

EVALUATING CHLAMYDIA AND GONORRHEA INFECTION AND DISEASE IN THE
US ARMY: IMPLICATIONS FOR HEALTH SURVEILLANCE AND PREVENTION

By

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Abstract

Background. US military members (particularly Army soldiers) have been classified as high-risk for sexually transmitted infections such as *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) and prioritized for enhanced surveillance and prevention. Yet studies examining the associated disease burden and risk differential relative to the general public are lacking. Furthermore, surveillance system capabilities in making this determination have not been adequately explored.

Methods. Age- and sex-adjusted CT and NG reported case rates were computed for US Army active component soldiers and US adults 18-64 years of age during 2015-2019. Army reporting system data were supplemented with military health system medical encounters and laboratory data. Using this comprehensive dataset, incidence rates, morbidity burden, and system-specific case capture were calculated. Multivariable generalized linear models were used to characterize risk by covariates of interest (e.g., age, sex, race/ethnicity, and education).

Results. Annual case rates increased for the Army and US cohorts. Unadjusted reported CT rates were nearly three-fold higher in the Army relative to US peers (RR=2.86; 95%CI: 2.84-2.89), whereas age-sex adjusted rates were just under two-fold higher (RR=1.84, 95%CI: 1.83-1.86). Unadjusted reported NG rates were 44% higher among soldiers (RR= 1.44, 95% CI: 1.40-1.47); however, age-sex-adjusted rates were significantly lower relative to US peers (RR=0.74, 95% CI: 0.72-0.75). The enhanced three-source dataset identified 17% and 24% of respective CT and NG cases missed through reporting (laboratory records identified 87% and 67% of respective cases while medical encounters identified 58% of each). System-specific case capture varied considerably across installations. The combined CT/NG incidence rate computed was 3,163

cases per 100,000 person-years in 2019 alone, with 19,022 estimated medical encounters. Age was the most influential risk factor (Adjusted RR, 95% CI for soldiers <25 versus soldiers 35+: 7.7 [7.4-8.1]).

Conclusion. Increasing disease burden among Army soldiers with elevated CT risk and decreased NG risk relative to US demographic peer-groups was documented. Substantial case capture gains, improved burden assessment, and a more robust characterization of risk factors were achieved through multi-sourced data. The findings provide MHS/DoD leaders with actionable data which support resource allocation for surveillance enhancements and targeted prevention to improve readiness and force health protection.

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LIST OF ABBREVIATIONS

AC	Active Component
AFHSD	Armed Forces Health Surveillance Division
AMR	Antimicrobial Resistance
BRFSS	Behavioral Risk Factor Surveillance Survey
CAPER	Comprehensive Ambulatory/Professional Encounter Records
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPP	Chronic Pelvic Pain
CSTE	Council of State and Territorial Epidemiologists
CT	<i>Chlamydia trachomatis</i>
DALY	Disability Adjusted Life Year
DHA	Defense Health Agency
DoD	Department of Defense
HRBS	Health Related Behavior Survey
DRSi	Disease Reporting System Internet
DUA	Data Use Agreement
EAPC	Estimated Annual Percentage Change
EP	Ectopic Pregnancy
EPT	Expedited Partner Therapy
ESSENCE	Electronic Surveillance System for the Early Notification of Community-based Epidemics
GASP	Global Antimicrobial Surveillance Programme
GBD	Global Burden of Disease
GISP	Gonococcal Isolate Surveillance Project
GLM	Generalized Linear Model
GOF	Goodness of Fit
HEDIS	Healthcare Effectiveness Data and Information Set (HEDIS)

HL7	Health Level 7
HR	Hazard Ratio
IET	Initial Entry Training
IR	Incidence Rate
IRR	Incidence Rate Ratio
M2	MHS MART (Management Analysis and Reporting Tool)
MDR	MHS Data Repository
MHS	Military Health System
MLE	Maximum Likelihood Estimation
MSM	Men who have Sex with Men
MSW	Men who have Sex with Women
MTF	Medical Treatment Facility
NAAT	Nucleic Acid Amplification Test
NASEM	National Academies of Sciences, Engineering, and Medicine
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCQA	National Committee for Quality Assurance (NCQA)
NDAA	National Defense Authorization Act
NHANES	National Health and Nutrition Examination Survey
NG	<i>Neisseria gonorrhoeae</i>
NNDSS	National Notifiable Disease Surveillance System
NMCPHC	Navy Marine Corps Public Health Center
NSSP	National Syndromic Surveillance Program
OR	Odds Ratio
PEACH	PID Evaluation and Clinical Health
PHI	Protected Health Information
PID	Pelvic Inflammatory Disease
RME	Reportable Medical Event
RR	Relative Risk/Rate Ratio

SARA	Sexually Acquired Reactive Arthritis
SD	Standard Deviation
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TED-NI	Tricare Encounter Data – Non-Institutional
TFI	Tubal Factor Infertility
USAPHC	US Army Public Health Center
USPSTF	US Preventive Services Task Force
WHO	World Health Organization

CHAPTER 1: BACKGROUND

Disease Burden

GLOBAL BURDEN

Sexually transmitted infections (STIs) have produced a sizeable global morbidity burden. The annual incidence exceeds one billion infections, many of which go unrecognized until notable deficits in quality of life occur such as impaired sexual and reproductive health and debilitating, sometimes fatal sequelae [160]. Of the more than 30 known STIs, non-viral infections are generally curable, including three common bacterial infections caused by *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Treponema pallidum* (syphilis), and a parasitic infection caused by *Trichomonas vaginalis*. These four conditions are periodically monitored by the World Health Organization (WHO) and both CT and NG are further highlighted in the 2016 WHO ‘Global Health Sector Strategy on Sexually Transmitted Infections’, which outlines increased countermeasures to combat health threats posed by STIs. Specifically, the increased risk of untreatable gonorrhea due to antimicrobial resistance (AMR) and rising rates of chlamydial infection in adolescents were addressed as a concern, and they further recommended targeting a 90% reduction in NG incidence by 2030 [160].

Despite renewed emphasis on prevention, CT and NG burden continues to mount and antimicrobial resistant gonorrhea has been increasingly identified worldwide. The WHO Global Antimicrobial Surveillance Programme (GASP) which conducts testing in 73 of 194 countries documented resistance to ceftriaxone, the currently recommended treatment for uncomplicated NG, in 21 (31%) of the 68 countries monitored [153]. Increased AMR is compounded by the high disease burden. In 2020, an estimated 129 million people worldwide contracted CT and 82

million contracted NG; however, annual estimates have been as high as 131 and 87 million, respectively [47, 115, 130, 161].

Repeat CT and NG infections are common as evidenced by case estimates which exceed the estimated number of individuals affected. Approximately 232.5 and 88 million respective CT and NG cases were estimated in 2019; respective age-standardized global incidence rates were 2,884 (95% CI: 2,161-3,763) and 1,124 cases per 100,000 (95% CI: 873-1,441) [60]. CT prevalence is assessed to be up to 4.2% (95% CI: 3.7-4.7%) among women 15-49 years of age and 2.7% (95% CI: 2.0-3.6%) among men in this age group [60, 76, 115]. NG prevalence is estimated to be up to 0.9% (95% CI: 0.7-1.1%) and up to 0.7% (95% CI: 0.5-1.1%) among women and men 15-49 years old, respectively [115, 130].

At the global scale, incidence rates have been fairly stable for both CT and NG, with the estimated annual percentage changes (EAPCs) from 2010 to 2019 computed to be roughly 0.3% and -0.5%, respectively [60]. Trends vary substantially by geographic region, however, with regions such as the United States, which are categorized as a high income North America region, reporting significant increases in age-standardized rates for both infections during this timeframe (EAPC: 1.23 [95% CI: 0.73-1.73] for CT and 0.77 [95% CI: 0.12-1.41] for NG) [60].

US BURDEN

In the US, CT and NG are classified among roughly 120 nationally notifiable conditions that are routinely monitored by the Centers for Disease Control and Prevention (CDC) and other public health authorities due to their public health significance [43]. Approximately 1.8 million CT cases and just over 600 thousand NG cases were reported in the US in 2019 [39]. However, the estimated burden is much higher. It is assessed that one in five or 68 million have an STI, and 16 million new infections are acquired annually - CT and NG make up roughly four million and

1.7 million infections, respectively [39, 96]. The associated economic burden attributed to CT and NG is high with the direct medical cost alone computed to be nearly \$1 billion, of which \$691 million is attributed to CT and \$271 million to NG [39, 47].

The incidence of reported CT has risen steadily since 1996, peaking in 2019 (553 cases per 100,000, all ages), reflecting a 19% increase in reported rates relative to 2015, for example [39]. These trends; however, were just before surveillance, healthcare access, and testing were compromised in 2020 due to the COVID-19 pandemic and reported rates subsequently dropped [44, 118]. National rates of reported NG, on the other hand, have continued to increase more aggressively despite the pandemic with rates climbing from a low in 2009 to reach 207 cases per 100,000 in 2020 (all ages); this reflects a 10% increase from rates reported in 2019, which in turn represents a 56% increase relative to 2015 [44].

An examination of national screening data from 2013 to 2016, revealed that approximately 1.7% (95% CI: 1.3-2.1%) of individuals 14-39 years of age were infected with CT [140]. A similar evaluation of screening data among this demographic group during 2000-2008, determined that 0.3% (95% CI: 0.1-0.5%) were infected with NG; however, the prevalence estimate pre-dates increases in reported cases that subsequently emerged in 2009 [139]. The resurgence of NG has occurred in tandem with rising antibiotic resistance - to date, more than half of all gonococcal isolates tested have been determined to be resistant to at least one antibiotic [44].

The high STI burden coupled with troubling increases in infection rates and antimicrobial resistance prompted the CDC to declare an urgent need for enhanced prevention in 2017 [33]. The US Department of Health and Human services further emphasized the need, issuing a national strategic plan to combat four STIs (CT, NG, syphilis, and HPV) which were prioritized

due to the high associated morbidity, documented inequalities, and impact on national health [151]. The call to action was echoed in 2021 when the National Academies of Sciences, Engineering, and Medicine (NASEM) released consensus STI prevention and control recommendations which include an emphasis on CT and NG [110].

US MILITARY BURDEN

The US military has long been plagued by STIs - prostitution and disease transmission have flourished around military encampments, affecting mission and combat operations [67]. During WWI, for example, 7 million lost duty days were attributed to STIs – this had a detrimental impact on force readiness that led military leaders to enact blame and shame tactics to include punitive actions (e.g., financial penalties for having an STI) that continued into WWII [55, 126]. With the emergence of medical advancements that began in 1945 with the use of antibiotics for gonorrhea and syphilis treatment, the operational impact was greatly reduced and misguided punitive actions were abandoned; however, this ushered in an era of complacency where STI prevention was largely neglected and STIs rebounded [62, 67, 72, 126].

Similar to what has been observed nationally, increasing case rates have been reported in the military; however, a higher percentage increase in CT rates has been observed. Specifically, a 39% increase in CT rates was documented in AC soldiers when comparing 2019 reported rates relative to 2015 rates, whereas the national increase in adults 18-64 during this timeframe was 19%; respective increases in NG rates were similar at 52% and 56% for the respective Army and US adult populations [39, 145]. Crude case rates are substantially higher in the military relative to those reported in the general population [11, 39]. One study found that the elevation remained among Soldiers at Fort Bragg NC (a large Army installation with roughly 40,000 active duty Soldiers assigned each year during the study period – 1985-1996) after adjusting for key

demographic factors; age- and race-adjusted rates examined independently among women and men were determined to be 3 to 6 fold higher for CT and roughly twice as high for NG, depending on the US comparison group [131]. More recently, the US Army Public Health Center (USAPHC) documented that age- and sex-adjusted rates of reported CT cases among Army AC soldiers relative to those reported nationally were roughly two times higher whereas reported NG rates were 17% higher nationally [145]. The differences observed between the two analyses demonstrate substantial epidemiologic changes over the intervening 20+ years.

Among the services, the Army has the highest documented CT and NG infection rates [11]. Specifically, CT incidence rates averaged 2,104 infections per 100,000 person years among Army AC Soldiers from 2011-2019 relative to rates among other service members, which averaged between 1,528 and 1,828 CT infections per 100,000 person years, depending on the service branch [11]. Likewise, NG incidence for the same period was 392 infections per 100,000 person years in the Army relative to 166 to 270 NG infections per 100,000 person years among members from the other services. Additionally, an examination of the incidence of diagnosed infection (etiologic or syndromic) by length of service found CT incidence as high as 3.5 and 0.7 per 100 person-years for women and men respectively, and the corresponding NG incidence was 1.1 and 0.4 per 100 person-years [55].

Studies employing universal screening have detected CT prevalence as high as 9.9% and 5.6% among Army female and male trainees, respectively and NG prevalence at roughly 0.4-1.0% for Army trainees [5, 20, 27, 66, 134]. Another study with repeated testing intervals found a CT acquisition rate of roughly 20% among women within the first 12 months of military service, highlighting the cumulative burden of infection [132]. A study examining four Navy and Marine Corps populations from Jan 1994-Aug 1996 found CT prevalence to be 4.2% [21]. Still

other studies examining clinic populations have found CT prevalence of 7.3% among Army active duty women being evaluated during annual Pap examinations; likewise, CT prevalence among patient volunteers at the Army's Epidemiology and Disease Control clinic at Fort Bragg was found to be 12.3% and NG prevalence was determined to be 4.9% [162].

Risk factors

DEMOGRAPHICS

Age is strongly associated with both CT and NG infections, with the highest rates identified in both national and military populations documented among adolescents and adults under 25 years of age [11, 39, 55, 96]. Nationally, roughly 64% of CT and 70% of NG infections have been reported among individuals 15-24 years old [39]. Higher rates are especially marked among women, particularly adolescent women who are biologically more susceptible due to increased cervical ectopy and therefore availability of cells that are the primary target of infection; however, the reported increased rates are also influenced by enhanced screening in this population given that annual CT/NG screening among sexually active women under 25 is recommended [39, 110, 135, 152]. In 2018, 2.35 million incident CT infections and 853 thousand incident NG infections were estimated among females, compared to 1.62 million and 697 thousand respective infections in males; the difference was most pronounced among 15-24 year-olds among whom a screening bias exists (1.7 million CT and 502 thousand NG infections in 15-24 year-old females versus 910 thousand CT and 277 thousand NG infections in 15-24 year-old males) [96].

Additional demographic predictors of risk include race/ethnicity and geographic residence - significantly higher rates have been frequently observed among minorities (e.g., Black and Hispanic populations) and individuals residing in southern US states [39]. For

instance, a 2014 study of NHANES participants found CT prevalence among Black, non-Hispanics of 5.2% which was 7 times higher than that among White, non-Hispanics; rates were highest among Black non-Hispanic females at 13.5% [139, 140]. The disparity in NG prevalence among study participants was even more pronounced with rates documented during 2010 being roughly 18 times higher among the non-Hispanic Black population [139].

SOCIAL DETERMINANTS

The observed disparity across minority populations is largely influenced by low socioeconomic status and poor access to healthcare which are correlated with increased risk and disproportionately affect these groups. Among socioeconomically disadvantaged young adults 16-24 years of age entering the National Job Training program, for example, the median state-specific CT prevalence was higher than in the general population at 12.5% (state-range: 5.7%-19.3%) in women and 6.6% (state range: 1.0%-13.3%) in men; NG prevalence was 2.2% (state range: 0.4%-7.6%) in women and 0.7% (0.0%-4.8%) in men [34].

Several high-risk sexual networks to include gay and bisexual men, commonly referred to as men who have sex with men (MSM), have also been identified. Among STD clinic patients (another notable high-risk population which also tend to be socioeconomically disadvantaged), rates exceed those in the general population, particularly among MSM patients. In 2018, CT positivity was 16.9% among MSM as compared to 13.8% among men who have sex with women (MSW) and 10.9% among women; the corresponding NG elevation for MSM was more pronounced at 20.5% compared to 9.1% for MSW and 5.4% for women [34].

THE MILITARY AS A HIGH-RISK GROUP

By age alone, the military constitutes a high-risk population due to the sheer preponderance of young adults in the high-risk under 25-year age group. In 2019, roughly 89-

98% of military active component (AC) accessions were under 25 years of age, depending on the service branch (89% Army/Air Force, 90% Navy, and 98% Marines); and due to high rates of attrition, more than half of enlisted AC service members (51.6% in 2020) fall within this age range at any given time [1, 149]. The proportion of soldiers under 25 is roughly three times the proportion estimated among the US adult population 18-64 years of age [147]. The military is also disproportionately represented by male members (e.g., 85% of Army AC soldiers are men), as compared to the US adult population which is relatively equally represented by both men and women across age groups [145, 147, 149, 157]. Although the Bureau of Labor and Statistics shows that the workforce is slightly skewed towards men who made up 53% of the 2019 employed adult population 18 years and over, it pales in comparison to that in the Army [23]. Additionally, the military and the Army, in particular, is more diverse with a larger representation of minority members for whom increased risk has been documented. For example, non-Hispanic Black soldiers make up approximately 21% of the AC soldier population, as compared with roughly 13% of US adults 18-64 years [55, 92]. Overall, demographic factors found to be associated with increased risk for STIs within the military population include enlistment (i.e., non-officers), Black race, Army affiliation, a home of record (i.e., residence at the time of enlistment) in the southern US, and being unmarried [11, 55, 61, 92, 134].

Unique occupational stressors such as a high operational tempo, particularly during contingency operations and deployments, and routine changes in duty stations that occur roughly every two to three years, may also contribute to increased risk as the associated stress can lead to risky behavioral practices such as increased substance use [134]. A study conducted by the Armed Forces Health Surveillance Division (AFHSD) to examine CT rates across the deployment cycle found statistically significant elevated rates in the pre-deployment phase

relative to other phases (post-deployment, deployment, and non-deployment) [134].

Additionally, roughly 10% of military members have extended overseas assignments each year, which could lead to participation in high-risk sexual networks [149]. Elevated rates of reported CT have been documented recently at overseas US Army installations located in the Pacific [145]. The increased case reports have been a concern for installation commanders in this region as is evidenced by a command directed CT screening and STI education program implemented in Korea during 2007-2009. The program which was administered to newly arriving soldiers found overall CT prevalence to be 4.2% with a higher prevalence documented in female soldiers (5.8%) [90].

Universal behavioral risk factors including unprotected sex, anal sex, the number of lifetime or recent sex partners, the rate of partner exchange, and substance use have also been well-documented among military members [67, 126, 135]. For example, the 2015 DoD Health Related Behaviors Survey (HRBS) found that 37% of participating service members reported that they didn't consistently use condoms during sex with only 22% reporting using a condom with their most recent sexual encounter [105]. For context, approximately 24% and 34% of US women and men 15-44 years of age reported condom use during their most recent sexual encounter when surveyed between 2011 and 2015 [49]. Substance use is also common in the military with roughly 30% of HRBS respondents reporting current binge drinking in 2015, which was above the 25% reported nationally among adults over 18; 35% were also determined to engage in hazardous drinking [105]. In reviewing the cumulative data which has demonstrated both a high STI burden and elevated risk factors relative to the general population, the NASEM reached a consensus expert opinion that the US military constitutes a high-risk population [110].

Clinical Features

SIGNS AND SYMPTOMS

The majority of CT and NG infections are asymptomatic. Specifically, 75-80% of women and approximately 85% of men show no symptoms for CT while 70% of women and up to 60% of men show mild or no symptoms of NG [69, 124]. The symptoms of CT and NG often overlap so it is difficult to distinguish between presentations. When symptoms are present, they can affect women and men differently. In women CT and NG infection can produce signs and symptoms of cervicitis (e.g., abnormal vaginal discharge) and urethritis (e.g., burning during urination). Pain during sex and bleeding between menstrual cycles or after sex may also occur with both infections. In men, symptoms of CT and NG infection can include penile discharge, burning during urination, and testicular inflammation. Rectal infections can also cause rectal pain, discharge and bleeding for both men and women [45]. Additionally, NG is associated with more rectal irritation when symptoms are present (e.g. itching, soreness, and painful bowel movements) [39, 69]. Pharyngeal infections can cause pharyngitis and lymphadenitis; however, most are asymptomatic [45].

