Adult Malaria Chemoprophylaxis Prescribing Patterns in the Military Health System from 2007–2011

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Abstract. The Military Health System (MHS), with 9.7 million beneficiaries, represents an enormous pool of potential travelers requiring malaria prevention measures. A systematic search of the MHS electronic pharmacy record was performed for prescriptions of atovaquone-proguanil (AP), chloroquine (CQ), doxycycline (DC), mefloquine (MQ), primaquine (PQ) to adult patients from 2007 through 2011. Over 1,000,000 were identified, including 161,341 primary prophylaxis prescriptions originating from civilian facilities. Military facility prescription volume rose from 50,128 (PQ < 1%, AP 4%, CQ 6%, DC 53%, MQ 36%) in 2007 to 166,649 (PQ < 1%, AP 3%, CQ < 1%, DC 94%, MQ 2%) in 2011. Mefloquine use diminished in all clinics over time. The majority of military facility prescriptions originated from primary care clinics (83%); primary care clinics predominantly and increasingly prescribed DC, whereas specialty travel clinics predominantly and increasingly prescribed AP. Prescribing patterns in the MHS varied by time, practice setting, beneficiary status, and provider specialty. These changes, including among non-active duty military patients, are temporally associated with policy changes intended for the active duty force.

INTRODUCTION

The World Malaria Report 2011, issued by the World Health Organization (WHO), estimated there were 216 million diagnosed malaria cases and 655,000 malaria deaths worldwide in 2010.¹ In the United States, ~1,500 malaria cases are diagnosed yearly, mostly in returning travelers.² Malaria has been a significant threat to military forces throughout history; current United States (U.S.) military operations are no exception. A recent review of malaria cases in U.S. service members revealed 423 cases reported in a 6-year period (2000–2005)³; with hundreds of thousands of U.S. forces deployed and stationed around the world, malaria prevention and treatment remain top military priorities. Additionally, the 9.7 million beneficiaries of the Military Health System (MHS) represent an enormous pool of potential travelers requiring malaria preventive measures.⁴

Few studies describing antimalarial prescribing patterns have been reported in the literature. Systematic reviews have been reported for New Zealand⁵ (1993–1998), South Africa⁶ (1994–2000), and Australia⁷ (2005–2009). No systematic reviews describing malaria chemoprophylaxis prescription trends within U.S. primary care settings have been conducted. A recent publication from Global TravEpiNet, a national consortium of 18 specialty travel clinics, reported malaria chemoprophylaxis data for 9,912 high-risk travelers from 2009 to 2011.⁸ Atovaquone-proguanil (AP) was the most commonly prescribed antimalarial (70%), followed by chloroquine (CQ) (13%), mefloquine (MQ) (11%), and doxycycline (DC) (6%). These data, though interesting, capture only a single timeframe for high-risk travelers evaluated at specialty travel clinics, and therefore may not be representative of broader U.S. practice patterns, particularly primary care settings.

In a review of MHS antimalarial prescribing patterns for children 8 years of age and younger from 2005 to 2010, MQ represented 50% of prescriptions, followed by AP (43%) and CQ (7%).⁹ Over time, however, AP prescriptions rose significantly and overtook MQ as the primary antimalarial pre-

scribed to pediatric beneficiaries. This occurred even in settings where travel duration favored MQ as the preferred medication. The authors suggest that military Force Health Protection (FHP) policies, and awareness of serious neuropsychiatric side effects from MQ use, may be affecting prescribing patterns.

In 2002, the U.S. Food and Drug Administration and Roche Pharmaceuticals strengthened the MQ label's warnings.¹⁰ Healthcare professionals were notified that major psychiatric conditions represented a contraindication to MQ use and advised the drug be discontinued if psychiatric symptoms develop while taking the medication. In response, the Deputy Assistant Secretary of Defense (Force Health Protection and Readiness) tasked the Armed Forces Epidemiological Board to review current antimalarial practice in the military.¹¹ The board concluded that concern among military personnel regarding MQ was not evidence based and suggested several areas of research to further understand the issue.^{12,13}

In 2009, the Assistant Secretary of Defense (Health Affairs) released policy guidance establishing requirements for MQ use in FHP malaria chemoprophylaxis¹⁴; although the policy does not ban MQ use, it establishes an algorithm favoring use of alternative antimalarials with DC as the first-line choice. Furthermore, MQ prescriptions require individualized screening and counseling of potential adverse reactions. Military FHP policies are intended for military clinicians caring for active duty troops traveling in the course of duty; however, it is unknown whether providers extend this guidance to all MHS beneficiaries.

