A Randomized, Placebo-Controlled, Double-Blind, Clinical Trial Evaluating Two Dose Regimens of Rifaximin (550mg daily or twice-daily) for Chemoprophylaxis Against Travelers' Diarrhea Among Deployed U.S. and U.K. Military Personnel (PREVENT-TD)

R. Gutiérrez MD, MPH[1,5]; D. Burns MD, DTM&H[4]; T. Lalani, MBBS, MHS[1,2,3,6]; D. Bennett-Carter, MS[2,3]; J. Fraser, MPH[2,3]; M. Riddle, MD, DrPH[1,2]; P. Connor, MD[4]; C. Porter, PhD, MPH[5]; T. Troth, MD4; R. Ruck, MD[12]; J. Barton, MD[12]; H. Tilley, MD, MPH&TM[9]; A. Kunz, MD[8]; M. Fairchok, MD[2,8]; H. Yun, MD[7]; B. Alvarez, MD[10]; R. Higgins, MS[10]; I. Mitra, MS[2,3]; L. Stewart, PhD, MSc, MPH[2,3]; A. Rahman, MA[2,3]; J. Rimmer, MD4; E. Hutley, PhD[4]; B. Swierczewski, PhD[11]; B.Tabberer[4]; and D. Tribble, MD, DrPH[1,2]

1-Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; 2-Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; 3-The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA; 4-Department of Military Medicine, Royal Centre for Defense Medicine, Birmingham, UK; 5-Naval Medical Research Center, Silver Spring, MD, USA; 6-Naval Medical Center, Portsmouth, VA, USA; 7-Brooke Army Medical Center, Fort Sam Houston, TX, USA; 8-Madigan Army Medical Center, Tacoma, WA, USA; 9-Naval Medical Center, San Diego, CA, USA; 10-Naval Medical Center, Camp Lejeune, NC, USA; 11-Walter Reed Army Institute of Research, Silver Spring, MD, USA; 12-Tripler Army Medical Center, Honolulu, HI, USA

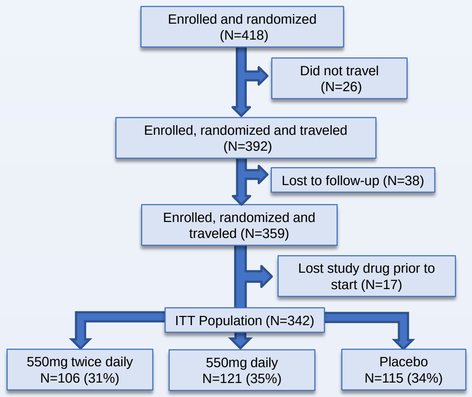
Background

- Travelers' diarrhea (TD) remains a leading threat to military readiness[1]. An effective vaccine against common TD pathogens is not available. Chemoprophylaxis alternatives suitable for military operations warrant study.
- Most trials of rifaximin chemoprophylaxis involve civilians or short-duration travel, whereas military travelers are exposed for longer periods, at austere locations, and are often physically taxed[1,2].
- In PREVENT TD we sought to assess the efficacy of two regimens among military personnel deployed overseas, vs. placebo.

Trial Design & Methods

- Multi-site, double-blind, placebo-controlled trial of deployed military personnel.
- Randomized (1:1:1; 6 randomizations/block) for duration of travel (up to 42 days)
- Travel Diaries were reviewed with subjects on return.
- Primary endpoint was time to first unformed stool (TFUS) in a TD episode. Other endpoints were assessed by intention to treat (ITT) and subgroups included incidence of any loose stool, meet criteria for TD, safety, efficacy, and adherence to regimen.