TRANSMISSION

The asymptomatic nature of CT and NG means that most infections in women and many infections in men go undetected, a characteristic that can facilitate transmission. Extragenital infections can also play an important role in transmission as these infections can be missed because testing is largely based on urogenital specimens; urogenital infections may also spread to extragenital sites such as the rectum even in the absence of rectal sex [58]. Differences in transmission risk and natural clearance have also been observed by anatomic site. For example, studies have found that 9% to 57% of CT infections may clear spontaneously depending on the

site of infection [107]. While less information is available for NG clearance, a recent study estimated a 20.5% clearance among men in the absence of treatment [107].

The time required for clearance can be up to 15 days for NG and considerably longer for CT where the duration of asymptomatic infections prior to clearance in women is estimated to be 1.36 years (95% CI: 1.13-1.63 years) [107, 124]. Persistent infections impose more risk for development of complications and provide a significant window of opportunity to spread infection. The risk of transmitting CT or NG during sexual intercourse is estimated to be 10-34% with higher transmission occurring from men to women [71, 124]. The probability of male to female transmission during intercourse is estimated to be 34% (22-65%) compared to 25% (17-49%) probability of transmission per sex act from women to men [71].

Coinfection with both NG and CT is common. According to a study by Creighton and colleagues, roughly 24% of heterosexual male and 38.5% of female genitourinary clinic patients with NG also had CT while 19% of heterosexual males and 13% of females with CT had NG [51, 99]. Other studies have shown that up to 50% of NG infected high-risk groups (e.g., adolescents and young adults attending STD clinics) are also co-infected with CT [59, 93]. Additionally, reinfection with both CT and NG occurs frequently, but is highly variable depending on the population examined with estimates ranging from 10 to 40% [137]. A systematic review of studies examining reinfection among men estimated overall CT and NG reinfection to be 11.3% and 7.0%, respectively [63]. Studies among US women have found overall reinfection rates of up to 13.9% and 11.7% for respective CT and NG infections [83]. Peak CT reinfection rates of up to 20% were observed within 10 months of initial infection [83, 137]. Studies examining repeat infections in the military have also demonstrated similarly high recurrence. A study among AC military service members from 2010-2014 found 15% and 11%

reinfection rates for CT and NG, respectively [117]. Higher prevalence of repeat infections has been observed among Army service members, among whom recurrent infections have been documented in up to 25% of CT infected female soldiers and roughly 14% of NG infected female and male soldiers [16, 17]. Recurrence is strongly associated with development of complications [16, 17, 124].

DIAGNOSIS AND TREATMENT

Diagnosis is typically based on nucleic acid amplification tests (NAATs) of cervical or vaginal swabs in women, urethral swabs in men, or urine samples. Rectal and pharyngeal swabs are also considered based on administered patient risk assessments and/or presenting symptoms. The NAAT, which is typically administered as a dual assay for both CT and NG, has an estimated sensitivity of 95% and a specificity nearing 100% [40]. Expanded use of the NAAT from 2000-2011, has largely replaced culture or enzyme immunoassays for diagnostic testing, and may partially account for increasing incidence rates given the lower sensitivity of culture (60–80%) [34, 40, 124].

Studies have found variation in case detection based on the anatomic site tested (urogenital, rectal, pharyngeal); therefore, prevalence or burden estimates generated predominately from urogenital testing (common practice) will be further under-estimated. One study conducted among users of an internet-based screening program who submitted specimens for dual rectal and urogenital testing found that 51% of CT or NG infections would have been missed in the absence of extragenital testing [91]. Extragenital testing is primarily limited to high-risk groups such as MSM or individuals reporting anal sex with multiple partners; however, evidence has accumulated that shows a high prevalence of extragenital infection even in the absence of these behaviors [45, 58].

Both CT and NG are treated with antibiotics. The current recommended treatment for CT is doxycycline (100 mg twice a day for 7 days or delayed release 200 mg daily for 7 days) [40]. Alternatively, clinicians may consider Levofloxacin (500 mg daily for 7 days) which has similar efficacy but is more expensive or, if compliance with multi-dose regimens is a concern, they may use Azithromycin (1 g single dose). Although Azithromycin was once considered equally efficacious as doxycycline, it has fallen from favor given the now documented reduced efficacy with rectal infections [32, 40]. Specifically, randomized trials assessing efficacy in treating rectal infections among MSM demonstrated cure rates of 100% with doxycycline compared to 74% for azithromycin. Among women, reduced efficacy in the treatment of rectal CT is also a concern given the high prevalence of rectal infection (33-83%) observed in women with urogenital CT regardless of anorectal sexual activity. However, Azithromycin is considered a safer choice during the 2nd and 3rd trimesters of pregnancy, and a test of cure 3-4 weeks after treatment is recommended to avoid potentially severe sequelae in mothers and infants due to persistent infections [40].

NG treatment has become more challenging due to the rapid development of antibiotic resistance. More than half of NG isolates have been found to be resistant to one or more antibiotics [39]. Due to rising fluoroquinolone-resistant NG, the CDC recommended that use of said antibiotics be halted, which as of 2007, left cephalosporins as the only remaining antimicrobial available for NG treatment. Disturbing increases in cephalosporin resistance continued, which consequently left one recommended treatment regimen when the CDC released treatment guidelines in 2015: dual treatment with Ceftriaxone (250 mg IM, single dose) and Azithromycin (1 g oral, single dose) [32]. Recommendations were again revised in 2021, to transition to a double dose of Ceftriaxone (500 mg IM, single dose) with a secondary antibiotic

course of Doxycycline (100 mg orally twice per day for 7 days) reserved for those also infected with chlamydia - cure rates of >99% (95% CI: 97.6-99.7%) using ceftriaxone have been demonstrated [40].

Because of the frequency of reinfection with both CT and NG, rescreening is recommended three months following treatment [40]. Expedited partner therapy (EPT) by which partners of CT and NG positive patients are treated presumptively is also recommended in tandem with patient treatment to prevent partner transmission and reinfection. The CDC recommends that providers routinely offer EPT to the CT and NG positive patient's sex partners within the prior 60 days of diagnosis; there are some exceptions if prohibited by law or regulations, but the practice is legal in the majority of states [40]. Barriers in the use of EPT have been documented both among patients and healthcare providers. Many people (especially adolescents) opt not to fill the prescription provided and EPT is drastically underutilized by healthcare providers [40]. For example, among surveyed healthcare providers, 30% had misconceptions about the legality and only 37% actually offered EPT [73].

SEQUELAE

Left untreated, CT and NG infections can progress to serious and even fatal complications. Both pathogens have been identified as a causative agent for several reproductive health outcomes which disproportionately affect women, including pelvic inflammatory disease (PID), chronic pelvic pain (CPP), ectopic pregnancy (EP), and tubal factor infertility (TFI) [3, 34, 106, 124, 127, 143]. CT has also been implicated in the development of cervical carcinoma, and two recent independent studies demonstrated associations between CT antibodies and ovarian cancer, with a doubling of risk observed when antibodies for current and prior CT were present [101, 142]. Additionally, CT and NG infections during pregnancy can lead to adverse

birth outcomes such as premature birth, low birth weight, spontaneous abortion, and neonatal infections which can result in conjunctivitis, blindness, pharyngitis, arthritis, and pneumonia [69, 87, 124]. In men, untreated CT and NG infections also cause inflammatory syndromes such as epididymitis, prostatitis, and proctitis which can lead to chronic scrotal pain [69, 86, 103, 133]. CT can also directly affect sperm production and there is growing evidence of CT associated infertility in males [109].

Furthermore, both CT and NG can facilitate HIV transmission; studies have demonstrated a 3-4-fold increased risk of HIV associated with infection [40, 87, 101]. Both women and men are also susceptible to develop sexually acquired reactive arthritis (SARA) as a complication within one to four weeks of infection [26, 57]. Up to 67% and 16% of SARA cases have been shown to be preceded by CT and NG, respectively, and the overall estimated incidence of SARA among CT positive study participants has ranged from 3% to 8.1% [26, 57]. Additionally, 0.5-3% of individuals infected with NG may develop disseminated gonococcal infection whereby the pathogen invades the bloodstream and spreads to other body sites, leading to complications such as septic arthritis and bacteremia [69].

Among the documented sequelae, PID is of particular concern because of the high morbidity burden attributable directly to PID and complications such as CPP, EP, and TFI for which PID is a necessary biological precursor. The disease is often asymptomatic or causes mild symptoms which may have a non-specific presentation (e.g., nausea, urinary frequency and abdominal pain) [95, 124]. This is compounded by the lack of a gold standard diagnostic test – thus diagnosis is challenging and the imprecision further complicates surveillance and the ascertainment of disease burden [16, 22]. Among National Health and Nutrition Examination Survey (NHANES) participants during 2015-2017, prevalence of self-reported PID in women

18-44 was estimated to be 3.6% (95% CI: 2.9%-4.5%), indicating that at the national level, 2.1-2.4 million (95% CI: 1.8-3.2 million) had a PID diagnosis in their lifetime [95]. Other studies have identified lifetime PID prevalence among US women as high as 8% [75]. These estimates, however, are likely conservative given that many cases of PID go unrecognized or diagnosed.

The likelihood of developing downstream sequelae such as EP or TFI and the severity of these outcomes have been shown to increase multiplicatively with the number of PID episodes. Approximately 36% (95% CI: 26%-48%) of women with PID are diagnosed with related reproductive tract damage, and it is estimated that an additional 12.5% (95% CI: 4%-25%) develop undiagnosed, asymptomatic complications [124].

Estimates of the proportion of PID cases associated with CT and NG infections has been highly variable depending on the population, testing/diagnostic techniques, and outcomes evaluated (e.g., overt vs subclinical PID cases; concurrent positive CT/NG lab tests vs CT/NG biomarkers vs prior CT/NG diagnoses). While more recent studies among symptomatic PID patients found CT/NG to be associated with 25% to 33% of PID cases, other studies report associations as high as 85% [81, 87, 108]. The estimated probability for CT infections progressing to PID have ranged from 10-40% [75, 78, 87, 124]. Taken collectively, Price et al, estimated that 17% of CT infections progressed to PID (95% CI 5.6%-28.9%) [124]. Increased severity of PID has been observed following NG infections as compared to CT [127].

The risk of developing PID has been shown to increase with repeat CT and NG infections. For example, a study among Army women, found that with each subsequent diagnosis of CT, the risk of developing PID increased by 28% (95% CI: 19%-38%) [16]. Another study examining CT laboratory tests among nearly 900,000 UK women 11-25 years of age found an increased hazard ratio (HR) with each subsequent positive test relative to women with negative

tests – demonstrating an increase from an age-adjusted HR for PID development of 3.4 (95% CI: 1.4-8.2) with a single CT infection to a HR of 4.8 (95% CI: 1.9-12.2) with 2 infections, and to 5.2 (95% CI: 1.8-15.3) with 3 or more infections [56].

CPP, which is defined as non-menstrual pain of 6 months or more duration that is severe enough to cause functional disability or require medical or surgical treatment, is a well-recognized complication of PID. In the PID Evaluation and Clinical Health (PEACH) trial, CPP developed in roughly 32% of participants [108]. Overall, CPP is common in women, with an estimated prevalence of 3.8% among US women 15–73 years of age [124].

EP rates reported in the US general and military populations have remained stable at <1% of total pregnancies annually [6, 108, 124]. Multiple longitudinal studies have found elevated risk for developing EP following a CT infection with relative risks ranging between 1.26 and 1.82 [127]. Among women 16–44 years, the proportion of EP that is attributable to CT is estimated to be 4.9% (95% CI 1.2% to 12%), and for every 1,000 CT infections in women 16–44 years, there are on average 2.0 EPs by age 44 [124].

Worldwide, an estimated 5%-15% of women of reproductive age (16-44 years) are infertile, as defined by the inability to conceive for 1 or more years [121, 124]. The PEACH trial documented infertility in 18% of participants with PID [108]. TFI, one of several forms of female infertility, is most associated with CT-related PID. According to a survey of patients undergoing in vitro fertilization, approximately 22% had TFI and another 30% had unexplained infertility; among women 16–44 years of age, 29% (95% CI: 9% to 56%) of TFI was estimated to be attributable to CT [124]. Another study found increased risk of TFI due to CT that ranged from 1.31 to 1.37 – notably the authors concluded that NG was less likely than CT to increase

risk of the long-term sequelae (i.e., EP and TFI) despite increasing the severity of PID episodes [127].

Collectively, these sequelae contribute to a high morbidity burden. In 2016, a panel from the Global Burden of Disease (GBD) study estimated the disability adjusted life years (DALY) attributed to CT to be 562,400 (95% CI: 350,300–851,100), and that attributed to NG to be 675,200 (95% CI: 467,700–974,900) [68]. Age-standardized DALY rates per 100,000 for CT and NG for 2016 were estimated to be 7.3 (95% CI: 4.8–11.0) and 8.8 (95% CI: 6.1–12.7), respectively [68]. A Netherlands study examining DALYs attributed to 32 infectious diseases, including CT and NG, estimated a relatively high CT burden, second only to HIV among the STIs examined; the authors determined the disease burden was primarily driven by infertility among women [158].

STI Surveillance

The CDC defines public health surveillance as, “the ongoing, systematic collection, analysis, and interpretation of health-related data essential to planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those responsible for prevention and control” [31]. It is a critical component of public health which facilitates detection and response to emerging issues and supports targeting of prevention efforts as well as the subsequent evaluation of their effectiveness. In practice, surveillance takes two main forms: passive surveillance and active surveillance. Sentinel and specialized surveillance such as syndromic surveillance are also commonly used and can be either active or passive – both are usually designed to obtain information that is not generally available to health departments [28].

The NASEM highlights surveillance gaps in STI surveillance in their report ‘Sexually Transmitted Infections: Adopting a National Sexual Health Paradigm’ [110]. They cite conflicting trends observed when comparing national reporting to sampling data and expound upon the potential biases and weaknesses of several surveillance efforts. They further call for a modernization of surveillance that better integrates data captured from fragmented systems to get a more complete and timelier picture of infection trends which can inform prevention and control.

PASSIVE SURVEILLANCE

Passive surveillance relies on existing health systems (e.g., medical claims data systems) which are often de-centralized and administrative in nature. Data collected are subject to inconsistent reporting practices from healthcare providers across hospitals, health departments, etc. as well as constraints imposed for reporting or data sharing/extraction within and between authorized jurisdictions. Therefore, the completeness, quality, and timeliness of data are variable and challenging to control [31, 116].

The National Notifiable Disease Surveillance System (NNDSS), managed by the CDC is one example of a passive surveillance system that is used extensively for monitoring CT and NG, both of which have had reporting mandates since 1995 and 1944, respectively [34, 39, 43]. Data are accessible in aggregate by a few key demographic factors (e.g., age, sex, and county) through the CDC’s National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) Atlas Plus [42]. The available CT data are also routinely used by public health organizations such as the United Health Foundation’s ‘America’s Health Rankings’ and the University of Wisconsin Population Health Institute’s ‘County Health Rankings’ in order to assess community level STI burden [154, 156].

The military's Disease Reporting System internet (DRSi) is the DoD's passive surveillance system equivalent to the NNDSS – it is used for tracking national notifiable conditions including CT and NG among military health system (MHS) beneficiaries using case definitions that are adapted from those used by the CDC [11, 145]. MHS providers are also required to report these conditions to their civilian counterparts in the local health department for submission through the NNDSS and to facilitate a coordinated response that may involve partner notification and outreach. As has been done nationally, the CT case report data are used to monitor burden within Army communities (i.e., installations) [145, 154, 155].

Under-reporting can be problematic given that these systems operate downstream from patient care that predominantly focuses on diagnosis and treatment of symptomatic patients. Outside influences such as the availability of testing resources, public awareness, and local public health priorities can affect the timeliness and completeness of reporting. For example, even though chlamydia became a notifiable condition in 1995, it was not reported by all 50 states and Washington DC until 2000 [39]. Additionally, changes in surveillance case definitions, and advancements in surveillance technology and diagnostic tests can impact case detection. These limitations can make it difficult to get an accurate depiction of true disease burden and changes over time [38]. The degree to which under-reporting is present is uncertain and highly variable across reporting channels.

Administrative data systems such as those that collect medical claims and laboratory orders are also used in passive surveillance for a variety of health outcomes including CT and NG. Such systems are subject to similar limitations as those outlined above, and diagnostic coding practices can inject additional variability and uncertainty. A recent review of administrative data that included diagnoses and laboratory results for 3.1 million enrollees

determined that the use of diagnosis codes for detecting lab confirmed CT and NG substantially underestimated the disease burden; the sensitivity for detecting CT and NG was 6.5% and 25.4% respectively while the specificity for detecting both infections was over 99.5% [102]. Additionally, access to these systems is often the rate limiting step that prevents widespread population-based surveillance as the systems are often specific to a confined network of healthcare providers.

ACTIVE SURVEILLANCE

Active surveillance is more accurate and timely than passive surveillance; however, it is more resource intensive, requiring staff outreach to collect the necessary data from healthcare providers or members of the population of interest [116]. Due to the more intensive resource requirements, active surveillance is typically very narrowly prescribed to targeted populations. Active surveillance programs or studies are often based on convenience sampling of patient populations or closed high-risk groups such as university students, prisoners, commercial sex workers and military members. Population-based studies designed to reach representative demographic sections of the community may also be implemented and may include universal screening to enrolled participants. The drawback of these forms of active surveillance is that it can be difficult to generalize the findings to the US population.

National surveys such as the NHANES and those used for the Behavioral Risk Factor Surveillance System (BRFSS), which have been used in numerous STI studies, incorporate representative sampling techniques which improve generalizability for non-institutionalized populations, but small sample sizes and potential sampling bias remain a limitation and it is not possible to tease out information for populations of interest such as military personnel [139, 140]. Another limitation is that the NHANES no longer conducts NG testing [110]. In the

absence of laboratory tests and medical records, surveys bear the added critique that they rely on self-reported accounts of infection or diagnoses and thus are susceptible to recall bias and it is often more difficult to distinguish the temporality between the exposure and the outcome [97, 110, 120].

SENTINEL SURVEILLANCE

Since reporting is widely recognized as yielding conservative estimates, the CDC's annual STD surveillance reports include data received from geographically diverse sentinel surveillance sites such as STD clinics and the National Job Corps which service high-risk populations [39]. Surveillance may be passive when access to existing information systems is granted or active if more extensive data collection is required. The STD Surveillance Network (SSuN) is one example where active data collection occurs, currently from 11 competitively funded state, city and county health departments that implement enhanced surveillance on a random sample of reported cases [35, 50]. The Gonococcal Isolate Surveillance Project (GISP) is yet another example which operates in 27 STD clinics; it provides testing for men with gonococcal urethritis, and also aids in monitoring trends in NG antimicrobial resistance and determining national treatment recommendations and research/prevention priorities [74].

Sentinel surveillance has proven to be timelier and more responsive in identifying and addressing emerging issues with findings informing prevention and treatment actions for CT and NG; however, the findings may not be generalizable given differing population and risk profiles for those evaluated relative to the general population. Patient symptomatology may also differ in these settings. For instance only 10% of men seen in STD clinics have been asymptomatic for NG compared to the nearly 60% in the general population who either have no symptoms or mild symptoms [69].