Current medication recommendations for malaria prophylaxis detailed by the Centers for Disease Control and Prevention (CDC) include AP, CQ, DC, MQ, and primaquine (PQ).^{15,16} Factors that must be considered before choosing a medication include malaria species present at the destination, drug resistance, travel duration, preexisting medical conditions, patient preferences, potential side effects, and cost. Additional considerations for military personnel include mission type, occupation, and adherence to the prescribed regimen. In light of the widespread geographic resistance patterns associated with CQ, the expense of AP, and the requirement for daily administration of DC, MQ remains an important medication in the antimalaria armamentarium.

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Understanding prescribing patterns in the MHS and the response to FHP policies will assist in identifying barriers to optimal care and guiding future military policies. Analyzing differential chemoprophylaxis choices based on provider specialty and patient demographics will provide useful information for understanding provider decision making and targeting preventive strategies to appropriate populations. The aim of this study was to describe adult malaria chemoprophylaxis prescription patterns in the MHS from 2007 through 2011. We sought to investigate whether active duty FHP policy guidance on MQ use issued in 2009 affected practice patterns despite beneficiary category. We also sought to analyze differences in prescribing patterns based on practice setting (military versus civilian) and provider specialty.

METHODS

We performed a secondary data analysis of all primary chemoprophylaxis antimalarial medications prescribed to patients 18–89 years of age in the MHS from January 2007 through December 2011. Data were obtained by a systematic search of the MHS Management Analysis and Reporting Tool pharmacy database. Medications included were AP, CQ, DC, MQ, and PQ. For each prescription, variables collected were patient age, gender, sponsor branch of service, beneficiary category, month/year of prescription, medication prescribed, amount dispensed, number of refills, and the medical expenses and performance reporting system (MEPRS) code, which designates the specialty of the prescribing clinic for military facilities. Although PQ can be used for primary prophylaxis, its primary major application remains presumptive anti-relapse therapy (PART) or radical cure for vivax and ovale malaria. Primaquine prescriptions were further aggregated by the amount dispensed to identify prescriptions of > 28 tablets, which would exclude any prescription that could have been for PART/radical cure using either the 15 or 30 mg base per day regimens. To target DC malaria chemoprophylaxis prescriptions more accurately, they were filtered to exclude prescriptions < 36 days in duration, the minimum amount prescribed for 1 week of exposure. Furthermore, DC prescriptions were examined individually—if topical dermatological medications and/or isotretinoin were concomitantly prescribed, those DC prescriptions were excluded from our dataset.

Data analyses were performed using SPSS version 20 software (SPSS, Inc., Chicago, IL). Descriptive statistics were generated for all variables. Prescriptions without an associated MEPRS code were categorized as civilian facility prescriptions for the purposes of analysis; prescriptions associated with a MEPRS code were categorized as military treatment facility (MTF) prescriptions. Results were stratified by beneficiary category: active duty/national guard/reserve (AD) and dependent/retiree (DR). The MEPRS codes were grouped according to provider specialty and results stratified to produce the following clinic categories for analysis: allergy/immunology, civilian, community/occupational health, infectious disease, primary care (including internal medicine and family practice), and other (including surgery and medical subspecialties). These distinctions were necessary because primary care providers or specialty travel clinics may provide travel medicine services within the MHS. Specialty travel clinics, with formal travel medicine training, may be run by allergy/immunology, community/occupational health, or infec-

tious disease clinics depending on the particular MTF. Allergy/immunology clinics, in particular, may perform travel medicine services because of their ownership of immunization services. Community/occupational health clinics are typically staffed by preventive/occupational medicine physicians and community health nurses. To target malaria chemoprophylaxis, MTF prescriptions were filtered to exclude DC prescriptions originating from dermatology clinics and CQ prescriptions originating from rheumatology clinics.