Enrollment Flowchart



Results

Table 1: *Study Population/Group Characteristics*

	Rifaximin 550mg twice daily	Rifaximin 550mg daily	Placebo	Total
Total N (%)	106 (31.0)	121 (35.4)	115 (33.6)	342
Age				
Median (IQR)	27 (22-33)	26 (23-30)	27 (23-32)	27 (23-32)
Gender				
Male	97 (91.5)	113 (93.4)	103 (89.6)	313 (91.5)
Duration of Prophylaxis (days)				
Median (IQR)	34 (23-39)	35 (31-41)	35 (31-41)	35 (30-41)
Race				
Caucasian	91 (85.9)	106 (88.3)	92 (80.0)	289 (84.8)
African American/ Black British	5 (4.7)	4 (3.3)	9 (7.8)	18 (5.3)
Active Duty				
Enlisted	92 (86.8)	103 (85.1)	95 (82.6)	290 (84.8)
Subject Group				
US	43 (40.6)	53 (43.8)	48 (41.7)	144 (42.1)
UK	63 (59.4)	68 (56.2)	67 (58.3)	198 (57.9)
Branch of Service UK binary (% out of UK)				
Infantry	39 (61.9)	41 (60.3)	38 (56.7)	118 (59.6)
Other	24 (38.1)	27 (39.7)	29 (43.3)	80 (40.4)
Branch of Service US (% out of US) (n=144)				
Navy	15 (34.9)	15 (28.3)	14 (29.2)	44 (30.6)
Army	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Marine Corps	0 (0.0)	1 (1.9)	0 (0.0)	1 (<1)
Air Force	26 (60.5)	36 (67.9)	31 (64.6)	93 (64.6)
Coast Guard	2 (4.7)	1 (1.9)	3 (6.3)	6 (4.2)
Region				
South America	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Sub-Saharan Africa	70 (66.0)	74 (61.2)	74 (64.4)	218 (63.7)
South-East Asia	12 (11.3)	22 (18.2)	18 (15.7)	52 (15.2)
East-North Asia	1 (<1)	0 (0.0)	0 (0.0)	1 (<1)
Central America	2 (1.9)	0 (0)	0 (0)	2 (<1)
South-Central Asia	2 (1.9)	3 (2.5)	1 (<1)	6 (1.8)
Multiple regions of travel	18 (17.0)	21 (17.4)	21 (18.3)	60 (17.5)

The intent to treat population is defined as subjects who are enrolled into the study and randomized to study drug, traveled and returned for follow-up. Subjects who were lost to follow-up or lost study-drug before departure are removed.

P-values were calculated using Chi-Square or Fisher's Exact Tests for categorical values and Wilcoxon Mann-Whitney test for continuous variables. All analyses were run on SAS v9.4

Diarrheal Disease Outcomes

	Rifaximin 550mg twice daily	Rifaximin 550mg daily	Placebo	Total	P value 2x vs P	P value 1x vs P
ITT Population N (%)	106 (31.0)	121 (35.4)	115 (33.6)	342		
Subjects who Reported Loose Stool	16 (15.1)	25 (20.7)	31 (27)	72 (21.1)	0.031	0.256
Number of Subjects who Met Criteria for TD	10 (9.4)	13 (10.7)	18 (15.7)	41 (12.0)	0.165	0.265
Multiple episodes of TD	4 (40)	1 (7.7)	2 (11.1)	7 (17.1)	0.147	1.000
TFUS (N=41; Days-Median (IQR)	5.9 (3.4-37.3)	14.4 (9.6-26.9)	12.4 (3.9-30.9)	12.3 (3.9-30.9)	0.792	0.704

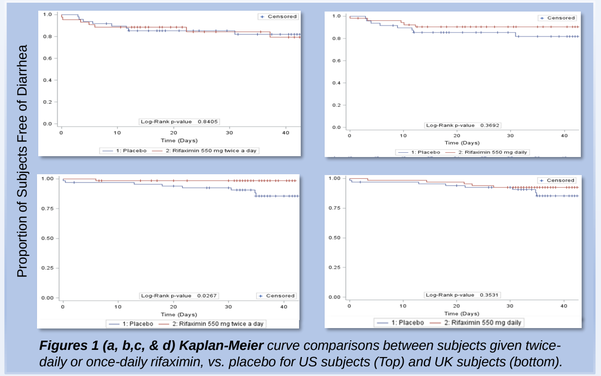
p-values were calculated using chi-square or Fisher's exact test for categorical values and Wilcoxon-Mann-Whitney test for continuous variables.