SYNDROMIC SURVEILLANCE

Syndromic surveillance is typically passive and relies on a network of administrative data (e.g., medical claims, laboratory orders, case reports, and pharmacy scripts) received on a near-real time basis (usually within 24 hours of the patient visit). The goal is to identify potential disease clusters, outbreaks, or other emerging issues of concern early in the process (before a diagnosis) to facilitate rapid response. Nationally, syndromic surveillance evolved from the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, and it is conducted through collaborative electronic record submissions from emergency departments, urgent/ambulatory care clinics, hospitals, and laboratories using a shared platform called BioSense [37]. In 2014, the CDC National Syndromic Surveillance Program (NSSP) which manages BioSense, adopted ESSENCE (Electronic Surveillance System for the Early Notification of Community-based Epidemics) as the standard analytic surveillance and visualization tool for the platform. ESSENCE was developed by the Walter Reed Army Institute for Research and Johns Hopkins University Applied Physics Lab in 1999 [24].

The system initially was limited to medical encounter data with ICD-coded diagnoses categorized into syndrome groups such as influenza-like illness and gastrointestinal disorders as well as a select number of reportable medical events (RME). System functionality has greatly improved over the years as more data sources have been incorporated and a growing network of data users have collaborated to share data and build customizable query tools to include machine learning techniques which evaluate text entries (e.g., patients' chief complaint). Not only has it proven useful in monitoring emerging events such as the COVID-19 pandemic, but users have been able to leverage the data to study non-communicable disease outcomes such as injury-related diagnoses, opioid use, and vaping. Although ESSENCE has developed mechanisms to

monitor CT and NG infections through multiple sources, it is primarily used as a local public health resource and has not been used to conduct a comprehensive population-based burden assessment.

Other innovative strategies to use social media searches for “STD symptoms” to predict potential STI outbreaks have also been explored. A study using such a strategy to determine the ability of such a symptom search to predict STIs including CT and NG in Chicago from 2011-2017 found the searches to be highly correlated for both CT ($r=0.90$) and NG ($r=0.94$) during 2012-2017 [89].

SCREENING BIAS

Burden estimates generated from surveillance activities are influenced by screening programs; therefore, understanding the contribution and potential biases introduced is an important consideration when interpreting the data. Screening is a cornerstone of CT and NG prevention given that the majority of infections do not produce symptoms which might prompt one to seek treatment. Because adolescents and adults under 25 comprise the majority of infections, and women are disproportionately affected from potential reproductive sequelae, the US Preventive Services Task Force (USPSTF) and the CDC recommend routine CT and NG screening for sexually active women under 25 years and pregnant women, with additional screening based on risk [152]. In general, studies have found screening programs to be cost effective among women when the underlying prevalence is at least 3.1% and the benefit of annual screening for sexually active women under 25 has repeatedly been ranked by the National Commission of Prevention Priorities as one of the 10 most beneficial and cost effective prevention services in the US [76, 100]. Targeted screening within high-risk populations to include the Army’s initial entry trainees has also been shown to be cost-effective, primarily from

the societal perspective [84, 85, 114]. And statistically significant decreased incidence of PID has been documented among Navy accessions who received screening during training relative to Army accessions who did not [18].

Annual screening of women under 25 years is recognized as a leading health indicator by the National Committee for Quality Assurance (NCQA) which has tracked adherence to the recommendation since 1999 as one of several Healthcare Effectiveness Data and Information Set (HEDIS) clinical performance metrics [111]. Nationally, approximately 47-58% of women 16-24 years of age met the annual screening target in 2019, with compliance varying by the civilian health insurer [111]. While national screening coverage has been steadily increasing, it pales in comparison to that achieved under the unified military health system; 2019 annual CT and NG screening coverage for AC women under 25 across Army installations was estimated to be between 62-95% with approximately 82% of Army women screened on average [141, 145]. While the Army performs relatively well in terms of screening compliance as tracked through this HEDIS metric, it is currently the only service not providing supplemental universal screening for female initial entry trainees – such screening was implemented in Air Force, Navy, and Marine Corps training sites by 2008 [55, 104].

The increased demand for screening, particularly among selected at-risk groups, as well as the considerable variation in implementation across population sectors provide important context when interpreting trends in infection. When comparing rates between populations or demographic groups it is important to take these potential screening biases into account.

Research Proposal

Elevated CT and NG rates have been documented among military members (most notably those in the Army) relative to the general population, leading public health authorities to

designate the military as a high-priority population for whom enhanced STI surveillance and prevention measures are warranted. However, the relative disease burden within the Army has not been adequately examined, and studies that evaluate the capability of existing surveillance systems to inform such an assessment are lacking. The proposed studies described herein address these knowledge gaps by: 1) comparing reported CT and NG case rates between Army AC Soldiers and US adult demographic peer groups while controlling for influential demographic factors (Aim 1); 2) assessing morbidity burden for CT and NG cases identified through an enhanced surveillance database comprised of multi-sourced data (Aim 2); and 3) examining gaps in CT and NG case detection across surveillance systems (Aim 3).

Prior to the Aim 1 work completed, the last published study to explore differences in standardized rates between a military population and their civilian counterparts, was conducted more than two decades ago when Seña and colleagues examined rate differences between Soldiers at Fort Bragg, NC and residents within the state and the US as a whole [131]. The proposed assessment contributes to the literature by expanding the analyses to the entire Army population during a period that better reflects the changing epidemiology of CT and NG infections. The work conducted also addresses methodologic limitations of the prior study by ensuring that comparable case definitions and data sources are utilized. Specifically, cases identified through similar reporting system databases (military and national) will be compared as opposed to comparing military cases identified from clinical data to nationally reported cases as was previously done. While the Army has periodically introduced standardized rate comparisons into annual reporting, the findings are relatively brief and can benefit from the more detailed analyses described herein, which include an exploration of population differences that may contribute to rate discrepancies (e.g., screening).

Aim 2, builds on the findings from Aim 1 by augmenting case reports with medical encounter and laboratory records to improve Army burden assessments and risk characterization. These data sources were only recently consolidated within the DoD in 2019, for annual STI reports, and prior to the work described, no such assessment had been published that was specific to the Army. Additionally, burden parameters such as estimated medical encounters for CT and NG diagnoses within this population are lacking. Current estimates are not specific to the Army and are grossly underestimated as they are limited to diagnosed infections [9, 14]. The analyses performed address this weakness to provide a more accurate depiction of disease burden. Furthermore, the findings may inform public health surveillance enhancements by offering a framework for standardizing service-specific surveillance and reporting. A practical application of surveillance for this population subset of Army service members (as opposed to an aggregated DoD view) may offer insights into the nuances of disease transmission and support prevention efforts that may be best understood and implemented at these tactical levels.

Aim 3 expands on the data consolidation performed for Aim 2 by evaluating CT and NG case identification across the three data systems to examine respective surveillance contributions. Prior to this work, there were no systems-based assessments of CT/NG case ascertainment within the Army or the larger DoD community using the three surveillance systems examined. The MHS is uniquely positioned to provide a mechanism for such an evaluation given the existence of readily available, centralized databases for capturing inpatient and outpatient medical claims from both MHS and civilian network providers as well as MHS laboratory orders and case reports. The proposed work is not only novel, but also provides a means to quantify overall and site-specific limitations encountered with burden estimation such as under-reporting. Additionally, these findings may be more broadly applicable to other population assessments

which incorporate these types of uncertainty estimates into predictive and economic models to improve burden approximation.

Collectively, the proposed studies address long standing knowledge gaps. They provide a sound basis from which to contextualize CT and NG disease burden experienced in the Army relative to a similar cohort of US adults. Additionally, the more rigorous analyses accomplished by using an enhanced three-source database provides a more complete estimation of disease burden and associated risk factors while also offering a platform to more effectively explore surveillance practices, prioritize needs, and to develop and evaluate targeted prevention efforts. Furthermore, it addresses recommendations from leading public health authorities to enhance STI surveillance, particularly among priority populations such as US military service members. Equipped with a more accurate accounting of disease burden as well as a better understanding of surveillance capabilities, Army public health leaders will be better positioned to advocate for the resources needed to combat CT, NG, and associated sequelae, and to also address deficiencies identified.

CHAPTER 2: METHODS

Aim 1

SPECIFIC AIM

Assess reported CT and NG case rates, trends in incidence density, and associated risk factors among US Army AC Soldiers relative to US demographic peer-groups.

Objective 1. Describe population demographics and incident CT and NG cases reported among Army AC soldiers and US demographic peer groups (i.e., Adults 18-64 years of age).

- a. Describe distribution of and trends in population-specific demographics.
- b. Assess the frequency, distribution, and rate of incident CT and NG cases reported by demographic strata.

Objective 2. Compare trends in reported CT and NG case rates between the two populations.

- a. Compare crude and age-sex-adjusted case rates.
- b. Evaluate statistical differences in observed case rates and annual trends.

Objective 3. Assess risk factors associated with reported CT and NG cases within the two populations.

- a. Evaluate statistical associations between independent variables (i.e., age, sex, race-ethnicity, and reporting geographic region categories) and case rates (CT or NG) within the Army cohort.
- b. Evaluate statistical associations between independent variables (i.e., age and sex categories) and case rates (CT or NG) within the US adult cohort.

Hypotheses: Empirical evidence supports the hypothesis that:

- 1) Reported case rates for both CT and NG will be elevated among Army soldiers relative to US demographic peer groups;
- 2) Standardization of case rates by age and sex will minimize the risk difference between the two cohorts;
- 3) Age-sex-adjusted CT and NG case rates among Army soldiers will remain elevated relative to those reported nationally; and
- 4) Risk factors among Army AC soldiers will be consistent with those documented in the literature (e.g., elevated rates among women, younger adults, racial/ethnic minority populations [e.g., Black, American Indian/Alaskan Native, and Hispanic], and geographic regions [e.g., Southern US]).

STUDY DESIGN AND STUDY POPULATION

A retrospective cohort study design was used to assess CT and NG cases reported among US AC soldiers and US demographic peer groups over a five-year timeframe (calendar years 2015-2019). The study population consisted of US Army AC soldiers and trainees who were in service at any point during calendar years 2015 to 2019. The restriction to AC soldiers was necessary due to the incomplete capture of patient care among Army National Guard and Reserve component soldiers who are only eligible for MHS care for brief periods of time when activated. US adults 18-64 years of age were also evaluated over the same time frame; this age range was selected as a reasonable approximation of average working age adults. Of note, AC soldiers comprise roughly 0.2% of the US adult population in this age group [147, 149].

DATA SOURCES

Grouped data (case reports and population data) for Army AC soldiers were obtained from the USAPHC. The data were processed according to USAPHC business rules established

for medical metric summaries, inclusive of CT, for the Center’s annual ‘*Health of the Force*’ report [145]. Although the report specifically focuses on CT, the Center also processes NG data in tandem with the CT analyses using these rules; therefore, grouped NG data were also obtained. Data rules for processing and aggregating the data entailed linkage of DRSi case records for CT and NG with Defense Manpower Data Center (DMDC) personnel records furnished by the Army Analytics Group (AAG) to validate affiliation with the Army AC and to assimilate necessary demographic information [113, 150]. Case records which could not be validated in this manner were removed as were all records (numerator and denominator) when the soldier’s unit zip code was not included in the designated installation look-up tables. Similarly grouped national data were retrieved from the CDC’s annual STD surveillance reports and Atlas Plus dashboard which pairs NNDSS case reports with US census data [39, 42, 43, 147]. Both the DMDC and Census data were used to calculate person-time at risk for respective Army and US rate computations. Descriptions of the data sources which correspond with the supported research aims are provided in **Table 1**.

MEASUREMENT

Primary Outcomes:

- Reported CT case rates, crude = New confirmed CT cases reported/100,000 person-years
- Reported NG case rates, crude = New confirmed NG cases reported/100,000 person-years
- Reported CT case rates, age-sex adjusted = $\sum (IR_{CT1} * W_{s1} + \dots + IR_{CTn} * W_{Sn})$

Where:

IR_{CT1} = CT incidence rate for the first age-sex stratum...up to the nth stratum

W_{S1} = Standard weight applied to first age-sex stratum...up to the nth stratum

Weights ($W_{S1} \dots W_{Sn}$) based on 2015 Army age and sex distribution

- Reported NG case rates, age-sex adjusted = $\sum (IR_{NG1} * W_{S1} + \dots + IR_{NGn} * W_{Sn})$

Where:

IR_{NG1} = NG incidence rate for the first age-sex stratum...up to the nth stratum

W_{S1} = Standard weight applied to first age-sex stratum...up to the nth stratum

Weights ($W_{S1} \dots W_{Sn}$) based on 2015 Army age and sex distribution

Cases:

Confirmed CT and NG cases submitted through the case reporting systems of record for the Army and the US (DRSi and NNDSS respectively) were included in the analysis [43, 113]. Although military healthcare providers are required to report cases through both DRSi and local or state health departments for submission to NNDSS, compliance with this standard is unknown and civilian healthcare providers have no mandate to notify military preventive medicine departments when cases are reported among military members. Both systems, however, use comparable case definitions, and healthcare providers are responsible for ensuring that established case criteria are met when reporting [10, 41]. System specific reporting criteria for confirmed cases are provided in **Table 2**.

Case processing was executed by the data management agencies (USAPHC and CDC) prior to the data extraction. For the Army, this entailed application of incidence rules per published surveillance case definitions which exclude duplicative and probable episodic case reports (i.e., reports with case onset dates within 30 days of a prior reported case onset) [8]. Additionally, cases which could not be verified as an AC soldier within a 90-day window of the case onset date were excluded – Army AC assignment was validated using monthly extracts of DMDC personnel data with information on the most closely matched DMDC record retained in

the analyses [113, 150]. Similar methodologic processes were implemented when producing the aggregated case counts for the national cohort of US adults 18-64 years-old, whereby only new or first reported cases and those reported more than 30 days from a prior infection were included [30, 36, 39].

Person time at risk:

Army denominator estimates were also pre-processed for demographic stratum of interest by USAPHC data analysts prior to extraction for use in Aim 1 analyses. Person-years at risk were derived from DMDC data based on aggregation of monthly record entries (thereby converting person-months to person-years); estimates excluded monthly records that could not be linked to a zip code used for regional surveillance [150]. Corresponding national population estimates for US adults 18-64 years of age were obtained from US Census data used for national rate computations; because data were aggregated by year (instead of months), a full person-year at risk was applied per capita [147].

Risk Analyses:

Given that the data sources were already aggregated for annual surveillance reports, demographic information was limited to shared variables deemed to be sufficiently complete and reliable (i.e., Army reported age categories [18-24, 25-34, 35-44, and 45-64] and sex). Although race/ethnicity was too incomplete to use for national data, it was available and relatively complete for Army data and assessed in the Army-specific analyses. Race/ethnicity groups were defined according to the Office of Management and Budget approved categories (i.e., Hispanic and Non-Hispanic racial groups: Black, White, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, and Asian) [145]. Army data were also analyzed by the soldier's assigned duty location (state/country and US census regions).

STATISTICAL ANALYSIS

Sample Size and Power Considerations:

Approximately 461,000 AC Soldiers and 200.5 million US adults 18-64 years of age comprised the annual populations evaluated during 2015-2019 [145, 147]. Corresponding annual reported cases were estimated to be approximately 10,000 CT and 1600 NG cases per year among AC Soldiers and 1.5 million CT cases and 486,000 NG cases among US adults 18-64 [39, 145]. Study populations this large which experience frequent occurrences of the outcome under study typically yield a high degree of statistical power as the number included often exceed recommended sample sizes to detect significant within and between group differences.

To evaluate differences between the Army AC cohort (exposed group) and the US adult population 18-64 years of age (unexposed group), a sample size of approximately 568,000 is needed to detect a 2-fold difference in CT case rates (1,303 Army AC soldiers and 566,694 US adults) in order to achieve 80% power with a two-sided significance level of 95%. A sample size of roughly 1.8 million is needed to detect a 2-fold difference in NG case rates between the two groups (4,171 Army AC, and 1,814,322 US adults) with 80% power and a 95% level of statistical significance.

These computations factored in a 435-fold order of magnitude in terms of sample size differences between the 2 populations. The calculation was also based on an estimated proportion of reported CT among the unexposed US cohort of 0.75 per 100 person-years, and an estimated proportion of reported NG among the unexposed US cohort of 0.24 per 100 person-years. Reported case rates and population estimates for the 5 year time frame under study (2015-2019) were used to derive these estimates [39, 145, 147]. OpenEpi, an open source application which includes power and sample size calculators for various study designs including cohort

studies, was used to perform the computations as noted in **Table 3** [52]. The results indicate that the study populations greatly exceed recommended sample size requirements even with higher power specifications of 90%, and thus the study has sufficient precision to estimate incidence rate differences between the groups being compared.

Sample sizes needed to explore group differences within the Army were also examined, comparing female and male soldiers. Applying the same specifications and sample size estimation techniques to reported case rate and population data furnished for Aim 1, it was determined that 5,117 AC soldiers (731 females and 4,386 males) were needed to achieve 80% power to detect a two-fold difference in reported CT rates, whereas 45,364 AC soldiers (6,481 females and 38,883 males) were needed for NG rate assessments (**Table 4**). The results demonstrate that sufficient sample sizes were met (even at 90% power) to reliably compare incidence rate differences between these groups. Some loss of power (and statistical significance) is expected when evaluating differences between smaller subsets of the population (data not shown).

Descriptive and Inferential statistics:

Statistical analyses (descriptive and inferential) were performed using IBM SPSS Statistics version 26.0, Microsoft 365 Excel, and OpenEpi version 3.0 software [52, 88]. Descriptive analyses entailed examining the frequency and relative distribution of new CT and NG cases reported in the study populations by demographic strata. Annual case rates per 100,000 person-years at risk were also evaluated to examine trends in incidence density between the two cohorts - Army AC soldiers and US adults 18-64 years old. Crude case rates were assessed independently for CT and NG.

Army and civilian case rates were adjusted by age and sex through direct standardization with the 2015 US Army population distribution selected as the common population standard. The standard was chosen based on consensus recommendations from subject matter experts who found that the Army standard was preferable to US census standards because it avoided assigning extremely large weights to sparsely populated subgroups in the Army which is highly skewed towards young males; they recommended calendar year 2015 as the standard (as opposed to an earlier period) because it was the first year that women were eligible to serve for all military occupations [159].

Inferential statistics such as chi-square tests for linear trend, incidence rate ratios (IRR), and 95% confidence intervals (CI) were generated to examine the statistical significance of the observed trends and differences in rates within groups and between study populations. The Goodness of fit (GOF) R^2 statistic generated from MS Excel linear trendlines was used to examine the significance and fit of annual trends. The Byar approximation of the exact method as implemented through the OpenEpi module was used to calculate unadjusted IRRs and CIs [52, 129, 138].

Multivariate analyses using generalized linear models (GLMs) examined differences in IRRs which were adjusted for independent variables such as age and sex. Because the dependent variables being evaluated in the models represented discrete count data (i.e., number of new CT infections or number of new NG infections) which were grouped over time and assessed as rates, GLMs with Poisson (log-linear) and Negative Binomial probability distributions with a person-time offset were deemed appropriate for multivariate analyses [25, 80, 94]. Univariate and multivariate analyses were analyzed for CT and NG cases, separately. Analyses for the Army

cohort were more extensive, with independent variables inclusive of race-ethnicity and geographic reporting region data which were not sufficiently available for the US cohort.

Both the Poisson and Negative Binomial GLMs assessed incorporated a log-link function. The primary difference between the 2 model types is that the Poisson distribution assumes that the mean and variance of the dependent or response variable are equal, whereas the Negative Binomial model includes a parameter that adjusts for variance from the mean [64, 79]. The data were assessed for dispersion indicative of excess variance (overdispersion) or its counterpart, under dispersion, to inform model selection as dispersed data (particularly the more common over-dispersed data) are better suited for Negative Binomial regression.