For each medication, we took the absolute number of prescriptions and expressed it as a proportion of total prescriptions for a particular time period. We performed two temporal analyses; all comparisons were made using χ^2 tests. First, prescriptions were compared by calendar year and trended over time. Second, we aggregated prescriptions into pre-policy (2007 through 2009) and post-policy (2010 through 2011) to assess whether a temporal association with the military FHP policy existed. Results were analyzed by practice setting, beneficiary category and prescribing clinic.

Over 50,000 prescriptions per year were identified. Using a two-tailed χ^2 test with significance level 0.05 and 90% power, we were able to detect a difference of 1%. Because of the large size of the dataset, all reported results were statistically significant ($P < 0.001$). Differences of > 5% were considered clinically meaningful. Uniformed Services University Institutional Review Board approval was obtained before study initiation.

RESULTS

Total population and comparison of MTF and civilian facility subsets. A total of 737,319 prescriptions for DC, MQ, AP, CQ, and PQ for primary prophylaxis were identified during the study period (Table 1A and Figure 1). The majority of patients (84%) were < 50 years of age and male (79%). Dependents and retirees constituted 29% of the total population. Twenty-two percent ($N = 161,341$) of prescriptions were not associated with a MEPRS code and are described in the civilian subset. The Army was the most common military sponsor branch of service (56%), followed by the Air Force (23%), and the Navy/Marine Corps (17%). Other branches of service such as the Coast Guard, Public Health Service, and National Oceanographic and Atmospheric Administration comprised 4%.

In total, prescription frequencies were as follows: DC 79%, MQ 12%, AP 6%, CQ 3%, and PQ (primary) < 1%. For the entire study population, although no clinically meaningful changes in CQ or AP proportions over time were demonstrated, the DC proportion showed an absolute 18% increase and the MQ proportion showed a corresponding decrease. Both military and civilian providers predominantly prescribed DC (Table 2 and Figure 2), although the proportions differed and widened over time. The most recent data showed that all providers, military and civilian, preferentially and overwhelmingly used DC, with MQ and AP used substantially less and in about equal proportions. Civilian providers, however, prescribed proportionally more MQ and AP than military providers.

During the study period, there were 280,071 prescriptions for PQ. Over time the annual prescriptions for PQ steadily rose from 22,673 in 2007 to 100,401 in 2011. The majority of PQ prescriptions were from military facilities, with 39,723

TABLE 1

Demographic characteristics for (A) total, military facility and civilian facility prescriptions and (B) active duty and dependent/retiree subsets at military facilities

(A)

Characteristic	Total, no. (%) (N = 737,319)	Military facility, no. (%) (N = 575,978)	Civilian facility, no. (%) (N = 161,341)	P value
Age in years				< 0.001
18–49	616,234 (84)	520,148 (90)	96,086 (60)	
50–64	65,580 (9)	36,030 (6)	29,550 (18)	
> 64	55,505 (7)	19,800 (4)	35,705 (22)	
Gender*				< 0.001
Male	584,339 (79)	476,440 (83)	107,899 (67)	
Female	152,967 (21)	99,243 (17)	53,438 (33)	
Patient category				< 0.001
Active duty	525,062 (71)	455,825 (79)	69,237 (43)	
Dependent/retiree	212,257 (29)	120,153 (21)	92,104 (57)	

* Gender was not recorded in 14 individuals.

(B)

Characteristic	Active duty,† no. (%) (N = 445,717)	Dependent/retiree,† no. (%) (N = 112,151)	P value
Age in years			< 0.001
18–49	437,966 (98)	66,508 (60)	
50–64	7,724 (2)	26,276 (23)	
> 64	27 (< 1)	19,367 (17)	
Gender*			< 0.001
Male	393,657 (88)	73,925 (66)	
Female	52,057 (12)	38,220 (34)	
Prescribing clinic			< 0.001
Primary care	395,220 (88)	71,406 (64)	
Community/ occupational health	5,562 (1)	4,532 (4)	
Infectious disease	2,252 (< 1)	6,333 (6)	
Allergy	1,163 (< 1)	2,593 (2)	
Other	41,520 (10)	27,277 (24)	
Sponsor service category			< 0.001
Army	276,646 (62)	47,718 (42)	
Air Force	99,967 (22)	24,216 (22)	
Navy/Marine Corps	65,600 (15)	20,160 (18)	
Other	3,504 (< 1)	20,057 (18)	

* Gender was not recorded in nine individuals.

