of ESBL-PE (212 travelers; 37%) was more common than acquisition of mcr-E (28 travelers; 4.9%) or CP-CRE (2 travelers; 0.4%). Among 28 travelers acquiring mcr-E, 24 (86%) also acquired ESBL-PE. Despite having the highest overall acquisition rates, South Asia was not associated with any mcr-E acquisition; this was most common during travel to South America (11%) and Southeast Asia (12%) (Figure 1A). Only 2 travelers acquired CP-CRE; these travelers visited South and Southeast Asia.

Of the evaluated dietary and behavioral factors, only consumption of undercooked or raw meat was associated with decreased risk (Figure 1C, Table 1). However, this was correlated with travel to low-risk regions (East Asia and Southern Africa) and was no longer a significant risk factor after adjusting for travel destination. Acquisition rates also differed by enrollment site (Table 1); this could be explained by differential travel

locations between sites, with travel to Western Africa being much more frequent among Bronx Care enrollees (48%) than others (6%). Diarrhea (3 or more episodes of loose stool in a 24-hour period) and antibiotic use were independently associated with acquisition of MDROs (Figure 1C). Many travelers experiencing diarrhea took antibiotics to treat symptoms (46/193; 24%), most commonly azithromycin (24/193; 12%) and ciprofloxacin (17/193; 9%). Among travelers with diarrhea, those who took antibiotics to treat symptoms were more likely to acquire MDROs than those who did not (65% vs 40%; $P = .004$); travelers taking ciprofloxacin had a particularly high MDRO acquisition rate (13/17; 76%). Diarrhea remained significantly associated with MDRO acquisition (odds ratio [OR], 1.11; 95% CI, 1.02–1.21; $P = .01$) after adjusting for travel destination, trip duration, and antibiotic use during travel.

Among travelers who acquired MDROs, 33% were colonized 3 months after returning and 17% at 6 months, significantly higher than pretravel colonization prevalence among all travelers ($P < .001$). At 12 months, 10% of those with acquired MDROs were still colonized, comparable to pretravel rates (Figure 1B). Relatively few mcr-E and CP-CRE were acquired, limiting our power to estimate long-term carriage of these specific organisms; however, 4/25 (16%) travelers acquiring mcr-E were colonized at 3 months, which was significantly higher than observed pretravel (0.2%; $P < .001$). Neither of the 2 travelers who acquired CP-CRE was colonized at 3 months. No clinical infections or hospitalizations were reported during the study follow-up.

Carriage rates varied slightly by travel destination, potentially suggesting geographic heterogeneity of acquired phenotypes. At 3 months, MDRO carriage rates ranged from 14% in travelers who visited Western Africa to 46% in travelers visiting Southeast Asia. Travelers experiencing diarrhea during their trip were more likely to acquire MDROs and were more likely to remain colonized during the follow-up period (Figure 1D). Among travelers who acquired MDROs, at 6 months post-travel, 24% of those who experienced travelers' diarrhea remained colonized with an MDRO, which was significantly higher than the 11% of those who did not report diarrhea ($P = .04$). Diarrhea remained a significant risk factor for travel-acquired MDRO carriage at 6 months (OR, 1.14; 95% CI, 1.01–1.29; $P = .03$) after adjusting for travel destination and duration. Diarrhea during travel, whether treated with antibiotics or not, was associated with elevated risk of post-travel carriage (HR of carriage loss for treated diarrhea, 0.54; 95% CI, 0.33–0.89; $P = .02$; HR for untreated diarrhea, 0.68; 95% CI, 0.46–0.99; $P = .04$; multivariable Cox proportional hazards model). The additional risk associated with antibiotic use was not significant ($P = .2$).

Subsequent international travel was reported by 18 (10%), 25 (17%), and 15 (17%) travelers with acquired MDROs at the 3-, 6-, and 12-month follow-up time points, respectively. This was a significant risk factor for carriage of MDROs during the follow-up period, though even after excluding these travelers, carriage remained significantly higher than pretravel levels at 3 months (33%) and 6 months (19%) post-travel. In a multivariable Cox proportional hazards model, subsequent travel (HR, 0.1; 95% CI, 0.03–0.33; $P = .0001$) and travelers' diarrhea (HR, 0.7; 95% CI, 0.5–0.98; $P = .038$) were both significantly associated with ongoing carriage (Figure 1D). Subsequent antibiotic use, reported by 57 travelers who acquired MDROs, had no significant effect on carriage duration (HR, 1.02; 95% CI, 0.72–1.44).

This is the first large prospective study of MDRO carriage and acquisition in US international travelers. Acquisition rates were consistent with previous European studies [3, 4] that focused on ESBL-PE acquisition. Acquisition and importation of bacteria with mcr-mediated resistance to colistin, an antibiotic of last resort, is concerning, particularly as many travel-acquired mcr-E are also ESBL-producing [6], leaving limited therapeutic options for infections with these organisms. Further dissemination via horizontal gene transfer is an additional concern for such mobilized resistance mechanisms. Notably, while travel to South and Southeast Asia is known to be associated with elevated risks of MDRO acquisition, we found South America to have one of the highest rates of mcr-E acquisition among our traveler cohort. These travelers visited Peru (13/14 acquisitions) and Ecuador (1/14), mostly traveling for leisure (12/14). Limited studies on colistin resistance in South America suggest that mcr-E circulates in agricultural settings [11] and that commercial chicken meat may be a reservoir for mcr-E [12]. Peru banned the importation and manufacture of colistin only in late 2019 [13].

Diarrhea is known to be associated with MDRO acquisition while overseas [5], but our study suggests that it is also associated with prolonged colonization. We found that antibiotic use, particularly ciprofloxacin, was also associated with increased acquisition risk, and its use as a treatment for diarrhea contributed to enhanced risk of acquisition and long-term carriage of MDROs. Diarrhea and antibiotic treatment are known to disrupt the gut microbiome, which can facilitate the colonization and persistence of MDROs [14]. Further studies are needed to determine the role of the gut microbiota in susceptibility to MDRO colonization in travelers.

We cannot ensure that MDROs detected at later time points are the same strains acquired during travel. However, carriage rates among participants with no subsequent travel remain significantly elevated after 6 months, which supports our hypothesis that MDROs acquired during travel can lead to long-term colonization. Furthermore, our observations of long-term post-travel carriage are consistent with a previous study of Dutch travelers, in which 17% of participants acquiring ESBL-PE during travel remained colonized after 6 months [4]. Future genomic sequencing efforts of travel-acquired MDROs will enable

longitudinal strain tracking and identification of genetic factors linked to gut persistence.

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Patient consent. Written consent was obtained from all participants in the study. Institutional review board approval was obtained from the human research committee at each participating enrollment site.

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