GOF statistics, namely Pearson chi-square residuals, Akaike's information criteria (AIC), and Bayesian information criteria (BIC), were examined to select the final model. Lower AIC and BIC results are indicative of a better model fit as are ratios of Pearson chi-square residuals relative to the degrees of freedom that are close to 1.0 which are considered ideal by GOF standards (values up to 2.5 are considered adequate) [25, 94]. For all models evaluated, two-sided 95% confidence intervals (CI) and p-values were generated for each non-referent coefficient in the model; CIs not inclusive of 1.0 and p-values with $\alpha < 0.05$ were considered statistically significant.

Aim 2

SPECIFIC AIM

Estimate CT and NG morbidity burden for Army AC soldiers using multi-sourced data that integrates medical encounter and laboratory records with case report data used in routine surveillance and described in Aim 1.

Objective 1. Describe population and case characteristics for CT and NG cases identified among Army AC soldiers.

- a. Assess population- and case-specific characteristics (individually for CT and NG cases and collectively for individuals with either infection).
- b. Assess the frequency, distribution, incidence, and prevalence of CT and NG cases.
- c. Assess frequency of recurrent and concurrent infections.

Objective 2. Estimate morbidity burden among AC soldiers for CT and NG independently and collectively.

- a. Estimate annual medical encounters for CT and/or NG infections.
- b. Determine the number of individuals affected by CT and/or NG.
- c. Evaluate annual trends for the morbidity burden metrics examined (i.e., medical encounters and individuals affected).

Objective 3. Assess determinants (risk factors) of documented CT and NG cases.

- a. Evaluate statistical associations between independent variables (e.g., age, sex, race-ethnicity, marital status, education level, and geographic region [home of record; duty assignment]) and incidence rates.
- b. Identify statistically significant predictors of risk for recurrent infection.

Hypotheses: Empirical evidence supports the hypothesis that:

- 1) Trends and correlates of infection will be consistent with those observed through reported case rates;
- 2) High reinfection rates (>10%) will be observed;
- 3) Morbidity burden estimates generated will exceed those currently available; and
- 4) Risk factors for infection (new or recurrent) will include those documented in prior publications (e.g., elevated rates among women, younger adults, and certain minority populations [e.g., Black, American Indian/Alaskan Native, and Hispanic]).

STUDY DESIGN AND STUDY POPULATION

Similar to Aim 1 analyses, a retrospective cohort study design was used to examine CT and NG burden among Army AC soldiers including trainees who were in active service at any point during calendar years 2015 to 2019. However, unlike Aim 1 analyses, which were limited to aggregated case report data, the Aim 2 study was based on integration of individual (person-level) case report data with similarly granular person-level MHS medical encounter and laboratory records with a documented CT or NG diagnosis or positive test result. At this level of detail, CT and NG could be examined both independently and concurrently with repeat and dual infections evaluated. Morbidity burden parameters (medical encounters and individuals affected) used in annual DoD reporting were also generated independently for each outcome [14]. Person-level DMDC data furnished by USAPHC were also used, which allowed inclusion of pertinent demographic information not available in the grouped data (e.g., marital status, education level, and assigned duty location).

DATA SOURCES

Three MHS databases as described in **Table 1** were used to identify CT and NG cases: DRSi case reports, M2 outpatient medical encounter data, and HL7 chemistry and microbiology laboratory databases. These databases contained common protected health information (PHI) such as SSNs which were used for linking case files with DMDC personnel records to obtain consistent and reliable demographic information and to determine person time at risk for incidence rate computations. Key variables from the databases that were used in the analyses are provided in **Table 5**. HL7 laboratory data were furnished by the NMCPHC while other datasets were furnished by the USAPHC. PHI data were safeguarded per established USAPHC data handling procedures described in **Appendix A**.

MEASUREMENT

Primary outcomes

- Incidence Rates (CT; NG; Either):
 - New confirmed CT cases/100,000 person-years
 - New confirmed NG cases/100,000 person-years
 - New confirmed CT or NG cases/100,000 person-years
- Prevalence Rates (CT; NG):
 - Proportion of AC soldiers with one or more CT infections
 - Proportion of AC soldier with one or more NG infections
- Recurrent Infections (CT; NG):
 - Proportion of new CT infections that are repeat infections (i.e., occurring >30 days from a prior documented infection)

- Proportion of new NG infections that are repeat infections (i.e., occurring >30 days from a prior documented infection)
- Concurrent Infection
 - Proportion of new infections that are dual or concurrent with both CT and NG documented within 30 days of each other
- Medical encounters
 - Average outpatient medical encounters per diagnosed individual (CT; NG)
 - Total outpatient medical encounters (CT; NG; Either):
 - $\text{Total CT encounters} = \text{Average CT medical encounters per diagnosed individual} * \text{Total individuals affected by CT}$
 - $\text{Total NG encounters} = \text{Average NG medical encounters per diagnosed individual} * \text{Total NG individuals affected by NG}$
 - $\text{Total encounters (CT or NG)} = \text{Total CT encounters} + \text{Total NG encounters} - \text{encounters for concurrent infections recorded the same day}$
- Individuals Affected (CT; NG; Either)
 - Number of unique individuals with CT infection(s)
 - Number of unique individuals with NG infection(s)
 - Number of unique individuals with either a CT or NG infection

Cases:

Cases were identified from the 3 data sources (DRSi, M2, and HL7) based on respective reportable condition, diagnostic, and lab result coding specified in surveillance case definitions [8, 10, 122, 123]. A 30-day gap in care incidence rule, commonly used in DoD surveillance for both CT and NG was used to define incident infections [8]. With this method a new infection is

detected when a gap of more than 30 days occurs in the continuum of care as tracked across the multiple data systems (i.e., medical event reports, inpatient or outpatient encounters, and lab tests). A 30-day look-back period was incorporated in the data pulls (1-31 December 2014) to enable exclusion of non-incident cases documented in January 2015. Case definitions used for reporting confirmed cases through the DRSi are described in **Table 2**. Laboratory identified cases were furnished by the NMCPHC using case detection algorithms validated for HL7 microbiology and chemistry records [122, 123]. AFHSD case definitions which specify diagnostic codes and inclusion criteria were used to query the M2 outpatient tables (CAPER and TED-NI) – details are provided in **Table 6** [8].

Person-time at risk

The DMDC database was used to define person time at risk and key demographic strata for Army AC Soldiers. Updated business rules implemented to compute person-time for Army reporting were used whereby all monthly personnel records (regardless of unit zip code assignment) contributed to person-months, which in turn, could be extrapolated to person-years at risk [146]. These estimates provide a more complete accounting of person-time, but differ slightly from estimates obtained from the grouped data used in Aim 1 where person-year estimates excluded DMDC records missing zip codes that could be linked to installation assignments used for Army installation-based surveillance [145].

Risk Analyses

CT and NG incident case counts were assessed independently and in combination (i.e., CT+, NG+, CT or NG+) to determine statistically significant risk factors. Univariate and multivariate analyses were conducted using case counts as the designated dependent variable and one or more independent covariates included as independent variables. Covariates included were selected a priori based on the strong body of evidence demonstrating significant associations

between the covariate and dependent variable. These include age, sex, race-ethnicity, marital status, geographic region of duty assignment, geographic region for the designated home of record, education level, and rank. The latter two serve as a proxy for socioeconomic status.

Table 7 outlines the independent variables assessed and designates the reference groups used when evaluating statistical associations. In general, categorical groups with the lowest incidence rates were chosen as the reference.

STATISTICAL ANALYSIS

Sample Size and Power Considerations

Approximately 461,000 AC Soldiers comprised the annual study population evaluated during 2015-2019, with corresponding annual cases identified through enhanced surveillance estimated to be approximately 11,000 CT and 1760 NG cases per year. The estimated case counts reflect reported cases used in the Aim 1 assessment multiplied by a factor of 1.10, which reflects a minimal hypothesized increase in case detection with the enhanced Aim 2 database of 10%. Case rates used in the sample size computation were similarly adjusted to reflect a probable 10% increase.

Age and sex-specific sample size requirements to detect 2-fold differences in incidence rates while achieving a minimum of 80% power at a 95% significance level were generated (**Table 8**). OpenEpi sample size and power calculators for cohort studies were used to perform the computations [52]. Using these specifications, a sample size of approximately 4,580 is needed to detect a 2-fold difference in CT case rates by sex (655 females and 3,925 males), and a sample size of roughly 24,282 (3,469 females and 20,813 males) is needed to detect a 2-fold difference in NG case rates between the two groups. These requirements are easily met even when a higher degree of power (90%) is used.

Sample size requirements to achieve a minimum of 90% power were also easily met by examining differences in CT incidence rates by age for each age category examined when up to four categories were used (<25, 25-34, 35-44, and 45+). However, the power to detect a two-fold difference in NG incidence across age categories was reduced to roughly 70% due to the lower expected incidence density. Combining smaller subsets (e.g., 35-44 and 45+ age groups) increased the power above 90% with the highest population sample size requirements being easily met. For example, the smallest age group evaluated (n=105,000) exceeded the required 8,077 and 31,691 needed to detect a 2-fold difference for CT and NG, respectively. To maximize statistical power, this age categorization was used in the analyses.

Descriptive and Inferential Statistics

Statistical analyses were performed using IBM SPSS Statistics version 26.0 software, MS365 Excel, and the OpenEpi version 3.0 module [52, 88]. Descriptive analyses were conducted to describe the study population and to assess CT/NG frequency distributions and trends for each independent variable outlined in **Table 7**. Annual incidence rates were calculated independently or in combination for CT and NG (CT+, NG+, CT and/or NG) for each population subset over the 5-year study period. Population characteristics for AC members with repeat infections were also evaluated. Chi-square tests for trend were used to identify statistically significant trends in infection (incident and recurrent).

For each calendar year, the number of unique individuals with at least one identified infection (CT and/or NG) was calculated to measure individuals affected, a common morbidity burden metric. Medical encounters for these individuals were imputed using the subset of cases with supporting medical records. Average annual encounters per person identified with

supporting diagnosis codes were used as a multiplier for all affected individuals to generate an estimate of total expected encounters per year.

Univariate analyses of each independent variable were performed using the Byar approximation of the exact method as implemented in the OpenEpi module in order to compute unadjusted IRRs and 95% CIs. A series of multivariate regression models were executed to evaluate predictors of risk, for which adjusted IRRs, 95% CIs, and two-sided p-values were generated to assess statistical associations between the independent and dependent variables. Multivariate GLMs with underlying Poisson (log-linear function) and Negative binomial distributions (log-link and maximum likelihood estimation [MLE] functions) were used to evaluate associations between independent risk factors and infection (incident or recurrent), with separate models run for CT and NG. Time at risk (i.e., person-years) was used to weight univariate analyses and also used as an offset in the GLMs to enable computation of IRR for each independent variable relative to a designated reference group. Additionally, multinomial logistic regression models were generated to evaluate predictors of repeat infection – individuals with one case (i.e., non-repeaters) and those with two or more cases (i.e., repeaters) were compared independently to those with no identified infections. Odds ratios (ORs), 95% CIs, and two-sided p-values were also generated from the models and used to assess statistically significant associations.

For all multivariate models, independent variables with a hypothesized or probable association with CT/NG infection were first assessed in univariate analyses. Highly correlated variables such as age and rank were categorized to maximize independence (a criteria for inclusion as an independent variable). For example, junior and senior enlisted and officer ranks which closely align to age categories were regrouped into categories for enlisted versus officer.

While the intention was to include variables selected a priori in the multivariate models using a manual stepwise entry to determine which factors yielded the most parsimonious model, that proved unnecessary as the full model was parsimonious.

Confounding was assessed for variables that were not considered intermediaries in the causal pathway between an exposure (secondary independent variable) and the outcome (CT/NG), and which were determined to be independently associated with the outcome and the potentially confounding variable. Chi-square and exact tests with a two-sided significance level of $p < 0.05$ were used to evaluate these associations. This was done to better understand changes in results between the univariate and multivariate models with the understanding that the multivariate models control for potential confounding. Interaction between independent variables selected was evaluated when demonstrated or probable associations were observed that might reduce their independence (e.g., age and education level) by including interaction terms in the multivariate models. A significance level of $p < 0.10$ was used as criteria for determining potentially significant interaction. Interaction terms examined proved to be statistically insignificant and were removed from the models.

Model fit for GLMs was assessed using Pearson Chi-square dispersion statistics. When overdispersion of the data was detected (i.e., variance is greater than the mean), better fitting models such as the negative binomial were selected. Similar to the Aim 1 assessment of model fit, GOF statistics were evaluated to select the better fitting model. These include AIC scores, ratios of Pearson chi-square residual values to degrees of freedom (ideal near 1.0, adequate < 2.5) and standardized deviance residuals to the predicted counts (values with ± 2 reflect better fitting models).

Aim 3.

SPECIFIC AIM

Evaluate CT and NG case ascertainment across the three MHS data systems used in Aim 2 analyses to identify surveillance contributions and gaps in detection.

Objective 1. Assess system-specific case capture

- a. Determine % case capture (CT, NG) for each data system (reporting, medical encounter, and laboratory record systems).
- b. Determine overlap in case capture across the data systems.
- c. Evaluate the contribution of outsourced or purchased care.
- d. Evaluate agreement in case identification between the three systems.

Objective 2. Evaluate annual trends in case detection.

- a. Assess system-specific annual variation in case detection.
- b. Determine gains in incidence estimation from enhanced surveillance compared to standard reporting

Objective 3. Assess geographic variation in case capture.

- a. Determine differences in reporting system capture by installation relative to the Army mean.
- b. Determine differences in laboratory system capture by installation relative to the Army mean.
- c. Determine differences in medical encounter capture by installation relative to the Army mean.

Hypotheses: Empirical evidence supports the following:

- 1) Incidence estimates will be substantially improved (more than 10% increase) through the consolidated three-source database relative to single-sourced reporting;
- 2) Gaps in case detection through reporting will narrow over time, presumably based on reporting system enhancements and training;
- 3) Laboratory records will afford a higher degree of case capture with medical encounter records providing the least; and
- 4) Significant geographic variability in case capture will be observed.

STUDY DESIGN AND STUDY POPULATION

The descriptive study uses Aim 2 retrospective cohort data to examine CT and NG case ascertainment across three passive surveillance systems. The study population is the same as that described in Aim 2 and consists of Army AC soldiers and trainees who were MHS beneficiaries at any point during 2015 to 2019.

DATA SOURCES

The data sources used for the analyses are described in **Table 1** and in the preceding Aim 2 methods summary. They include three MHS databases: DRSi (case reports), M2 (outpatient records), and HL7 (laboratory records). DRSi and M2 data were provided by the USAPHC while HL7 data were provided by the NMCPHC. DMDC personnel records were also used to generate person-time at risk which enabled incidence rate computation. Data were safeguarded using USAPHC data protection rules described in **Appendix A**.

MEASUREMENT

Primary Outcomes

- % Cases (CT or NG) identified from:
 - DRSi

- HL7
- M2 CAPER (MHS encounter)
- M2 TED-NI (Non-MHS encounter or purchased care)
- % Overlap in Cases Identified:
 - DRSi and HL7
 - DRSi and M2
 - HL7 and M2
 - All sources
- Annual Incidence Rates by Data Source (CT, NG)
 - Number of new CT cases identified through DRSi per 100,000 person-years
 - Number of new GC cases identified through DRSi per 100,000 person-years
 - Number of new CT cases identified through HL7 per 100,000 person-years
 - Number of new GC cases identified through HL7 per 100,000 person-years
 - Number of new CT cases identified through M2 per 100,000 person-years
 - Number of new GC cases identified through M2 per 100,000 person-years
 - Number of new CT cases identified from anysource (DRSi, HL7, or M2) per 100,000 person-years
 - Number of new GC cases identified from any source (DRSi, HL7, or M2) per 100,000 person-years

STATISTICAL ANALYSIS

Descriptive analyses were conducted to examine proportions of CT/NG cases identified through each MHS data source. Annual trends in proportions (case capture) and incidence rates as computed per source system were assessed using chi-square tests for linear trend. Overlap in

case capture between systems was also assessed, and Kappa statistics were computed to test the agreement between the data systems. Cohen's kappa was used for two-source comparisons while Fleiss kappa was used to compare agreement in all three sources. Pearson chi-square tests were used to evaluate system-specific variation in case capture across installations to identify statistically significant differences in regional surveillance practices.

Installation case capture for each surveillance system was also evaluated against the Army mean using Z-score computations whereby the difference between the installation and Army percentage case capture was divided by the standard deviation in percentage case capture across installations evaluated. Installations included in the evaluation had to meet a case threshold of 20 or more cases per year, a threshold commonly used in surveillance to improve reliability of comparisons [145]. Z-scores ≤ -2 were classified as a statistically significant indicator of poor system performance for case detection relative to the Army average, with scores between -1 and -1.9 considered indicative of moderately poor performance. All analyses were done independently for CT and NG.

CHAPTER 3: COMPARING CHLAMYDIA AND GONORRHEA CASE RATES REPORTED AMONG US ARMY SOLDIERS AND US DEMOGRAPHIC PEER GROUPS (AIM 1)

This chapter expands upon information included in a published manuscript that was completed in pursuit of Aim 1 objectives.

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INTRODUCTION

This study is the first of three studies designed to assess *chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) disease burden and correlates of risk among Army active component (AC) soldiers to inform surveillance and prevention practices. It focuses on reported case rates among AC soldiers and comparable US adult demographic peer groups. By using military and national disease reporting system data which serve as a primary means for health surveillance, this initial study provides a foundation from which to evaluate and compare burden across population sectors and to subsequently assess the contribution reporting systems can provide in estimating disease burden.

The long-term goal is to better understand disparities in reported CT and NG case rates among soldiers, and to inform surveillance practices so that prevention can be bolstered accordingly. The overall objective is to contextualize disease occurrence among Army AC soldiers relative to comparable civilian counterparts (adults 18-64 years of age) by comparing age- and sex-adjusted reported case rates. A comparison of crude rates between populations (overall and age-sex stratified) shows a substantial elevation in reported rates among soldiers. While crude rates have been periodically compared, the last peer-reviewed manuscript to compare population rates while controlling for these influential demographic factors was done more than twenty years ago and does not reflect the changing epidemiology of these infections. At the time of the study, reported gonorrhea rates were consistently declining (a trend that has since reversed), and chlamydia reporting was incomplete as it had not been fully implemented across all 50 states; the study also did not account for methodologic differences in data collection between the populations being compared.

The central hypotheses are: direct standardization of case rates by age and sex will substantially narrow the divide observed when comparing crude rates between the Army and

civilian populations; age- and sex-adjusted Army case rates will remain elevated relative to rates among comparable US adults; and risk will be significantly elevated among female soldiers, those under 25 years, racial and ethnic minorities (e.g., Black soldiers), and soldiers located in regions such as the Southern US census region and overseas regions such as the South-Pacific – findings that are consistent with documented risk factors. These hypotheses will be tested by pursuing three objectives: 1) Describe population characteristics and corresponding CT and NG case rates for the two cohorts (AC soldiers and US adults 18-64 years), 2) Compare trends in crude and age-sex-adjusted case rates between the two groups, and 3) Independently assess risk factors associated with CT and NG (i.e., age, sex, race-ethnicity, and geographic region) within the Army cohort.

The research proposed is significant because it provides a better understanding of relative incidence of infection reported among a high-risk population (Army soldiers) than was previously available. It also addresses an inadequately covered topic using current and similarly assimilated epidemiologic data which ensure a more meaningful and valid comparison. Furthermore, it provides a platform from which to conduct a more comprehensive burden assessment through multi-sourced data and to assess military health surveillance capabilities, which are addressed in the subsequent studies in this series.