† Military facility prescriptions filtered to remove doxycycline prescriptions associated with dermatology or dental and chloroquine associated with rheumatology.

FIGURE 1. Flow diagram of prescriptions for primary prophylaxis.

TABLE 2

Comparison of military facility and civilian facility prescriptions in total and by aggregated years (pre- and post-policy memorandum)

Facility/medication	Total, no. (%)	2007–2009, no. (%)	2010–2011, no. (%)	P value
Military facility	575,978	238,564	337,414	< 0.001
Chloroquine	10,249 (2)	7,732 (3)	2,517 (1)	
Doxycycline	474,260 (82)	164,507 (69)	309,753 (92)	
Mefloquine	70,186 (12)	55,766 (23)	14,420 (4)	
Atovaquone-proguanil	20,301 (3)	9,976 (4)	10,325 (3)	
Primaquine-primary	982 (< 1)	583 (< 1)	399 (< 1)	
Primaquine-PART*	239,357 (42)	87,125 (37)	152,232 (45)	
Civilian facility	161,341	87,278	74,063	< 0.001
Chloroquine	9,300 (6)	5,939 (7)	3,361 (4)	
Doxycycline	111,655 (69)	56,365 (65)	55,290 (75)	
Mefloquine	17,262 (11)	11,391 (13)	5,871 (8)	
Atovaquone-proguanil	22,618 (14)	13,253 (15)	9,365 (13)	
Primaquine-primary	506 (< 1)	330 (< 1)	176 (< 1)	
Primaquine-PART*	39,226 (24)	13,773 (16)	25,453 (34)	

* Primaquine-PART not included in overall totals and shown as a percentage of all non-primaquine prescriptions.
PART = presumptive anti-relapse therapy.

civilian site prescriptions accounting for only 14% of the total. Prescriptions to AD personnel accounted for 94% of all PQ prescriptions. Within the DR subset of 16,559 prescriptions, PQ prescriptions showed a slower rate of rise, from 2,597 in 2007 to 4,030 in 2011. Civilian sites accounted for 3,066 (18%) of prescriptions to DR beneficiaries. Primaquine as primary prophylaxis was rare, accounting for < 1% of prescriptions regardless of prescription site for AD/DR status.

MTF prescriptions and comparison of AD and DR subsets.

Civilian prescriptions likely represent a mix of primary care and specialty providers; because provider specialty codes were not associated with these prescriptions in the source dataset, civilian prescriptions were excluded from the remainder of the analysis (Figure 1). After filtering prescriptions by MEPRS code, as described previously, a total of 557,868 primary prophylaxis prescriptions remained (Table 1B and Figure 1). The DR subset was composed of older patients than the AD population, with 40% of prescriptions written to patients over the age of 50 (compared with < 3% in the AD subset). Addition-

ally, females comprised a larger percentage of the DR subset as compared with AD (34% versus 12%). DR patients were more likely than AD patients to be seen by non-primary care providers, with 36% of prescriptions written by non-primary care providers compared with 12% in the AD group.

The MTF prescription volume, which included both AD and DR subsets, rose from 49,957 (PQ < 1%, AP 5%, CQ 6%, DC 53%, and MQ 36%) in 2007 to 166,527 (PQ < 1%, AP 3%, CQ < 1%, DC 94%, and MQ 2%) in 2011, with DC representing the majority of the increase. Analysis of trends pre- and post-policy memorandum confirmed absolute and proportionate increased use of DC and diminished use of MQ; AP use though dropping as a proportion of the total, gained in absolute number of prescriptions.

The DR prescription volume rose from 13,840 in 2007 to 34,875 in 2011. For the entire study period, DC was the most commonly prescribed antimalarial medication, accounting for 78% of prescriptions, with AP at 9%, MQ at 9%, CQ at 4%, and PQ < 1%. This contrasts with the AD population,

Abbreviations: PQ, Primaquine-primary; CQ, chloroquine; AP, atovaquone-proguanil;

MQ, mefloquine; DC, doxycycline

Primaquine-PART prescriptions not shown

P<.001 for trend over time and aggregated pre- (2007–2009) and post- (2010–2011) policy memorandum based on a two-sided X² test

FIGURE 2. Comparison of military facility and civilian facility prescription proportions to both active duty and dependent/retiree individuals for the period 2007–2011.