Table 2: *Diarrheal illness (TD & Loose Stool) by treatment groups was reported more frequently by placebo recipients, but only loose stool reached statistical significance. TFUS was similar across treatment groups.*

	Rifaximin 550mg twice daily	Placebo	Incidence Rate Ratio (95%CI)	Efficacy (1-IRR) (95%CI)
	Incidence Rate per 100 person-days (95%CI)	Incidence Rate per 100 person-days (95%CI)		
Total	0.29 (0.16-0.55)	0.48 (0.3-0.76)	0.62 (0.28-1.33)	38.4% (-25-72)
US participants	0.67 (0.35-1.28)	0.64 (0.34-1.19)	1.05 (0.43-2.58)	-4.7% (-61-57)
UK participants	0.05 (0.01-0.35)	0.36 (0.18-0.73)	0.13 (0.02-1.07)	86.6% (-7-98)

	Rifaximin 550mg daily	Placebo	Incidence Rate Ratio (95%CI)	Efficacy (1-IRR) (95%CI)
	Incidence Rate per 100 person-days (95%CI)	Incidence Rate per 100 person-days (95%CI)		
Total	0.32 (0.18-0.55)	0.48 (0.3-0.76)	0.66 (0.32-1.35)	33.8% (-26-68)
US participants	0.45 (0.22-0.9)	0.64 (0.34-1.19)	0.70 (0.28-1.78)	29.6% (-44-72)
UK participants	0.21 (0.09-0.52)	0.36 (0.18-0.73)	0.59 (0.19-1.81)	40.9% (-45-81)

Tables 3a & 3b: *Incidence rates (TD), by treatment groups and traveler type. Incidence rates for TD overall were lower than expected in our travel population. Among UK participants, twice-daily dosing yielded a statistically significant decrease in TD incidence.*



Figures 1 (a, b,c, & d) Kaplan-Meier *curve comparisons between subjects given twice-daily or once-daily rifaximin, vs. placebo for US subjects (Top) and UK subjects (bottom).*

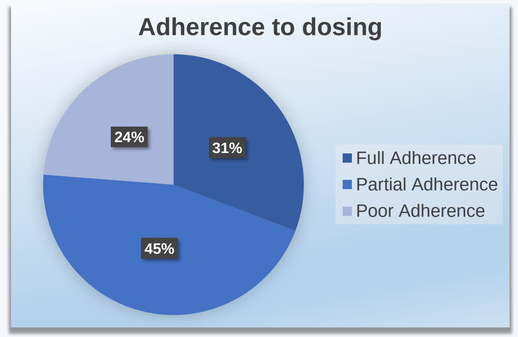


Figure 2: *Missed doses were common in all treatment groups, with "poor adherence" reported at higher rates than other similar studies among travelers[2].*

Conclusions

- First evaluation of two high-dose rifaximin regimens as TD prophylactic. Longer prophylaxis than prior studies.
- Travelers' diarrhea incidence low overall. Highest rate in US personnel traveling to Asia.
- Among UK travelers (all to the same region in Kenya), twice-daily rifaximin decreased loose stool and TD incidence.
- Lower efficacy than prior studies perhaps due to low TD incidence, poor adherence and potentially variable microbial pathogens.
- Treatment was well-tolerated with similar Adverse Events across treatment groups. No Serious Adverse Events attributable to treatment.

REFERENCES

1. Grange, C: *J Royal Army Medical Corps*, 2005:151(2):101-104
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Disclaimers

The authors have no conflicts of interest to disclose. The views expressed are those of the authors and do not necessarily reflect the official views of the Uniformed Services University of the Health Sciences; the National Institutes of Health; the US or UK Governments; the US Department of Health and Human Services; Naval Medical Research Center; the US Department of Defense and the Departments of the US Army, US Navy, and US Air Force; the UK Ministry of Defence; the Henry M. Jackson Foundation for the Advancement of Military Medicine; Naval Medical Center Portsmouth; Brooke Army Medical Center; Madigan Army Medical Center; Naval Medical Center San Diego; Naval Medical Center Camp Lejeune; Walter Reed Army Institute of Research; and Tripler Army Medical Center. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government. The investigators have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46. Several authors are military service members or US government employees. This work was prepared as part of their official duties. Title 17 U.S.C. 105 provides that 'copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. 101 defines a U.S. Government work as work prepared by a military service member or employee of the U.S. Government as part of that person's official duties."

Funding Statement: This work, IDCRP-080, was conducted by the United Kingdom Ministry of Defence, and the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed by the Uniformed Services University of the Health Sciences (USU) through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been supported with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter- Agency Agreement Y1-AI-5072, from the Defense Health Program, U.S. Department of Defense, under award HU0001190002, and the United States Navy Bureau of Medicine and Surgery, under award HU0001-14-1-0012.