METHODS

The study populations examined consisted of AC soldiers and trainees eligible for MHS care during 2015-2019, and corresponding age and sex stratified US adult demographic peer groups 18-64 years of age. Army population characteristics were assessed using Defense Manpower Data Center (DMDC) personnel data received in aggregate from the US Army Public Health Center (USAPHC); national population characteristics were likewise based on aggregate US census data [147, 149]. Army population estimates were derived from person time

computations which consider the dynamics of the highly mobile population which may not be employed as active service members for the entire year, whereas US population estimates were computed per capita for the relatively stable cohort. Grouped Army case data collected through the Defense Health Agency (DHA) Disease Reporting System internet (DRSi) were furnished by the USAPHC, while national case data collected through the CDC National Notifiable Disease Surveillance System (NNDSS) were retrieved from CDC published reports and the Atlas Plus dashboard [42, 43, 113]. Case data from both reporting systems use similar surveillance case definitions for confirmation and analogous incident case classification rules which count case reports received greater than 30 days apart as a new case [8, 10, 30, 36, 41].

Annual Army population trends were assessed using chi-square tests for linear trend with the trendline R^2 values evaluated to determine how well the trendline explained variation for the population characteristic over time (values near 1.0 reflect a good fitting linear trendline and values ≥ 0.95 were considered statistically significant). Annual trends in reported case rates were also evaluated for the overall Army, along with ranges in installation rates. Rates for installations with less than 20 cases reported annually were suppressed from the ranges. Reported CT and NG case rates (crude and age-sex-adjusted with 95% Confidence Intervals [CIs] for each rate) were assessed independently and compared between the two populations. Age- and sex-adjusted case rates were computed using direct standardization with the 2015 age and sex distribution for the Army AC soldier population as the standard [159]. Differences in reported case rates between the AC soldier and US adult cohorts were evaluated through univariate analyses using exact probability testing and multivariate analyses using Generalized Linear Models (GLMs) with Poisson (log linear) and Negative Binomial (log-linked) distributions and a person time offset.

Risk factors for the Army cohort were similarly evaluated using univariate and multivariate analyses including all available demographic categories as independent variables in the model (i.e., age, sex, race-ethnicity, and geographic reporting region categories). The negative binomial model with maximum likelihood estimation was selected as the final model based on identified data over dispersion and improved model fit as determined by goodness of fit (GOF) statistics (e.g., lower Akaike's information criteria [AIC], and ratios of Pearson chi-square residuals to degrees of freedom <2.5) [25, 119]. Models included incidence rate ratios (IRRs), 95% CIs and p-values with a 0.05 significance level. IBM SPSS version 26.0 was used for the analyses. For more details regarding study methodology please refer to Chapter 2, Aim 1.

RESULTS

Population characteristics

Army AC Soldiers

The Army AC soldier population averaged 460,688 per year during 2015 to 2019 (range: 456,245 - 466,359) based on person-time computations. While the overall population was somewhat stable, population dynamics fluctuated from year to year for demographic subsets. For example, female soldier representation increased consistently over the 5 years to reach a cumulative 7% increase by 2019, when women made up 15% of the workforce as compared to 2015 when women made up 14% (R^2 for linear trend = 0.95). The annual male soldier population, on the other hand, was more dynamic with no significant linear trend (**Figure 1**). The proportion of AC soldiers under 25 years of age increased by approximately 9% cumulatively from 2015 to 2019 (R^2 for linear trend = 0.89), whereas all other age groups declined in population; a significant downward trend was observed for soldiers 35-44 years of age (R^2 for linear trend = 0.96) as they experienced a decrease of 8% over the 5 years (**Figure 2**).

Representation by some minority race-ethnicity groups increased among Army AC soldiers over

the 5 years. Specifically, those identifying as Hispanic had a 19% overall growth from 2015 to 2019 (R^2 for linear trend = 0.99); AC soldiers identifying as Asian or Native Hawaiian/Pacific Islander also had substantial population gains (R^2 for linear trend > 0.95) (**Figure 3**). No significant linear trends in geographic distribution by assigned US census or overseas regions were observed (data not shown).

Army and US Population Comparison

The Army AC population is roughly 0.2% of the overall US adult population 18-64 years of age, which averaged roughly 200,489,000 per year during the 5-year timeframe evaluated. The US population estimates (overall and by age and sex) were relatively stable with modest population growth each year from the low of 200,090,000 in 2015 (0.2% cumulative growth).

As expected, profound differences in the demographic make-up between the two populations was observed ($p < 0.001$), which are consistent with published reports [147, 149]. The Army AC population evaluated was overwhelmingly comprised of men (85%) and was skewed towards younger ages with roughly three-fourths of the population under 35 years of age, whereas US adults 18-64 years of age had a more uniform population distribution by sex with 38% under 35 years old (**Figure 4**). Statistically significant differences ($p < 0.001$) in racial and ethnicity distributions between the two populations were also present, with the Army AC soldier population being more diverse. For example, 21% of Army soldiers identified as Black or African American as compared with 13.6% of US adults 18-64 years of age (**Figure 5**).

The majority of AC soldiers (53%) were assigned to Army installations located in the southern US Census region, which is where a greater number of installations are located (**Figure 6**). Approximately 20% were assigned to the Western US census region, the second most populated, and roughly 10% were stationed in non-US countries overseas (e.g., Europe or Pacific

regions). About 8% were classified in command regions which didn't align with the US census regions or were unknown. For example, the Army data included categories for 'Other – Atlantic' which encompassed both Northeastern and Southern US census regions located along the Atlantic seaboard.

Reported Case Rates

Chlamydia

Army Rates

Over the five-year period the overall rate of reported CT was 2,149 cases per 100,000 person-years. There was a statistically significant upward trend in case rates (R^2 for linear trend = 0.99) with variation in crude rates observed across Army installations. The lowest reported installation rate occurred in 2015 (673 cases per 100,000 person-years) and the highest was observed in 2016 (5,934 cases per 100,000 person-years) (**Figure 7**). Relative risks when comparing crude installation rates (lowest versus highest) ranged from 3.74 in 2019 to 7.12 in 2016. Rates varied by age and sex, with higher rates reported among women (5,037 cases per 100,000 person-years) and soldiers under 25 years of age (4,127 cases per 100,000 person-years) (**Table 9**). Women under 25 had the highest rates of all the age and sex categories examined with rates as high as 10,404 cases per 100,000 person-years (**Table 10**).

Unadjusted or crude reported CT rates among AC soldiers increased by roughly 40% over the 5-year period, rising from 1,775 to 2,481 cases per 100,000 person-years (2019:2015 RR=1.40, 95% CI: 1.36-1.44). Rates were elevated among female soldiers relative to males (RR=3.05; 95% CI: 3.00-3.11). Rates were particularly elevated among younger soldiers under 25 compared to those 35 years of age and older (RR=14.77; 95% CI: 14.04 - 15.55). Relative to White, Non-Hispanic soldiers, those identifying as Hispanic or Non-Hispanic Black, Native

Hawaiian/Pacific Islander, or American Indian/Alaskan Native had elevated risk with Rate Ratios ranging from 1.57 (95% CI: 1.41-1.74) for American Indian/Alaskan Native soldiers to 3.23 (95% CI: 3.16-3.29) for Black soldiers. Relative to AC soldiers with assignment to the US Northeast census region which had the lowest incidence rates, statistically significant elevations in the other regions were noted, most notably among soldier stationed outside the US in the Pacific region (RR=1.85; 95% CI: 1.74-1.96), followed by those in the Western US region which includes Pacific states outside the continental US (OCONUS), namely Alaska and Hawaii (RR=1.35; 95% CI: 1.28-1.42). These univariate results are provided in **Table 9** along with results from multivariate models which control for potential confounding for each of the independent variables examined.

Multivariate modeling confirmed the statistical associations observed with univariate analyses. The overall strength of association diminished slightly for each covariate included in the model, apart from geographic regions where slightly higher RRs were observed after adjustment for the other covariates in the model. Examination of potential interactions between covariates yielded no statistically significant findings. Age remained the strongest predictor of risk in both univariate and multivariate models.

Comparison with National Rates

Unadjusted rates of reported CT among AC soldiers exceeded those reported nationally among adults 18-64 years of age for each of the age and sex categories examined (**Figure 8**). Crude Army rates were nearly 3-fold higher than rates reported among the US adult peer groups examined (RR=2.86, 95% CI: 2.84-2.89) (**Table 10**). Differences among women were more pronounced with rates reported among Army females over 5 times higher than those in US

women (RR=5.20; 95% CI: 5.12-5.28) while reported rates in Army men were 3-fold higher overall (RR=3.11; 95% CI: 3.08-3.15).

Similar trends in reported CT case rates were observed between Army and civilian demographic peer groups as both experienced consistent annual increases. This was true for most demographic subsets examined; however, case rates reported among female soldiers began to stabilize in 2019 and rates among soldiers 35 years and older dropped in 2018 while US rates for both subsets continued to increase (**Figures 9-10**). There were notable differences when comparing rates by location of reporting (state or country). The Army had high case rates reported in countries overseas which would have not been detected through national surveillance. Notably the Pacific region, which includes Korea and Japan, reported the highest case rates; CT incidence reported from European countries also made the top 10 (**Figure 11**). Stateside reported case rates among soldiers did not align well with rates reported among US adults residing in states where Army installations are located. For example, reported CT rates were relatively high among soldiers with duty locations in Hawaii and Texas as compared to other Army duty locations (ranking first and second among US states), whereas case rates for US adult peer groups within these states ranked lower than other states hosting Army installations (ranking 12th and 19th, respectively). (**Figures 11-12**).

When comparing age and sex adjusted rates between AC soldier and US Adults 18-64 years to crude rates, the near three-fold difference (RR=2.86) was minimized, dropping to roughly a two-fold difference overall (RR=1.84; 95% CI: 1.83-1.86). These differences were statistically significant throughout the five years examined ($p<0.001$), with the risk difference

increasing each year (2015 RR=1.80 relative to 2019 RR=1.87). **Figure 13** shows trends in crude and adjusted rates.

Gonorrhea

Army Rates

Over the five-year period the overall rate of reported NG was 348 cases per 100,000 person-years (95% CI: 341-356 per 100,000 person-years). As was seen with CT, there was a statistically significant upward trend in annual case rates (R^2 for linear trend = 0.98) and there was considerable variability in reported rates across the Army installations reviewed. To illustrate the extreme variability, the lowest installation rate was reported in 2015 (99 cases per 100,000 person-years) while the highest was reported in 2019 (1,068 cases per 100,000 person-years); relative risks between installations with low and high reported rates ranged between 4.04 and 6.74 each year (**Figure 14**). Notably, less installations (n=18) were included in the NG comparison than in the CT comparison (n=39) due to low case counts (<20 reported cases on average per year).

Case rates also varied by age and sex, with higher rates reported among women (498 [95% CI: 474-521] cases per 100,000 person-years) and soldiers under 25 years of age (625 [95% CI: 608-642] cases per 100,000 person-years). Women under 25 had the highest rates of all the age and sex categories examined (1,014 [95% CI: 959-1,068] cases per 100,000 person-years) (**Table 11**).

Crude NG rates reported among AC soldiers increased by approximately 57% over the 5-year period, rising from 265 to 417 cases per 100,000 person-years (2019:2015 RR=1.57, 95% CI: 1.46 – 1.69). Unadjusted rates were also elevated among female soldiers relative to males (RR = 1.57; 95% CI: 1.46 - 1.69). Rates were particularly elevated among younger soldiers

under 25 compared to those 35 years of age and older (RR = 8.03; 95% CI: 7.28 – 8.86). Relative to White, Non-Hispanic soldiers, those identifying as Hispanic or Non-Hispanic Native Hawaiian/Pacific Islander, Black, or American Indian/Alaskan Native had elevated risk with Rate Ratios ranging from 1.86 (95% CI: 1.72 - 2.02) for Hispanic soldiers to 7.31 (95% CI: 6.93 - 7.71) for Black soldiers. Relative to AC soldiers with assignment to the US Northeast census region, statistically significant elevations in the other regions were noted, most notably among soldiers stationed in the Southern US region (RR=2.46; 95% CI: 2.08-2.91), followed by those in the Western US region (RR=2.33; 95% CI: 1.96-2.77). Multivariate modeling confirmed the statistical associations observed with univariate modeling with modest decreases in parameter estimates for each covariate. Age remained the strongest predictor of risk followed by Black, Non-Hispanic race/ethnicity. Univariate and multivariate results are provided in **Table 12**.

Comparison with National Rates

Except for women under 25, crude rates of reported NG among US Adults exceeded those reported among AC soldiers for each of the age and sex categories examined (**Figure 14**). However, when reviewed for the overall Army AC population or total female or total male soldiers, Army rates exceeded national rates. This could be due to the skewing of the Army population towards the higher risk younger members whose case rates would be more heavily weighted than in the US adult population. Overall, Army unadjusted rates were 1.44 times higher than rates reported among the US adult peer groups examined (RR=1.44, 95% CI: 1.40 - 2.43) (**Table 11**). Differences among women were more pronounced with rates reported among Army females being more than two times higher (RR=2.56; 95% CI: 2.44 - 2.68) while reported rates in Army men were 11% higher (RR=1.11; 95% CI: 1.08 - 1.13).

Consistent annual increases in reported NG case rates were observed for men and women in both the Army and US adult populations examined (**Figure 16**). Case rates were higher among Army females relative to males, whereas the opposite was observed nationally with rates among men elevated relative to those among women. Reported NG case rates were very similar between the Army and US adult males. With the exception of the 25-34 year old age group, reported NG rates were similar between the two populations; however, rates for US adults 25-34 years of age were elevated relative to Army soldiers in this age group (**Figure 17**).

Reported NG case rates varied by reporting location (US state or non-US countries) and discordance was observed relative to reporting CT locations. Although high rates of CT were reported among Army soldiers assigned to non-US installations in the Pacific region, corresponding NG cases rates were relatively lower (**Figure 18**). Reported NG rates in Texas, Washington, Colorado, and Kansas were similarly high among Army soldiers, with rates in these states rounding out the top 5 US states for both NG and CT (**Figures 12 and 18**). Stateside reported case rates among soldiers did not align well with rates reported among US adults residing in states where Army installations are located. For example, soldiers with duty locations in Texas or Washington had higher NG case rates relative to other Army state locations (ranking 1st and 2nd), while case rates for US adult peer groups in these states were lower (ranking 13th and 18th among states with Army installations); reported rates within Louisiana were similarly high relative to other states reviewed for both populations. (**Figures 18-19**).

When comparing age and sex adjusted rates between AC soldiers and US Adults 18-64 years to crude rates, the rate differences not only diminished, but were reversed. Crude rates reported in the Army were significantly elevated (RR=1.44, 95% CI: 1.40 - 1.47), whereas adjusted rates were significantly lower (RR=0.74, 95% CI: 0.72 - 0.75). These differences were

statistically significant throughout the five years examined ($p < 0.001$). **Figure 20** shows trends in crude and adjusted rates.

DISCUSSION

Overall, annual trends in CT and NG case rates were similar between Army AC soldiers and US adults 18-64 years of age, with rates consistently increasing over the 5-year period. Exceptions were observed with reported CT rates among female soldiers for whom rates stabilized in 2019 and among soldiers 35 years and older who experienced a decline in reported case rates in 2018. Crude CT and NG rates within the Army were elevated relative to the US adult population. This was also true for CT rates when examined independently for women and men for each age category evaluated (18-24, 25-34, and 35-64); however, crude NG rates were elevated among US adults for all subsets except for women 18-25 years. The contrast observed when comparing NG rates between the two total populations with that observed when comparing age and sex stratified rates, illustrates the need for rate adjustment to control for these factors when assessing overall incidence density within the larger population. Not doing so masked important differences between the two populations given that total Army NG rates became skewed to reflect the higher incidence among younger adults who are over-represented.

Age and sex standardization enabled a more valid comparison of population rates, and it substantially narrowed the divide observed when comparing crude, population-level cases rates. CT rate differences between the two populations decreased from the near 3-fold elevation observed in the Army relative to US adults to just under a 2-fold elevation. While age and sex rate adjustment for NG also minimized the rate difference between the two populations, it also revealed an unexpected elevation among US adult peer groups relative to AC soldiers. Unadjusted NG rates were 44% higher in the Army cohort relative to the US cohort ($RR=1.44$);

however, the difference reversed with standardization and a protective effect was observed as risk decreased by 26% (RR=0.74) for the Army relative to the US adult cohort.

Our study compliments and updates findings published by Seña et al, in 2000, when crude and age-adjusted rates documented among the Fort Bragg soldier clinic population were compared to those reported within the state and nationally for both men and women [131]. Our review provides a more comprehensive assessment of the Army population, and refines the analytic strategy by employing an Army population standard that is better suited for comparing rates within this heavily skewed population, and by utilizing inclusion criteria that better aligns the study populations, data sources, and case definitions [10, 41, 159]. Considerable changes in surveillance practices and disease transmission have also ensued in the intervening two decades which necessitates a reassessment. A more complete picture of CT burden has since been realized thanks in part to diagnostic and surveillance enhancements to include reporting mandates across the 50 states; and the declining trends in NG rates documented in both populations have since reversed [12, 34, 39, 92, 136, 145]. Notably, the relatively lower rate of NG reported in the Army following age-sex-adjustment is a departure from previous studies which reflect epidemic cycles experienced nationally during the last century [15, 72, 131].

The contrasts in age- and sex-adjusted rates observed between the Army and US cohorts evaluated, may reflect differences in healthcare access, screening and surveillance/reporting practices, as well as differences in actual disease burden. The screening bias is particularly pronounced when comparing rates between men and women regardless of which population is being evaluated given that CT and NG screening are prioritized for sexually active women under 25 years of age and also encouraged during pregnancy. Further screening biases are evident when comparing rates for Army women under 25 to their civilian counterparts. Routine

assessments of screening compliance have demonstrated sizeable screening disparities between the populations which may influence differences in case rates. For example, approximately 82% of Army females under 25 received screening in 2019 relative to only 47-58% of insured US women [111, 152]. This screening disparity may explain why elevated NG case rates were only observed among female soldiers under 25 relative to US women in this age group.

The increased healthcare access afforded to soldiers may further increase the likelihood of case detection relative to that among the general population, however, the impact is lessened due to the asymptomatic nature of infection which reduces care seeking. It is also possible that reporting is more complete in the military health system given the existence of a unified system within military medical treatment facilities.

The analyses confirmed documented risk factors among Army soldiers, with statistically significant elevations in both CT and NG rates observed among females, adults under 25 years, and racial/ethnic minority groups including those identifying as Hispanic or select Non-Hispanic minority sub-groups (i.e., Black, American Indian/Alaskan Native, or Native Hawaiian/Pacific Islander) [12, 34, 39, 92, 136, 145]. Case rates varied by geographic region with inconsistencies observed between nationally reported incidence and that reported among soldiers. In both populations CT rates were lowest for the Northeast US census region; lower NG case rates were also reported among soldiers in the Northeast whereas national rates were lowest in the Midwest [34]. Unique to the military, cases were reported internationally with the highest CT rates reported in Pacific countries, followed by the Western US census region which includes the Pacific state of Hawaii, and then European countries, whereas US CT rates were highest in the South census region. NG rates were highest in the South US census region for both the Army and US adult cohorts. When CT and NG rates were examined across US states, there were notable

contrasts in how the states ranked for each population with several states ranking high for the Army being ranked on the lower extreme nationally, and vice versa. Considerable variability in case rates across Army installations was also observed; however, installation comparisons like the state comparisons were limited to crude rates.