TABLE 3

Comparison of active duty and dependent/retiree prescriptions in total and by aggregated ears (pre- and post-policy memorandum) at military facilities

Beneficiary status/medication	Total, no. (%)	2007–2009, no. (%)	2010–2011, no. (%)	P value
Active duty	445,717	181,045	264,672	< 0.001
Chloroquine	5,775 (1)	4,444 (2)	1,331 (< 1)	
Doxycycline*	369,195 (83)	123,087 (68)	246,317 (93)	
Mefloquine	60,038 (14)	48,538 (27)	11,494 (4)	
Atovaquone-proguanil	10,054 (2)	4,586 (2)	5,469 (2)	
Primaquine-primary	655 (< 1)	390 (< 1)	265 (< 1)	
Primaquine-PART†	226,169 (51)	80,492 (45)	145,677 (55)	< 0.001
Dependent/retiree	112,151	48,900	63,251	
Chloroquine	4,474 (4)	3,288 (7)	1,186 (2)	
Doxycycline*	86,976 (78)	32,815 (67)	54,161 (86)	
Mefloquine	10,136 (9)	7,218 (15)	2,918 (5)	
Atovaquone-proguanil	10,238 (9)	5,386 (11)	4,852 (8)	
Primaquine-primary	327 (< 1)	193 (< 1)	134 (< 1)	
Primaquine-PART†	13,188 (12)	6,633 (14)	6,555 (10)	

*Doxycycline prescriptions filtered to remove those from dermatology and dental clinics.

†Primaquine-PART not included in overall totals and shown as a percentage of all non-primaquine prescriptions.

PART = presumptive anti-relapse therapy.

which predominantly used DC (83%) followed by MQ at 14%, AP at 2%, CQ at 1%, and PQ at < 1% (Table 3). Pre- and post-policy memorandum prescription changes in the DR population showed a proportional 19% increase in DC prescriptions, whereas MQ use decreased by 10% and AP use decreased by 3%. Larger proportional changes in DC (25% increase) and MQ (23% decrease) were observed in the AD subset (Figure 3). Primaquine-PART prescriptions were made to 12% of the DR population and 51% of the AD population. This is in contrast to only a 3% rate of civilian site prescriptions for primaquine-PART to non-active duty individuals (data not shown).

Comparison by prescribing clinics. Analyzing DR prescriptions by clinic, prescribing patterns differed among specialty travel clinics (i.e., allergy/immunology, community/occupational health, and infectious disease) and between these clinics and primary care clinics (Figure 4). In total, 12% of military site prescriptions came from clinics not typically associated with travel medicine or primary care functions, such as surgical

clinics or were source coded for the pharmacy (7%). Potential reasons for pharmacy coded prescriptions may include bulk drug orders from deploying units or handwritten prescriptions from either a military or civilian clinic. For this reason, these “other” sites were not included in the clinic-specialty comparison analysis. Primary care clinics predominantly prescribed DC, with MQ and AP used substantially less commonly, whereas infectious disease and allergy/immunology clinics predominantly prescribed AP. Community/occupational health clinics occupied the middle ground between primary care clinics and allergy/immunology and infectious disease clinics, exhibiting a more balanced distribution of antimalarial prescriptions. Primary prophylaxis with PQ was uncommon regardless of medical specialty, accounting for no more than 2% of prescriptions from infectious disease clinics and 1% or less from the others.

Over time, primary care clinics and community/occupational health clinics increasingly prescribed DC with no clinically meaningful change in AP proportion use during the study

Abbreviations: PQ, Primaquine-primary; CQ, chloroquine; AP, atovaquone-proguanil; MQ, mefloquine; DC, doxycycline

Doxycycline prescriptions filtered to remove those from dermatology and dental clinics

Primaquine-PART prescriptions not shown

P < .001 for trend over time and aggregated pre- (2007–2009) and post- (2010–2011) policy memorandum based on a two-sided X^2 test

FIGURE 3. Comparison of military facility prescription proportions in the active duty and dependent/retiree subsets for the period 2007–2011.

Abbreviations: PQ, Primaquine-primary; CQ, chloroquine; AP, atovaquone-proguanil; MQ, mefloquine; DC, doxycycline
 Doxycycline prescriptions filtered to remove those from dermatology and dental clinics
 Primaquine-PART prescriptions not shown

FIGURE 4. Comparison of proportionate use in the dependent/retiree subset by military facility prescribing clinic for the period 2007–2011.

period (Table 4). Infectious disease and allergy/immunology clinics modestly increased both DC and AP proportions. The MQ use diminished in absolute numbers and relative proportion in all clinics over time.

In the AD subset, the observed changes over time by prescribing clinic were different than the DR subset (Table 5). Primary care clinics increased DC prescriptions by 27% and decreased MQ by 25%; infectious disease clinics, on the other

TABLE 4

Comparison of prescribing patterns at military facilities in the dependent/retiree subset by prescribing clinic and by aggregated years (pre- and post-policy memorandum)

Clinic/medication	Total, no. (%)	2007–2009, no. (%)	2010–2011, no. (%)	P value
Allergy/immunology	2,593	1,066	1,527	< 0.001
Chloroquine	237 (9)	146 (10)	91 (9)	
Doxycycline*	442 (17)	227 (15)	215 (20)	
Mefloquine	448 (17)	322 (21)	126 (12)	
Atovaquone-proguanil	1,466 (57)	832 (54)	634 (59)	
Primaquine-primary	0	0	0	
Primaquine-PART†	33 (1)	15 (1)	18 (1)	
Infectious disease	6,333	3,574	2,759	< 0.001
Chloroquine	431 (7)	298 (8)	133 (5)	
Doxycycline*	833 (13)	371 (11)	462 (17)	
Mefloquine	999 (16)	651 (19)	348 (13)	
Atovaquone-proguanil	3,951 (62)	2,188 (62)	1,763 (65)	
Primaquine-primary	118 (2)	66 (2)	52 (2)	
Primaquine-PART†	272 (4)	172 (5)	100 (4)	
Primary care	71,416	25,435	45,981	< 0.001
Chloroquine	2,071 (3)	1,555 (5)	516 (1)	
Doxycycline*	60,711 (85)	18,419 (72)	42,292 (92)	
Mefloquine	5,545 (8)	4,061 (16)	1,484 (3)	
Atovaquone-proguanil	2,962 (4)	1,334 (5)	1,628 (4)	
Primaquine-primary	127 (< 1)	66 (< 1)	61 (< 1)	
Primaquine-PART†	10,927 (15)	5,233 (21)	5,694 (12)	
Community/Occ health	4,532	2,318	2,214	< 0.001
Chloroquine	513 (11)	371 (16)	142 (6)	
Doxycycline*	2,181 (48)	869 (38)	1,312 (59)	
Mefloquine	977 (22)	633 (28)	344 (16)	
Atovaquone-proguanil	831 (18)	418 (18)	413 (19)	
Primaquine-primary	30 (1)	27 (1)	3 (< 1)	
Primaquine-PART†	663 (15)	339 (15)	324 (15)	

*Doxycycline prescriptions filtered to remove those from dermatology and dental clinics.

†Primaquine-PART not included in overall totals and shown as a percentage of all non-primaquine prescriptions.

PART = presumptive anti-relapse therapy.

TABLE 5

Comparison of prescribing patterns in the active duty subset by prescribing clinic and by aggregated years (pre- and post-policy memorandum)