Soldier populations are dynamic due to scheduled changes in duty assignments and mobilizations to support operational requirements, and this likely contributes to the discordance in geographic distribution of reported cases when compared to US demographic peer groups. Soldiers typically change permanent duty locations every two to four years, with roughly 10% of those assignments occurring at installations in foreign countries [149]. Increased travel and relocation afford soldiers with a larger sexual footprint than the average US adult and introduce a myriad of potential exposures that are unique to the population which may explain the elevated rates of CT reported. Frequent lifestyle interruptions and high-risk operational endeavors can also induce stress that in turn may trigger risky sexual behavior [19, 135]. Increased case rates have been documented pre- and post-deployment and during changes with duty location [125, 134]. These social and cultural factors which are ingrained in the Army lifestyle may influence sexual partnerships and disease burden within a sexual network whereby soldiers may serve as a bridging population [4].

By contrast, factors contributing to the decreased incidence of reported NG among soldiers relative the US demographic peer groups are not as clear cut. The lower risk may reflect differences in the population make-up given that the US gonococcal epidemic is largely driven by increased transmission within high-risk sub-groups (e.g., MSM and HIV pre-exposure prophylaxis users) as well as other distinct cultural, sociodemographic, and geographic

subpopulations which may be less represented in military populations [34, 39, 82, 125]. Other unmeasured confounders may have also been present.

Controlling for age and sex differences between the two dissimilar populations yielded more reliable comparisons as did the use of analogous reporting system data. However, comparisons remain limited due to inevitable differences in data collection and reporting. As discussed, universal healthcare access coupled with higher rates of screening and the existence of a unified military health system, can increase case detection and reporting among soldiers relative to the general population. Estimated case rates generated from the respective reporting systems are further limited due to under reporting, which is widely accepted as problematic and largely unknown for both populations. Estimates generated from such systems are considered conservative not only due to this phenomenon, but more so from the high percentage of asymptomatic infections which go undiagnosed and reported [69, 70, 96]. Incidence rates derived from case reports have been shown to be less than half of those estimated from studies employing representative sampling and advanced mathematical modeling that take into account factors such as reporting practices [96].

The analyses were also limited to aggregated data with few shared risk factors between the two population (specifically age and sex). While national data were also summarized by other covariates of interest such as race and ethnicity, which were available in Army data, they were deemed unreliable based on the high degree of missing information [39]. There were also differences in the age strata examined. While it was possible to filter the national data for adults in the commonly recognized working ages of 18-64 years, the Army data were grouped into a limited number of age categories which may have reduced the precision of the age adjustment. The pre-defined groups were also comprised of all soldiers on active service; therefore, a small

subset of soldiers who were 17 years of age or 65 years and older may have been included. Given the low proportion of the population at these age extremes, the effect on case rate computations is believed to be negligible and would have most likely biased the results toward the null. Likewise, the unavoidable inclusion of Army case and census data in the national estimates would have also had an inconsequential impact on the comparisons made as the Army represents roughly 0.2% of the national population.

These limitations notwithstanding, the study provides a thorough assessment of CT and NG case rate trends and associated risk factors for a high-risk population (Army soldiers) which has been prioritized for STI surveillance and prevention [110]. In so doing, the analyses not only addressed a significant gap in the literature, but they also added to the body of evidence in characterizing risk and revealed novel findings. Specifically, our findings regarding the discordant geographic distribution of reported CT and NG cases between the two populations are notable and warrant further exploration to better delineate transmission dynamics at a more granular level (e.g., counties and installations); such comparisons would also benefit from age and sex standardization. Additionally, the lower NG risk identified among the Army cohort relative to their civilian counterparts after controlling for age and sex differences is striking. Not only do the analyses emphasize the importance of standardization when comparing rates between dissimilar groups, but they also reveal underlying factors which may be contributing to the risk differences that may inform further study and prevention efforts.

In summary, the study documents increasing rates of reported CT and NG both nationally and within the Army, and confirms documented risk factors (i.e., age, sex, and race/ethnicity). Age- and sex-adjusted CT rates were elevated among Army soldiers who had case rates that were almost twice those reported among demographic peer groups. Age- and sex-adjusted NG

rates, however, were 26% lower in the Army cohort. The comparisons performed aid in contextualizing risk among soldiers who are among several high-risk groups prioritized for prevention. Furthermore, the study provides a foundation from which CT and NG surveillance can be further explored to better quantify disease burden and to characterize risk and transmission dynamics. Collectively, the findings may support implementation of interventions such as surveillance enhancements and targeted screening for high-risk groups.

CHAPTER 4: ESTIMATING CHLAMYDIA AND GONORRHEA DISEASE BURDEN AMONG US ARMY SOLDIERS USING ENHANCED SURVEILLANCE (AIM 2)

This chapter expands upon a published manuscript completed in partial fulfillment of Aim 2 objectives.

Citation

Jordan NN, Gaydos JC, Garges EC. Estimating Chlamydia and Gonorrhea Burden Among US Army Soldiers From Military Health System Data: Mind the Gap. *Sex Transm Dis.* 2022 Nov 1;49(11):755-761. doi: 10.1097/OLQ.0000000000001693. Epub 2022 Aug 11. PMID: 35948284.

INTRODUCTION

This study builds upon the Aim 1 work presented in Chapter three by augmenting Army reporting system data with Military Health System (MHS) electronic medical encounter and laboratory records. The enhanced three-source surveillance database allows for a more complete accounting of *chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) incidence for the Army active component (AC) population to include an estimation of morbidity burden from attributable medical encounters. Increased precision from the risk characterization can also be achieved from the more robust dataset. Additionally, the integration of multiple data sources facilitates the evaluation of surveillance system capabilities covered in Aim 3 (Chapter five) of the study series.

The long-term goal is to better understand CT and NG disease burden and associated risk factors among soldiers, as well as the benefits of enhanced surveillance to inform prevention. The overall objective is to assess morbidity burden and characterize risk among Army AC soldiers using reproducible surveillance and analytic processes. The study strives to improve routine Army analyses which rely on case reporting alone and typically exclude NG data, while also providing detailed Army-specific data not available through multi-sourced DoD analyses. Additionally, the study employs methodologic techniques to enhance morbidity burden estimation which is currently limited to DoD aggregations of diagnosed CT infections that consequently miss cases identified through MHS laboratory and reporting systems. Using the more complete database, the study further aims to assess the contribution of and risks associated with incident and recurrent infections.

The central hypotheses are that integrating laboratory and medical encounter records with reporting system data will substantially improve morbidity burden assessments (a >10% increase over current estimates is expected); high repeat infection rates ($\geq 10\%$) will be observed; and

infection trends and risk factors which are consistent with those previously documented will be confirmed. These hypotheses will be tested by pursuing three objectives: 1) Assess the frequency, distribution, and rate of CT and NG infections (incident and recurrent) among Army soldiers by demographic subsets, 2) Estimate morbidity burden in terms of associated medical encounters and individuals affected, and 3) Independently assess risk factors associated with incident and recurrent CT and NG (i.e., age, sex, race-ethnicity, education, marital status, soldier type [enlisted, officer], and geographic region [home of record, duty location]).

The research proposed is significant because it provides a more accurate assessment of CT and NG incidence, morbidity burden, and correlates of risk among Army soldiers than was previously available. The information gained can equip Army public health leaders with a more complete picture of the problem, which, in turn, will leave them better positioned to advocate for necessary preventive medicine resources to target interventions more effectively toward high-risk populations. Furthermore, the findings are expected to demonstrate a clear benefit to data integration which could be adopted as a standard for routine service-specific surveillance. This would be beneficial due to the unique aspects and differences between the service branches and their interaction with the civilian world. Lastly, the data fusion performed sets the stage for further exploration of surveillance system capabilities to be conducted as the final study in this three-part series.

METHODS

The study population consisted of Army AC soldiers, including AC trainees who were in active service at any point during calendar years 2015-2019. Data for the AC soldier cohort were extracted from four data sources which are described in **Table 1**: the Defense Manpower Data Center (DMDC) monthly personnel records, the Disease Reporting System internet (DRSi) case

records, MHS Health Level 7 (HL7) laboratory records, and the MHS Management Analysis and Reporting Tool (M2) outpatient records.

CT and NG case data were extracted from the latter three data sources when the recorded event date (i.e., case report onset date, laboratory specimen collection date, or medical encounter date) occurred between Dec 1, 2014, and December 31, 2019. Reported cases retrieved from DRSi were limited to those recorded as confirmed cases based on established DRSi case definitions [10, 113]. Diagnosed cases recorded during MHS and non-MHS outpatient medical encounters were extracted from M2 based on international classification of disease (ICD) codes included in case definitions developed by the Armed Forces Health Surveillance Division (AFHSD) [8, 53, 54]. CT and NG positive laboratory records were furnished by the Navy and Marine Corps Public Health Center (NMCPHC), which extracted HL7 chemistry and microbiology records based on validated case detection algorithms [122, 123].

Incidence rules commonly used in CT and NG surveillance were implemented; specifically, a 30-day ‘gap-in-care’ rule was used to flag new or incident cases. The 30-day specification reflects consensus recommendations to allow sufficient time for infection resolution following treatment [40]. Records with a recorded event date within 30 days of another linked MHS record for the same individual were deemed follow-up or episodic care and were excluded from incident rate computations. The ‘gap in care’ rule was adapted for CT surveillance by the DoD in 2015 based on use by investigators conducting NG surveillance. Within the DoD population, it was determined to be more specific than using an absolute 30-day window when an individual can be considered a new case every 30 days, and using the gap in care rule resulted in the removal of 2% of records that were likely attributable to follow-up care [7]. Records retrieved during December 2014 were used to identify and remove incident cases that occurred

before the 2015-2019 surveillance period. While records occurring within these 30-day windows were removed from incidence rate computations, all M2 records for individuals seen on different encounter dates were considered in the morbidity burden estimation for attributable medical encounters.

The consolidated MHS derived case data were merged with DMDC personnel data to validate Army AC affiliation, import pertinent demographic information, and to derive person time at risk for both cases and non-cases. Differences in time at risk were observed when comparing the grouped data used in Aim 1 to that generated from the person-level data used in Aim 2. Some discrepancies may have been due to unexplained deviations in data processing between the data management groups furnishing the DMDC files (the Army Analytics Group [AAG] for Aim 1 and DMDC for Aim 2). Other contributing factors were more readily apparent, including Aim 2 study refinements which improved data retention. Specifically, a restriction applied to the grouped data was removed which allowed inclusion of records for soldiers whose unit zip codes did not align with pre-defined installation reporting units used for routine surveillance. These changes resulted in negligible differences in case capture between the two analyses, however, there was an increased capture of monthly personnel records which increased person-time estimates and thus reduced reported case rate computations for Aim 2 relative to what was reported in Aim 1. This difference narrowed over time (e.g., Aim 2 person-time estimates were 3.9% higher in 2015 compared to 1.0% in 2019).

Annual and overall incidence rates (IRs) per 100,000 person-years at risk were computed for CT and NG independently and collectively. Incidence density and annual trends were evaluated across available demographic strata. For each IR, 95% Confidence Intervals (CIs) were calculated using techniques described by Rothman-Greenland and implemented in Open Epi

[129, 138]. Chi-square tests for linear trend were used to examine the statistical significance of annual trends with the derived R^2 values evaluated to determine how well the linear regression explained the observed variance.

For both CT and NG infections, three common morbidity burden metrics were computed: 1) number of unique individuals affected per year, 2) total cases per year, and 3) number of medical encounters per year for both CT and NG. Medical encounters had to be estimated based on the large proportion of cases missing ICD-coded medical records (42%). Average medical encounters per person per year for CT or NG were computed for the subset of cases with medical encounter data, excluding same-day encounters. Total expected medical encounters per year were then estimated by multiplying the average annual encounters computed from this subset by the total number of individuals affected.

Univariate and multivariate generalized linear models (GLMs) using Poisson and Negative binomial distributions were generated to assess statistically significant associations between probable risk factors and CT or NG incidence. Multinomial logistic regression models were also evaluated to determine predictive risk factors for single (non-repeat) and repeat infections among infected soldiers relative to non-infected soldiers. Independent categorical covariates assessed in the models included: age group (<25, 25-34, 35+), sex (Female, Male), race/ethnicity (American Indian/Alaskan Native Non-Hispanic, Asian Non-Hispanic, Black Non-Hispanic, Hispanic, Native Hawaiian/Pacific Islander Non-Hispanic, and White Non-Hispanic), education level (High school [HS] or less, Some College, Undergraduate or Graduate Degree), marital status (Never Married, Previously Married, Married), soldier type (enlisted, officer), home of record region (US census regions: West, Midwest, South, and Northeast), duty region (US census regions: West, Midwest, Northeast, South, and Non-US regions: Pacific, Europe, and

Central Command), and calendar year (2019, 2018, 2017, 2016, 2015). Soldier rank was also examined exclusively in univariate analyses included rank (junior enlisted [E1-E4], senior enlisted [E5-E9], junior officers [O1-O3], senior officers [O4+, Warrant Officers]) due to multicollinearity with other variables, most notably with age. Covariate categories with the lowest incidence rate were selected as the reference group.

Models were run independently for CT and NG infections along with a model examining risk for either infection. Univariate analyses employed exact tests to compare incidence rate ratios (IRRs) between groups for each independent variable. GLMs were run with Poisson (loglinear) and negative binomial (log-link and Maximum Likelihood Estimation [MLE]) distributions using a person-time offset. Multinomial logistic regression models were similarly weighted by person-time. GLM models produced nearly identical results and had adequate fit (e.g., Pearson chi-square value to degrees of freedom ratios near 1.0 and <2.5); the Poisson model results are presented [25, 79, 94]. Data were analyzed using IBM SPSS Statistics version 26.0 software [52, 88]. For more details regarding study methodology please refer to Chapter 2, Aim 2.

RESULTS

During the 5-year study period a total of 840,138 soldiers were in active service (2.8 +/- 1.7 observable person-years per soldier, on average), among whom 5.5% had at least one documented CT infection (n=45,895) and 1% had at least one documented NG infection (n=8,923). Among soldiers with CT infections 21.4% had one or more repeat infections (9,803/45,895) whereas 13.6% of soldiers with NG infections had one or more repeat infection (1,216/8,923) documented during the study period. A total of 58,935 CT infections (range: 1-9

infections per infected soldier) and 10,524 NG infections (range: 1-14 infections per infected soldier) were identified (**Table 13**).

Relative to soldiers with no identified infections, those with single or recurrent infections were disproportionately represented by soldiers characterized as: under 25 years of age, female, Non-Hispanic Black, Junior enlisted (E1-E4), never married, less educated (high school diploma or less), or with a home of record in the Southern US census region. The disparity tended to be more pronounced for those with recurrent infections. For example, approximately 21% of soldiers not infected with NG were Black relative to 59% of soldiers with single occurrence NG infections and 70% of soldiers with repeat NG infections. **Table 13** summarizes population demographics for soldiers with single and repeat infections along with soldiers with no identified infections.

Approximately 4.8% of soldiers had at least one documented CT infection exclusive of NG, 0.4% had at least one documented NG infection exclusive of CT, and 0.6% of soldiers had one or more of both infections, bringing the total cumulative prevalence to roughly 6% for either infection during the 5 years (**Figure 21**). Annual prevalence for either infection increased each year, rising from 1.8% in 2015 to 2.4% in 2019 (**Figure 22**).

For both CT and NG infections identified, approximately 58% had documented medical encounters, and an average of 1.4-1.5 medical encounters per affected individual were recorded each year. When extrapolated to compensate for missing medical encounter data, a total of 82,356 medical encounters were estimated during the study period (roughly 16,500 per year, on average). Overall, 49,743 AC soldiers had at least one CT or NG infection with an overall incidence rate for the full study period of 2,787 cases per 100,000 person-years. Estimated annual morbidity burden measures (i.e., numbers of cases, individuals affected, and medical

encounters) are summarized in **Table 14**. Overall trends for CT and NG incidence and morbidity burden are also visually depicted in **Figure 23**. Consistent and significant linear increases in annual trends were observed (R^2 for linear trend >0.95 , data not shown). Incidence rates reached a high of 3,163 CT or NG cases per 100,000 person-years in 2019 (2,844 CT and 517 NG cases per 100,000 person-years). Relative to 2015, this reflects a 36% increase in CT and a 46% increase in NG rates.

Incidence rates over the five-year period were highest among female soldiers and those under 25 years of age, with rates as high as 12,159 CT and 1,329 NG cases per 100,000 person-years among women <25 years (**Figure 24**). Statistically significant disparities in incidence rates were observed across all demographic subgroups examined. Crude and adjusted IRRs for the independent variables assessed are outlined for both CT and NG in **Table 15**. Univariate analyses revealed common risk factors associated with both CT and NG infections. Statistically significant associations were observed by age group (e.g. <25 versus 35+), rank (e.g. Junior enlisted vs Senior officers), sex (Female versus Male), race/ethnicity (e.g., Black Non-Hispanic versus White Non-Hispanic), soldier category (Enlisted versus Officer), marital status (e.g., Never Married versus Married), education level (e.g., High School or Less versus Undergraduate/Graduate Degree), home of record region (e.g., South versus Northeast), and duty region (e.g., Non-US Pacific versus US Northeast). Soldiers under 25 years and junior enlisted ranks had the highest risk relative to their younger and more senior ranked Army peers. For example, soldiers under 25 had a near 14-fold higher incidence of CT and more than 7-fold higher incidence of NG than those 35 and older ($IRR_{CT} = 13.9$, 95% CI: 13.2 - 14.6; $IRR_{NG} = 7.3$, 95% CI: 6.7 - 8.0). This was even more pronounced when examining by rank with junior enlisted

soldiers having a nearly 23- and 13-fold higher risk relative to senior officers for CT and NG, respectively ($IRR_{CT} = 22.7$, 95% CI: 20.5-25.0; $IRR_{NG} = 12.9$, 95% CI: 10.7 - 15.4).

Soldiers originating from the Southern US census region had increased risk for both CT and NG when compared with referent soldiers (those from the Northeast US census region). Although risk was still elevated when the soldier had a duty location in the Southern US census region, particularly for NG ($IRR_{NG}=2.2$, 95% CI: 2.0 - 2.5), the elevation was less pronounced for CT where rates were highest in non-US countries in the Pacific region such as Korea and Japan ($IRR=1.7$; 95% CI: 1.6 - 1.8).

Most risk factors included in the multivariate model remained statistically significant. However, the elevated risk for NG infections observed among female soldiers relative to males during univariate analyses was not observed in multivariate analyses when other potential confounders were controlled. Age remained the strongest predictor of risk for either CT or NG among those analyzed in multivariate analyses (Adjusted $IRR_{CT/NG} = 7.7$ [95% CI: 7.4 - 8.1]); age was also strongly correlated with other associated risk factors such as rank, education, and marital status. Controlling for these potential confounders with multivariate analysis weakened the strength of association observed in crude univariate assessments for these covariates but did not negate their statistical significance.

Statistically significant risk factors identified for CT and NG incident infections were confirmed when assessing predictors of repeat infection (**Table 16**). Generally, the strength of association increased when assessing predictors of a singular occurrence infection compared to a recurrent infection. For example, odds of having a CT infection were roughly seven times higher in soldiers under 25 compared to those 35 and older ($OR = 7.1$, 95% CI: 6.6 - 7.6), whereas the odds were 13 times higher for soldiers under 25 having a repeat infection relative to older

soldiers (OR = 13.3, 95% CI: 11.1 - 15.9). An exception was observed when examining NG repeat infections for female soldiers – while they were significantly more likely than men to have a single case, they had lower odds of having a repeat infection. Black, Non-Hispanic soldiers had stronger odds of recurrent NG infection compared with White, Non-Hispanic soldiers. Home of record was not particularly predictive of recurrence; however, duty location was. As was seen with incident infections, duty assignment within the Southern US census region was predictive for NG infections (single occurrence and recurrent) more so than for CT infections. Assignment in non-US countries, particularly those in the Pacific, were also predictive for both CT and NG.