Clinic/medication	Total, no. (%)	2007–2009, no. (%)	2010–2011, no. (%)	P value
Allergy/immunology	1,163	706	457	< 0.001
Chloroquine	69 (6)	37 (5)	32 (7)	
Doxycycline*	487 (42)	253 (36)	234 (51)	
Mefloquine	170 (15)	144 (21)	26 (6)	
Atovaquone-proguanil	434 (37)	269 (38)	165 (36)	
Primaquine-primary	3 (< 1)	3 (< 1)	0	
Primaquine-PART†	219 (19)	75 (11)	144 (32)	
Infectious disease	2,252	1,171	1,081	< 0.001
Chloroquine	167 (7)	127 (11)	40 (4)	
Doxycycline*	289 (13)	159 (13)	135 (13)	
Mefloquine	334 (15)	219 (19)	115 (11)	
Atovaquone-proguanil	1,379 (61)	622 (53)	757 (70)	
Primaquine-primary	83 (4)	49 (4)	34 (3)	
Primaquine-PART†	232 (11)	147 (13)	85 (8)	
Primary care	395,220	157,122	238,098	< 0.001
Chloroquine	4,703 (1)	3,580 (2)	1,123 (< 1)	
Doxycycline	328,275 (83)	105,340 (67)	222,935 (94)	
Mefloquine	55,111 (14)	44,857 (29)	10,254 (4)	
Atovaquone-proguanil	6,636 (2)	3,050 (2)	3,586 (2)	
Primaquine-primary	495 (< 1)	295 (< 1)	200 (< 1)	
Primaquine-PART†	211,419 (54)	73,335 (47)	138,084 (58)	
Community/Occ health	5,562	2,301	3,261	< 0.001
Chloroquine	324 (6)	268 (12)	56 (2)	
Doxycycline*	3,723 (67)	1,295 (56)	2,428 (75)	
Mefloquine	681 (12)	405 (18)	276 (8)	
Atovaquone-proguanil	826 (15)	326 (14)	500 (15)	
Primaquine-primary	8 (< 1)	7 (< 1)	1 (< 1)	
Primaquine-PART†	1,422 (26)	816 (35)	606 (18)	

*Doxycycline prescriptions filtered to remove those from dermatology and dental clinics.

†Primaquine-PART not included in overall totals and shown as a percentage of all non-primaquine prescriptions.

PART = presumptive anti-relapse therapy.

hand, increased AP prescriptions by 17% and decreased MQ use by 8%, while maintaining a steady use of DC. Though relatively small in total number ($N = 83$), PQ as primary prophylaxis accounted for 4% of prescriptions to active duty personnel seen at infectious disease clinics.

DISCUSSION

Malaria chemoprophylaxis prescribing patterns for adult MHS beneficiaries have changed during the past 5 years, whether receiving care from military or civilian medical providers. The DC proportions rose, whereas MQ diminished and AP remained approximately stable. This pattern of change might be expected based on the military FHP policy directed at military providers. Although it is unlikely civilian providers are cognizant of military FHP policies, we observed a similar trend in their prescription patterns. This was likely caused by increased awareness of MQ adverse reactions by the healthcare community in general.

Prescription volume rose dramatically during this time period. For AD, this coincides with troop buildups in Afghanistan, and perhaps to increase international vacationing. For the DR population, the upward trend coincides with the roughly 43% increase in international travel by U.S. citizens reported by the U.S. Department of Commerce during this time period.¹⁷ Prescribing patterns for the AD population were different than the DR population at baseline, although trends were similar over time. We found a temporal association between changes in prescribing patterns and the

2009 military FHP policy memorandum in both beneficiary subsets. The MQ use diminished dramatically in absolute numbers and relative proportion in both subsets, although the magnitude of change varied. The DC emerged as the clear preference for primary chemoprophylaxis. Particularly in the DR population, this shift may reflect a change in physician attitudes regarding the safety of mefloquine, a “requirement” to use DC as a first-line therapy for all travelers. Alternatively, patients may arrive at the medical visit with pre-conceived expectations based on either the community reputation of a medication, or their own prior experience, or that of a family member, with a given medication. Likely, all of these factors contribute to the trends observed. This study was not designed to assess these influences on prescription choice, but they warrant additional investigation.

The bulk of malaria chemoprophylaxis prescribed in military facilities was handled by primary care clinics, and we found striking differences in prescribing patterns between primary care and specialty travel clinics. Patients seeking travel advice from specialty travel clinics, such as infectious disease clinics, were far more likely to receive AP than DC or MQ regardless of beneficiary category. Patients seeking travel advice from primary care clinics were prescribed DC predominantly. Changes over time were also more dramatic in primary care clinics than in specialty travel clinics.