DISCUSSION

Integration of multiple MHS data sources yielded more accurate estimates of CT and NG incidence rates, from which a more robust assessment of recurrent infections, risk characterization, and associated disease burden among US Army soldiers could be made. Consistent with prior studies, repeat infections in soldiers were found to be common - 27% of women and 19% of men had recurrent CT infections during the study period, while 12% of women and 14% of men had recurrent NG infections ($p < 0.01$). For morbidity burden in particular, the estimated medical encounters nearly doubled over current reported DoD estimates which are limited to a small subset of diagnosed cases [9]. For example, 2019 CT medical encounters for Army AC soldiers were estimated to be approximately 17,300 as compared to roughly 10,200 encounters reported for all DOD AC service members inclusive of soldiers. The more complete case identification also improved risk characterization which had largely been limited to the DoD aggregate. While the findings generally confirm trends and risk factors reported nationally and within the DoD AC population, notable discrepancies were identified

such as the continued increase in NG incidence within the Army relative to the decline observed in the DOD [11].

The findings highlight the benefits of more comprehensive service-specific surveillance. The study also supports the National Academies of Science Engineering and Medicine 2021 consensus recommendations to increase STI surveillance measures, particularly among ‘people with military experience’ who they identify as a vulnerable, high-priority population [110]. The authors reflect on the disproportionate burden of STIs among military members and the social and societal interplay between service members and civilians. Within the report the authors call on public health agencies to modernize surveillance activities to improve the timeliness of data sharing and to explore new data sources to better capture STI incidence.

By augmenting reporting system data with two additional MHS data sources our study enhances Army surveillance and generates incidence estimates using methods that are in congruence with surveillance processes used in annually published DoD surveillance reports [11, 145]. The study provides a detailed summary of Army-specific trends and determinants of infection that was previously only available in aggregate for all DoD service branches. A modified means of quantifying attributable medical encounters was also implemented which addresses deficiencies with existing DoD morbidity burden measures for CT and also provides NG burden estimates that were not available. These refined estimates better reflect estimated healthcare utilization specific to the Army which can aid in determining associated costs (direct and indirect) and potential impacts to soldier readiness. The techniques used are definable and reproducible and support routine, systematic surveillance enhancements which can inform burden assessments within the Army.

Although the analyses did not identify new determinants of CT or NG risk which might aid in targeting public health interventions, the results provide a more comprehensive and complete accounting of disease burden which can better equip Army public health leadership in terms of resource procurement and allocation. The analyses added to the body of evidence, confirming the association between CT and NG infection with demographic correlates such as sex, race-ethnicity, and age. Documentation of relative risk by race-ethnicity provides an important metric which may aid public health officials engaged in eliminating such disparities. Age remained the most striking predictor of risk for both incident and recurrent CT and NG infections even after controlling for other factors. The strength of association increased when examining factors correlated with repeat infection. These findings provide further justification for targeting prevention towards populations with higher concentrations of young soldiers (e.g., initial entry training installations). Increased risk observed among women, however, may reflect a screening bias given that annual screening for both CT and NG are recommended for pregnant women and sexually active women under 25 [152]. The Army has a good track record relative to what has been reported in the general insured population in providing annual screening for over 80% of this target population on average each year [145]. Additionally, the analyses explored geospatial distribution of cases which may facilitate local prevention efforts; however, those findings should also be interpreted with caution as they may reflect more robust local screening and surveillance practices as opposed to true elevations in incidence. Likewise, potential lapses in data collection which are confined to a particular location may mask disparities in documented incidence. This may have contributed to the lower rates observed in the Central command region, for example, where data capture has been shown to be problematic [134].

While the more comprehensive database used in our analyses represents a surveillance improvement, the incidence and burden estimates produced remain conservative due in part to the asymptomatic nature of infection. Approximately 75% to 85% of CT infections are estimated to produce no symptoms which might prompt care seeking behavior [124]. Likewise, up to 60% of NG infections cause either mild or no symptoms [69]. This represents a significant public health challenge that makes surveillance enhancements even more important.

To further improve burden estimation, other data sources such as pharmacy scripts warrant further exploration for identifying missed cases [134]. Complimentary sources such as hospitalization data were ruled out for consideration based on exclusion from surveillance case definitions [8]. This omission was deemed inconsequential based on a review of morbidity burden estimates for CT which demonstrated that only 9 hospital days were documented in 2019 across all military service branches [9]. Other inherent limitations when using passive administrative data systems to find cases include under-reporting and erroneous or insufficient provider coding practices which can contribute to under-coding of infections [2, 102]. Complexities encountered when using laboratory records can also inhibit case detection given the reliance on non-standardized free-text fields; data entry errors and inconsistencies in recording practices can result in missed cases by the case detection algorithms [122, 123]. Additionally, some laboratory testing may have been outsourced to non-MHS laboratories and only captured through the MHS if the recorded diagnoses codes were updated to reflect the test result.

Also compounding interpretation of the data is the difficulty in surmising the extent to which changing trends in incidence rates or healthcare usage reflect true shifts in disease burden or variation in screening and surveillance practices. Systemic changes due to diagnostic or

technological advancements may also contribute to observed annual differences. As a case in point, data losses have been observed with recent changes in the MHS architecture. Specifically, the MHS began transitioning medical treatment facilities from the Armed Forces Health Longitudinal Technology Application (AHLTA) to MHS GENESIS for medical record keeping in 2017. During the study period, one installation transitioned to MHS GENESIS in Oct 2017 and another in Sep 2019 [145]. Although the completeness of data captured through the newer system is uncertain, the change likely resulted in a loss of medical and laboratory data for these two installations. Given that soldiers assigned to these two installations made up less than 5% of the Army AC population, and that the reporting system was not affected, the impact of this potential data loss is likely to have been negligible in terms of the overall rate and burden estimation [145].

Although these limitations result in conservative estimates, there are advantages afforded by the unified military health system which are not achievable through decentralized, national health and surveillance systems. Not only is more robust surveillance possible through consolidating multiple data sources, but the population evaluated constitutes a high-risk population with universal access to care, which further increases the likelihood of case identification. Additionally, the focus on AC soldiers (as opposed to all soldiers inclusive of National Guard and Reserve members who are only sporadically covered by the MHS) and the restriction to a timeframe that is not inclusive of the COVID-19 pandemic which impacted healthcare access, ensures a more complete burden assessment that is less subject to surveillance artifacts. The increased data capture obtained is advantageous as it is more responsive to epidemiologic shifts in incidence rates, and results in higher analytic power which may allow

detection of otherwise missed statistical associations within smaller population or exposure subgroups, including those within local and regional groups.

In conclusion, the study addresses important information gaps by providing a comprehensive picture of CT and NG incidence, disease burden, and correlates of risk within the Army AC population, which was not previously available. Improved burden estimates can better inform resource procurement and allocation and also inform clinical policies (e.g., testing policies that emphasize retesting positive cases within 30 days and increased use of expedited partner therapy [EPT] based on the high-reinfection rates). Additionally, the data consolidation performed minimizes problems that may be encountered with single-source data systems (e.g., missed disease clusters or outbreaks), and can also facilitate detection and correction of reporting deficiencies. The techniques used are reproducible and warrant consideration for standardization across each military service branch which also lacks similarly detailed burden assessments. Each service has unique operational and mission requirements and there are differences in how they interact with the civilian world; therefore, surveillance that is service-specific supports tactical prevention campaigns that capitalize on respective community needs. At this more granular level, nuances in population dynamics, local operations/policy, and possible enablers or impediments to intervention(s) can also be more readily ascertained and leveraged or countered as appropriate.

More work is needed to elucidate the full disease burden attributable to CT or NG within the Army and overall military population, to include an assessment of associated sequelae. Economic analyses should also be contemplated as they would further compliment such efforts and could assist in the identification of optimal, cost-effective prevention measures. Furthermore, continued exploration of data system capabilities to support routine surveillance and community

burden estimation is needed to identify and resolve gaps in case detection and public health response. The data consolidation performed herein paves the way for such analyses – the findings of which may have broader implications as identified deficiencies may reflect systemic problems with health surveillance that affect the wider military population and expand beyond these two infections.

CHAPTER 5: EVALUATING GAPS IN MILITARY HEALTH SYSTEM DATA FOR SURVEILLANCE OF CHLAMYDIA AND GONORRHEA IN US ARMY SOLDIERS (AIM 3)

This chapter expands upon a published manuscript completed in partial fulfillment of Aim 3 objectives.

Manuscript Citation

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INTRODUCTION

This study expands on the Aim 2 work described in Chapter four by examining *chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) case capture across the three Military Health System (MHS) databases used in the analyses (i.e., reporting system, outpatient encounter and laboratory record databases). As the last study in the series, it contextualizes the findings of the initial studies by quantifying and elaborating on the gains achieved in case capture through multi-sourced surveillance (Aim 2) relative to routine reporting (Aim 1). Additionally, the study explores system-specific gaps in case detection which may shed light on the quality and completeness of the data collected.

The long-term goal is to better understand MHS data system capabilities for CT and NG surveillance within the Army in order to improve disease burden assessments and to inform surveillance system refinements and public health practice. The overall objective is to determine system-specific case ascertainment and the benefits afforded by the multi-sourced surveillance performed relative to routine single-sourced surveillance. By examining the contributions of each data system, the study aims to identify gaps in surveillance or deficiencies such as under-reporting or under-coding which can, in turn, be used to inform local and enterprise level public health leaders and practitioners who are better positioned to execute targeted data collection and quality assurance initiatives.

The central hypotheses are that multi-sourced data will substantially improve incidence estimation among Army AC soldiers over single-sourced data (a >10% increase over reporting-based estimates is expected); gaps in reporting system case detection will narrow over time; laboratory records will offer the highest degree of case detection while medical encounters will provide the least; and substantial regional variation in case capture will be evident. These hypotheses will be tested by pursuing three objectives: 1) Assess system-specific CT and NG case

capture, 2) Examine system-specific annual trends in case detection, and 3) Evaluate geographic variation in case detection for each system (e.g., proportion of cases identified through installation reporting relative to the Army average).

The research proposed is *significant* because it provides context for CT and NG incidence and burden estimation using available MHS data, which can facilitate optimization of surveillance practices to include system enhancements and quality assurance initiatives. The study provides a practical example of applied epidemiology whereby a reproducible process for cross-referencing surveillance system case extracts can be used to identify and address deficiencies such as under-reporting. Additionally, the findings may support advanced statistical analyses designed to improve the accuracy of incidence rate and morbidity burden estimates by adjusting for expected reporting and coding inadequacies. For example, the CDC used statistical models that incorporated epidemiologic and clinical parameters, including under-reporting estimates, to conclude that CT and NG incidence rates were roughly twice those derived from reporting [97]. Thus, the knowledge gained from our evaluation of system-specific capabilities may be more broadly applicable to infectious disease burden estimation within and outside the Army as it can inform selection of modeling inputs.

METHODS

The study population consisted of Army AC soldiers, including AC trainees, who were active service members at any point during 2015 to 2019. The consolidated database used for Aim 2 analyses was repurposed for the study. The database consisted of CT and NG case data extracted from three MHS systems described in **Table 1**: the Disease Reporting System internet (DRSi), the MHS MART (Management and Analysis Reporting Tool) referred to as M2, and MHS Healthcare level 7 (HL7) laboratory data. Defense Manpower Data Center (DMDC)

personnel data were also used to generate person-time at risk estimates for incidence rate computations.

The proportion of CT and NG cases captured for each database (DRSi, M2, and HL7) was evaluated for each infection independently. Annual incidence rates generated from each system and the attributable percentage case capture were calculated and plotted for each system independently. The contribution of outsourced non-MHS outpatient care as derived from M2 was also evaluated. Reported case rates derived exclusively from DRSi, the Army's primary source for surveilling these notifiable conditions, were compared to rates derived from the enhanced three-source database. Annual percentage increases in incidence rates from this data supplementation were computed by comparing the single-source DRSi derived rates against the three-sourced derived rates.

Chi-square tests for linear trend were used to assess statistically significant variation over time. Cohen's kappa statistics were evaluated to examine agreement in case identification between paired data systems; agreement between all three data systems was assessed using the Fleiss kappa statistic. Customary kappa cut-points were used to interpret results (i.e., values ≤ 0 were considered indicative of no agreement, whereas kappa values of 1.0 were classified as indicative of perfect agreement; values between 0.81-.99, 0.61-0.80, 0.41-0.60, 0.21-0.40, and 0.01-0.20 were considered indicative of near perfect, substantial, moderate, fair, and none to slight agreement, respectively) [46, 48, 98]. Cases identified exclusively from outsourced care captured in M2 were excluded from the kappa computation given that this data source would not be expected to overlap with DRSi and HL7 identified cases.

Variation in case ascertainment by data system was also evaluated for each Army installation using methods which were consistent with Army reporting standards [144, 145].

Installation assignment for cases was determined based on Defense Medical Information System identifiers (DMIS IDs) for submitting medical treatment facilities (MTFs). Only installations included in routine Army reporting were evaluated and those with fewer than 20 CT or NG cases per year were excluded from the analyses to improve the reliability of the comparison. The proportion of cases captured from DRSi, M2, and HL7 for each installation were compared against the Army average. Standard deviations between installation capture and overall case capture within the Army were calculated and used in z-scores computations to examine statistically significant deviations from the Army average. Z-scores ≤ -2 were considered statistically significant and deemed to be an indicator of significant reporting or coding deficiencies at the installation, while those with values between -1 and -1.9 were flagged as moderate deficiencies. For more details regarding study methodology please refer to Chapter 2, Aim 3.

RESULTS

During the five-year study period, DRSi captured 83% of CT cases and 76% of NG cases, whereas HL7 laboratory records captured 87% and 67%, respectively, and M2 outpatient medical encounter data captured roughly 58% for each infection (**Table 17**). Approximately 83% of CT and 70% of NG cases were validated by secondary sources, of which nearly 45% and 31%, respectively, were documented in all three sources. A total of 387 CT cases (1.1%) and 376 NG cases (6.2%) were identified exclusively from medical encounters from non-MHS MTFs with no associated MHS medical encounters, lab results or case reports.

Agreement between systems was high for both CT and NG case capture (**Table 18**). Agreement between DRSi case reports and positive HL7 laboratory records was the highest when examining system paired data (Kappa for CT=0.90; kappa for NG=0.79). Agreement

between M2 medical encounter records and other systems was lower, however, it remained substantial (kappa for CT=0.65-0.69, kappa for NG=0.58-0.59). Agreement between all three systems was likewise substantial (kappa for CT=0.75, kappa for NG=0.65). System agreement was stronger for CT detection than for NG, which was expected given that it is more prevalent.

CT and NG incidence rates from the enhanced three-source database consistently increased each year, with the trend most closely reflecting that observed when the reporting system was used exclusively as compared with trends observed when laboratory or medical encounter records were examined independently (**Figures 25-26**). Incidence rates generated through medical encounter surveillance, albeit much lower, followed a similar trend with rates consistently increasing from year to year. Although trends were similar when comparing rates produced exclusively from laboratory surveillance to those from the enhanced three-source surveillance, a deviation occurred when laboratory generated rates dipped slightly in 2019.

Overall incidence rates derived from the enhanced three-source database were higher relative to rates generated from the single-source reporting system, reflecting a 17% and 24% increase in respective CT and NG incidence rates over the five-year period (**Figures 27-28**). The rate differences between the two databases (i.e., single-source reporting system versus the enhanced 3-source system) decreased over the study period, most remarkably in 2018. For CT, the percentage of missed cases which drives the rate differences decreased from 18.2% in 2015 to 14.6% in 2019. Similar declines in missed NG cases also occurred with the proportion of missed cases dropping from 27.3% in 2015 to 21.7% in 2019.

An examination of system-specific case capture by Army installation revealed considerable variability by location (**Figures 29-34**). CT case capture from the reporting system increased substantially (by 3 percentage points for the total Army AC population) in 2018 and

remained steady in 2019 at 85.4% (**Figure 29**). CT case capture through the medical records system increased by 10 percentage points in 2016 relative to 2015, rising from a low of 50.8% case capture to become relatively stable with 57.6% capture observed in 2019 (**Figure 30**). CT case capture from laboratory records consistently declined over the five-year study period, dropping from a high of 89.8% in 2015 to 81.5% in 2019 (**Figure 31**).

System performance in terms of CT detection varied considerably each year by installation with several installations showing moderate to significant reductions in system case capture relative to the Army average (**Table 19**). The reporting system showed the least variability in case-capture across installations; the most extreme deviations were observed in 2017, when installation case capture varied between 33% and 97%. For the medical record system, the most extreme differences when comparing installation case capture were observed in 2015 (30% compared to 100%), and for the laboratory system the most extreme differences occurred in 2019 (15% compared to 100%). One installation which transitioned to the MHS GENESIS record management system subsequently had significant drops in case capture through both the medical and laboratory records systems. Another installation had an extreme and mysterious drop in laboratory system capture that occurred in 2019 - dropping from 90% to 15% case capture.

Similar trends in system-specific case capture were observed for NG cases (**Figures 32-34**). NG case capture from the reporting system increased from approximately 73% in 2015 to 78% in 2019 with a substantial jump of 5 percentage points beginning in 2018 (**Figure 32**). NG case capture through the medical records system revealed no discernable trend with rates fluctuating between the 55% observed in 2015 and the 57% observed in 2019 (**Figure 33**). NG

case capture from laboratory records consistently declined over the five-year study period, dropping from a high of 76% in 2015 to 60% in 2019 (**Figure 34**).

System-specific NG case ascertainment varied considerably each year by installation (**Table 20**). Roughly half the installations that were evaluated with CT were excluded from the NG assessment due to low case counts. Of those that remained, several had moderate to significant decreased case capture relative to the Army average. Case capture varied the most for the laboratory system which had percentage capture extremes across installations from 1% to 96% for the latter four years. This differential was driven by one installation which had a drop in case detection from 51% in 2015 to a sustained 1% to 3% for the remaining years. If this outlier were removed the variability was more reasonable, with the next lowest case capture at 51%.

DISCUSSION

The study describes a sizable data gap between the military reporting system (the surveillance standard used in Army reporting) and enhanced surveillance achieved through integration of laboratory and medical encounter data. The multi-sourced data improved case capture, generating estimates over the study period that were approximately 17% higher for CT and 24% higher for NG. Further examination of these missed cases provides insight into under-reporting, which is known to be problematic albeit not well understood.

The evaluation of system-specific case capture also sheds light into other potential surveillance gaps. Notably, medical encounter records proved to be the least effective source for capturing both CT and NG cases with roughly 42% of both cases missed in the absence of the other two databases. Laboratory data had better performance in identifying CT cases relative to the reporting system (87% capture versus 83%); however, that was not observed for NG for which reporting performed better (76% capture versus 67%). Additionally, system performance

in terms of case capture through the laboratory system decreased for both infections over the five years. Overall, gaps in case detection were more prominent for NG with 30% of cases identified solely from one data system compared to the 17% of CT cases identified exclusively from a single source.

Although no single source provided optimal case ascertainment, agreement in case capture between systems was strong, demonstrating reliability of the data. MHS reporting and laboratory record system agreement for CT case capture was classified as ‘near perfect’ ($\kappa=0.90$), and all other surveillance system pairings for CT case capture had substantial agreement ($\kappa: 0.65-0.75$). Agreement between systems for NG case ascertainment was diminished relative to CT detection. Moderate agreement was observed when M2 was paired with either DRSi ($\kappa=0.59$) or HL7 ($\kappa=0.58$) and substantial agreement was observed when DRSi was paired with HL7 ($\kappa=0.79$) or all three sources were used ($\kappa=0.65$).