That prescription patterns change over time is not surprising. As new medications are developed, older medications are replaced or clinical use of medications changes, providers will alter their prescribing habits. Physicians tend to prescribe

familiar medications, particularly when pressed for time or dealing with a variety of health issues—common situations for primary care physicians. Use of DC as the default medication for malaria chemoprophylaxis is certainly acceptable in many situations. Knowing when it may not be the optimal choice is an important aspect of travel medicine services. Its short half-life requires punctual, daily adherence for reliable antimalarial coverage, as well as continuation for 4 weeks post-travel. Patients that are unable or unwilling to adhere to this strict regimen may benefit from an alternative medication. Assessing these issues takes time, patience, and familiarity with travel medicine standards.

As intended, military FHP policies influence decisions by military providers. Broad implementation of those policies to the DR population, however, may not be optimal. Recognition of this finding in our study, and understanding the differences in prescribing patterns between expert travel medicine providers and primary care providers, will be important for crafting rational policies and ensuring adequate support to military providers. Policymakers need to know who is performing the majority of travel medicine services and what influences their decisions. With the majority of prescriptions originating from primary care clinics, ensuring providers have travel medicine training and/or access to relevant clinical decision-making tools will ensure chemoprophylaxis decisions are individualized and optimized for all MHS beneficiaries.

Our study confirms findings of previous studies that malaria chemoprophylaxis patterns change over time.^{5–9} The most recent published comparable data comes from Australian prescriptions from 2005 to 2009.⁷ Consistent with our data, DC was the predominant antimalarial, with MQ and AP contributing comparably and considerably less. Also consistent with our data, pediatric MHS prescriptions showed an increase in overall prescription volume over a similar period, as well as a decline in MQ prescriptions.⁹ The AP emerged as the antimalarial of choice in the pediatric study, similar to our DR population (excluding DC).

LaRocque and others⁸ described malaria chemoprophylaxis choices for high-risk patients being seen in specialty travel clinics from 2009 to 2011. As previously described, AP was the majority choice (70%), followed distantly by the remaining antimalarials. Our DR subset seeking care in infectious disease clinics seems an appropriate comparison group and patterns appear similar (AP 62%, DC 13%, MQ 16%, CQ 7%, PQ 2%). Usage of primaquine-PART varies by provider medical specialty, active duty versus dependent/retiree status, and whether care is delivered in military versus civilian facilities.

This study had several limitations. First, DC is not solely an antimalarial, and therefore we anticipate some misclassification bias. Likely non-differential, this would tend to bias results toward the null hypothesis. Second, we may not be capturing all overseas prescriptions or those dispensed in bulk by deployed units under force health protection policy. Third, the determination of purpose for PQ use was abstracted based on the number dispensed, with those in excess of 28 tablets being deemed for primary prophylaxis. This would potentially undercount the true number of primary prophylaxis uses for trips of short duration. Finally, travel duration and destination were unknown.

This study had several strengths. The large sample size provided adequate power for detecting small differences in a

variety of subset analyses. Inclusion of prescriptions originating from civilian facilities enhances our generalizability to the larger U.S. population. The availability of longitudinal data from primary care and specialty travel clinics provided us with the opportunity to compare changes in prescribing patterns over time, something that has not yet been reported in the U.S. adult population. Although longitudinal studies recording prescribing patterns in specialty travel clinics are ongoing—TravEpiNet⁸ and TravMil¹⁸ are two examples—these studies may not reflect broader national practice patterns, particularly in non-travel medicine specialty clinics. Our study provides an aggregate look at civilian prescribing patterns, which includes a variety of clinic settings such as primary care and specialty clinics. We were also able to show primary care patterns separately, albeit those originating from MTFs.

CONCLUSIONS

In conclusion, our research showed that adult malaria chemoprophylaxis prescribing patterns in the MHS from 2007 through 2011 varied by practice setting, beneficiary status, and provider specialty. Specifically, we showed a temporal association between changes in prescribing patterns and military FHP policies in the dependent and retiree population. Understanding the impact of military FHP policies on all MHS beneficiaries will be important information for policymakers to consider when crafting policy guidance. Knowing where and by whom travel medicine advice is being provided in the MHS will help leaders ensure providers have adequate training and access to clinical tools to provide optimal care to all MHS beneficiaries.

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