To our knowledge, our study is the first to assess system performance and agreement for STI detection using these data systems and it further adds to the body of literature which recommends surveillance enhancements through integration of multi-sourced CT and NG case data. For example, a study examining CT or NG rates within deployed and overseas military populations using two data sources (MHS laboratory and medical encounter data), also found that laboratory data identified a substantially higher proportion of cases relative to ICD-coded encounter data [128]. They further attest that exclusion of additional administrative data systems contributed to conservative estimates as compared to studies among deployed military members using four sources (laboratory, reporting system, medical encounter, and pharmacy records), and advocate for enhanced surveillance using all available data [134].

Similar conclusions have been reached when assessing CT and NG reporting system data. A 2013 study evaluating the predictive value of case reports for CT and NG detection concluded that reporting alone will underestimate incidence and burden estimation [13]. The authors found that the MHS reporting system had a positive predictive value over 80% for both infections when compared against the laboratory records as the gold standard. Although the specificity was high at over 98%, the sensitivity was lower at 65% for NG and 62% for CT.

Notably, the gap in reporting system case detection (a proxy for under-reporting) decreased over time. This may reflect systemic enhancements to the reporting system as well as educational campaigns to improve reporting compliance. For example, a case finding module was added in 2011 to facilitate identification and reporting of laboratory confirmed cases of reportable conditions [113]. Although this functionality was available for the full study period, awareness and use of the module likely increased over time, especially as public health centers began monitoring completeness and timeliness of reporting as an MHS performance metric. Increased reporting during routine medical encounters or local screening initiatives may have also contributed. Additionally, the contrasting decline in laboratory system capture allowed for the reporting system to capture a larger share of identified cases.

Another contributor to changes in system-specific case capture occurred during the study period when the MHS began transitioning MTFs to the MHS GENESIS platform for medical record keeping. Two installations transitioned, one in Oct 2017, and another in Sep 2019, which likely contributed to decreased medical and laboratory data for these affected installations [145]. This change may have contributed to the 2018 drop in CT and NG case capture from enhanced surveillance. The impact of this potential data loss in terms of overall rate computation, however,

is believed to have been negligible given that soldiers assigned to these installations made up <5% of the AC soldier population [145].

In addition to providing a proxy for under-reporting which may be used to improve disease modeling and estimation efforts, our study examined regional system-specific case ascertainment for CT and NG cases in the Army using three administrative data systems commonly used for surveillance. Integration of the data enabled an assessment of reporting and coding practices (strengths and deficiencies) across installations. The considerable variation observed across Army installations warrants further exploration to facilitate targeted interventions that improve reporting/case documentation, and potential data-driven public health response. Some concerning drops in medical and laboratory case detection were noted at installations transitioning to MHS GENESIS with 0% of CT and NG cases identified from laboratory records. Another installation dropped to a near 0% for laboratory case capture, but only for NG. It's possible that this was driven by a local change such as outsourced testing of NG isolates. The systemic drop in laboratory case capture warrants exploration as it may reflect changes to coding practices that should be considered in the case detection algorithms. By examining these types of metrics, public health professionals can zero in on what is causing the anomaly and take corrective actions as warranted and also inform surveillance practices in the process.

While the multi-sourced database used in our study leverages the power of three commonly used MHS systems, the incidence and burden estimates generated remain conservative. Like the authors before us, we acknowledge the benefit of integrating additional data sources such as pharmacy records as another means of finding additional missed cases. However, unavoidable limitations when evaluating CT and NG burden cannot be overcome

when relying on administrative surveillance systems, regardless of how exhaustive the data integration process is. Aside from missed asymptomatic infections not detected through recommended or enhanced screening initiatives, under-reporting can also be problematic and provider coding practices can result in under-coding of infections [2, 102]. Data entry errors or inconsistencies can also result in missed cases during surveillance – this is particularly true for case detection using laboratory records given that identification relies on pre-defined algorithms to query non-standardized free-text fields [122, 123].

Regarding the gaps identified between data sources, many factors may contribute. Reduced case detection using medical encounter records may reflect use of presumptive symptom-based or screening-based ICD codes which do not get updated with a definitive CT or NG diagnosis upon receipt of laboratory confirmation or a confirmed case report. Additionally, laboratory testing could have been performed at non-MHS laboratories – under these circumstances, a CT or NG diagnosis and/or case report may have been recorded for positive tests received, but there would be no corresponding MHS laboratory record to query in the HL7 data. Likewise, if CT or NG was diagnosed by a non-MHS healthcare provider and submitted as a medical encounter claim for MHS reimbursement, the associated M2 MHS encounter record would have no corresponding HL7 laboratory or DRSi case report.

In summary, the integration of multiple data sources substantially improved case capture to yield more reliable incidence estimation over reporting alone and the process facilitated a review of surveillance practices which can aid in further system and surveillance enhancements. Additionally, the study demonstrates how system-specific gap assessments can be used to drive local surveillance refinements to improve reporting and coding practices. Continued gap assessment is a worthwhile endeavor to identify and address deficiencies – more frequent

assessment (e.g., quarterly) would be beneficial to enable timely resolution. Because the discrepancies and deficiencies identified are not unique to the Army, analyses and resulting surveillance enhancements could potentially be standardized across the military services. Furthermore, the findings may have broader implications as they can inform national modeling efforts to improve CT and NG estimation while also facilitating similar modeling within the military..

CHAPTER 6: SUMMARY AND DISCUSSION

Synopsis

AIM 1

Aim 1 analyses confirmed population level trends in reported CT and NG case rates and demographic correlates of infection (i.e., age, sex, and race-ethnicity) among Army soldier and US adult study subjects which were consistent with those published in the literature. As expected, crude population rates were elevated among Army AC soldiers relative to US adults 18-64 years of age. Standardizing reported CT case rates by age and sex diminished the risk difference between the two populations as hypothesized without eliminating the observed elevation. The risk difference dropped from a near three-fold elevation among soldiers (unadjusted $RR=2.86$) to a near two-fold elevation among soldiers (sex- and age-adjusted $RR=1.84$). Surprisingly, the same could not be said for reported NG rates. Although comparative population level NG rates were elevated in the Army, crude case rates tended to be higher nationally for each age and sex stratum evaluated, with the exception of females under 25 years old. This deviation may be due to the fact that women in this age group are prioritized for annual screening, which is more effectively implemented for female soldiers than for their civilian counterparts [111, 141]. With sex- and age-adjustment it became apparent that nationally reported NG case rates were elevated when these population dynamics were controlled. The 44% increase in reported case rates within the Army relative to the US adult population (unadjusted $RR=1.44$) dropped to the point that the rate differential was significantly lower among Army soldiers (sex- and age-adjusted $RR=0.74$). Not only was this finding contrary to the hypothesized effect, but the results also differed from previous studies which showed elevations in adjusted NG rates among soldiers [131]. The disparity may reflect a disproportionate under-representation

of high-risk sub-groups within the Army population (e.g., MSM) or other unmeasured confounders [34, 82].

The study also highlights regional differences in reported case rates between the two study populations that are not readily available. While detailed community level data are routinely published for both populations, the data are segregated and regional comparative studies have largely been limited to comparisons of crude rates [145, 154, 155]. Additionally, the previous comparisons made focused on specific clinic or installation populations [77, 131, 162]. This study addressed the information divide by using comparative US census regions to examine rates between the two populations. Regional elevations in CT and NG reported case rates observed among AC soldiers differed from those reported nationally given that the Army is a more mobile population with deployments and duty assignments within foreign countries. These population dynamics may contribute to the contrasts observed when comparing the geographic spread of infection between AC soldiers and US adults. For example, the greatest CT rate elevations were observed among Army members with duty locations in Pacific countries which would not be captured through national surveillance. While the lowest rates of reported CT and NG infections were observed within the Northeast US census region for both the Army and US adult cohorts, there was deviation in terms of ranking (e.g., the Southern US census region had the highest national rates for both infections, while this region [albeit elevated] ranked lower among Army soldiers) [34].

AIM 2

Aim 2 analyses expanded upon those conducted in Aim 1 by supplementing the Army reporting system data with MHS medical encounter and laboratory records. Because the MHS represents a unified healthcare system and all service members are universally insured through a

common healthcare payer (TRICARE), a more complete population level assessment of disease burden can be made relative to that afforded by national data which are further limited to disparate administrative data systems which many uninsured Americans may be less likely to access. The data augmentation performed with Aim 2 not only provides an improved estimate of CT and NG incidence within the Army AC soldier population, but it also offers insight into what might be expected nationally had similarly centralized data been available. The Army data consolidation also facilitated a more in-depth review of incidence patterns, risk characterization for both incident infections and recurrent infections, and attributable morbidity burden in terms of estimated medical encounters. Both recurrence (a risk factor for sequelae such as pelvic inflammatory disease and infertility) and attributable healthcare burden are notable metrics as they provide a glimpse of the potential impact on soldier health and medical readiness.

The enhanced three-source data system affirmed trends and risk factors observed among AC soldiers through reporting system data while also providing a more comprehensive Army-specific risk characterization that was not available. Additionally, high rates of reinfection (21.4% for CT and 13.6% for NG) were confirmed which were generally higher than those reported nationally [63]. Rates of recurrent infections were also higher than those found in the DoD (15% for CT and 11% for NG) when two of the data sources were examined (reporting system and medical encounter data) [117]. Risk factors associated with repeat infections were consistent with those documented for incident infections; however, the strength of association increased. Differences in risk by duty location and home of record were observed with incidence rate ratios by home of record regions more closely aligning with those reported nationally and duty assignment regions capturing risks associated with military overseas assignments. Finally, the study provided an improved accounting of morbidity burden parameters such as attributable

medical encounters. Estimates generated included NG burden estimates not available in published reports, and CT burden estimates accounted for undiagnosed cases which were missed in these assessments. Approximately 17,000 CT and 3,300 NG visits were estimated in 2019 alone, with the CT estimate reflecting nearly twice the burden reported for the entire DoD during 2019 [9].

The study illustrates the necessity of consolidating MHS data sources to more reliably estimate CT/NG incidence and associated morbidity burden. It also makes a compelling case for standardizing the process by conducting similarly enhanced service-specific analyses. Providing leaders with information specific to their population can facilitate resource allocation and implementation of targeted interventions which capitalize on the tactical expertise of local public health assets who understand the nuances and population differences which are unique to each service. Furthermore, the observed high morbidity burden as well as the high rates of recurrent infection support the need for increased screening in high-risk populations to include a renewed emphasis on recommended rescreening and administration of EPT for those testing positive.

AIM 3

The Aim 3 analyses again build on work performed for the prior Aim, by examining the contributions of the three passive surveillance systems used in detecting CT and NG. Gaps in case detection identified between systems provide insight into under-reporting and other deficiencies in case capture that contribute to conservative estimation of incidence and morbidity burden. While substantial agreement between data systems was observed, the gaps were also substantial with roughly 42% of cases missed through diagnosis codes documented during medical encounters. Under-reporting for CT and NG was estimated at 17% and 24%,

respectively. Notable declines in laboratory system case capture were also documented over the study period.

The study affirmed the hypothesized substantial increases in rate estimation with enhanced surveillance as well as the higher contribution in case ascertainment achieved through reporting and laboratory system data relative to medical encounter data. Decreased reporting system gaps were also confirmed over the surveillance period which may be suggestive of system enhancements or improved reporting practices. The consistent drop in laboratory system capture, on the other hand, was unexpected and warrants further exploration as this may be indicative of increased outsourcing of tests and/or data recording practices which fall outside the case detection algorithm. Additionally, considerable geographic variability in case capture was documented across Army installations; therefore, leveraging the integrated data to conduct gap analyses can inform local action to correct identified deficiencies such as under-reporting or under-coding.

Strengths and limitations

STRENGTHS

The studies contribute to a better understanding of the epidemiology of CT and NG infections among Army AC soldiers who constitute a high-risk population that has been prioritized for prevention and surveillance by a consortium of experts [110]. Each study addresses long-standing knowledge gaps not fully explored in the literature while also updating and addressing limitations of prior studies. Collectively, the studies provide a more accurate accounting of soldier morbidity burden attributable to CT and NG which can inform surveillance and disease prevention as a means to improve soldier health and medical readiness.

A major strength common to each of the three studies, lies in the data used in the analyses. The MHS is uniquely positioned to allow more robust population assessments given the universal healthcare coverage provided to active service members and the existence of a unifying health system to document care received. The data examined cover large numbers of at-risk soldiers (approximately 840,000 with 2.35 million person-years of observation) which add to the statistical power of the studies. The study participants included exceed sample size requirements needed to reliably assess statistically significant differences within and between groups.

Additionally, methodologic techniques were used to ensure optimal statistical power and valid comparisons. For example, Aim 1 analyses were designed to compare Army and civilian populations using similarly collected and defined reporting system data – this constitutes an improvement over prior comparisons made using Army clinic population data from a single installation and national case report data. Direct standardization techniques used in the Aim 1 study also employed a standard more suitable to the highly skewed Army population age and sex distribution.

Aim 2 analyses further leveraged multiple MHS data systems to improve upon CT and NG risk characterization as well as incidence and morbidity burden estimates. The more robust dataset confirmed findings from the Aim 1 risk analysis, producing similar results for shared variables with increased precision in the estimates generated as other covariates were controlled in the model. This information was previously only available in aggregate for DoD service members with limited Army specific analyses of incidence rates and associated risk factors obtained from single source surveillance. Sub-optimal morbidity burden estimates were also restricted to the DoD and provided an incomplete picture of disease burden directly attributable

to CT; NG burden was likewise incomplete and not discernable from other STI conditions with which it was presented in aggregate. By providing a comprehensive assessment specific to the Army, the findings provide stronger evidence that may aid in developing targeted interventions which are appropriately tailored for the affected community.

Aim 3 analyses compliment this work by exploring surveillance system capabilities in assessing disease burden. Statistical techniques used to examine the reliability or agreement between systems can provide evidence-based performance standards for assessing system data quality and completeness. Furthermore, a strength of all of the analyses performed is that they are based on standardized case definitions and data which are common to military beneficiaries. Therefore, they are reproducible and show promise for standardized service-specific burden assessments and provide a mechanism to further explore and enhance quality assurance, surveillance, and prevention practices.

LIMITATIONS

A limitation shared across the inter-related studies is that the CT and NG estimates generated remain conservative based on the preponderance of asymptomatic and mild infections which can evade detection in the absence of screening. These clinical aspects negatively impact surveillance which is reliant on patient care seeking behavior. Thus, when a case is identified it can be difficult to determine when and where transmission occurred. This can complicate geographic assessment, particularly for a highly mobile population such as Army AC soldiers. Inadequate provider coding and reporting practices are also problematic and can result in lower case detection [2, 102]. The HL7 messaging data used for recording laboratory test orders and results are also have drawbacks given the reliance on non-standardized free-text fields; therefore, it is possible that some cases were not detected due to inconsistent or erroneous entries (e.g.,

misspelled terms) [122, 123]. The extent to which the data are compromised by these limitations is not well understood and highly variable from one facility to the next. While the studies conducted provide a better understanding of surveillance system capabilities and disparities in Army case detection, the findings are subject to changes in system/healthcare infrastructure, technology, supporting personnel, and clinical coding/reporting practices, to name a few. Continued monitoring and more in-depth analyses are needed to optimize system performance, surveillance, and prevention.

Another limitation is that the analyses were restricted to AC soldiers, a common practice in military health surveillance given the incomplete capture of healthcare data for Army Reserve and National Guard members who are only eligible for MHS care during brief periods of service activation. Army cadets were also excluded from the analyses because they are not included in the DMDC personnel data necessary to determine person time at risk and pertinent demographic information. Family member beneficiaries were likewise excluded. While restricting the analyses to AC soldiers maximizes confidence in the estimates generated, the omission further underestimates morbidity burden for Army beneficiaries. The AC soldier population examined may not be generalizable to these beneficiary populations or other US population sectors.

Aim 1 analyses were further limited due to the reliance on abbreviated grouped data which prevented more in-depth risk characterization and geospatial analyses. While this limitation was improved with the acquisition of person-level data for Aim 2 analyses, some data elements were lacking (e.g. zip codes). The DMDC personnel data extracts also differed between studies, which introduced negligible anomalies in person-time at risk and rate computations between the studies with slight reductions in reported case rates estimated from the enhanced multi-sourced database used in Aim 2 relative to those generated in Aim 1. Another limitation in

comparing data capture as was done in Aim 3, is that the HL7 laboratory data were limited to positive cases. Therefore, it was not possible to delve further into discrepancies in laboratory testing or screening practices, or to use the lab data as a gold standard as previous studies have done in order to examine metrics such as sensitivity, specificity, and positive predictive value for the other two datasets [13]. An assessment of variability in case detection by anatomic site was also not possible given this limitation – such an assessment would aid in determining extragenital testing practices and attributable burden for available paired multi-site specimens.

It should also be noted that the morbidity burden assessment performed in Aim 2 is limited to direct care for CT and NG infections. While measures were taken to extrapolate the available medical encounter data to account for cases missing such data, the estimates likely remain conservative. Given that 42% of cases were missing medical encounter records with CT and NG diagnoses, it is possible that the cases with documented encounters, which were used in the extrapolation, also lacked a complete capture of encounters required per individual affected. Indirect productivity losses associated with the direct care identified are also not included nor is the morbidity burden due to potential sequelae attributable to untreated infections. The burden associated with CT and NG attributable sequelae is likely to surpass that directly observed for CT and NG care given the potential need for more intensive and complicated treatment requirements (e.g., hospitalizations, emergent surgical requirements for ectopic pregnancy, and frequent infertility treatments).

Furthermore, there are limitations when evaluating incidence trends over time as it is challenging to distinguish true changes in disease rates from changes introduced by diagnostic or technological advancements or from differences in screening and surveillance practices. The same holds true when comparing incidence across installations or regions. Increased rates may

be indicative of improved coding/reporting/screening practices and/or true differences in rates or morbidity burden. For example, a screening initiative in South Korea was shown to introduce disproportionately high installation rates until the program was discontinued [90, 128].

Implications and Path Forward

IMPLICATIONS

The analyses address imbalances or lapses in information concerning CT and NG infections within the Army AC soldier population which have implications for surveillance and prevention. The Aim 1 study uses comparative data to contextualize the complex relationships between AC soldiers and the broader US adult population which can influence reported incidence rates. The analyses provide a much-needed update to a topic that was last addressed in the peer-reviewed literature more than two decades ago when the epidemic trajectory contrasted greatly with recent events. The improved estimates of relative risks between and within groups revealed unexpected elevations in reported NG rates among US demographic peer-groups relative to AC soldiers. The standardization processes used in the study also illustrate foundational epidemiologic principles that should be applied when comparing dissimilar populations. We recommend reinforcing rate adjustments by age and sex as a common practice to avoid the tendency to make misleading comparisons of crude data. This holds true not only for military to civilian population comparisons, but also for comparing population subsets (e.g., Army installations) which may have disproportionate representation by these key factors.

Aim 2 analyses give additional perspective for the Army's reported case rates while solidifying the need to supplement reporting system data to improve incidence and morbidity burden estimation. The study provides a more accurate accounting of CT and NG incidence within the overall Army AC population and important subsets of the population to include risk

characterizations that were not readily available. The results generated also revealed trends that were masked by DoD analyses. Additionally, the study offers information on morbidity burden that was previously only obtainable in aggregate for the DoD and limited to diagnosed CT infections. In generating these burden estimates, we provided a mechanism to compensate for the sizeable data gap that occurs when relying exclusively on ICD codes to identify cases. These improved estimates not only yield a better approximation of the impact these infections pose on productivity and medical readiness, but they can also aid military public health leaders in advocating for appropriate prevention and clinical resources. Additionally, the assessment of recurrent infections provides a necessary update for the Army population using a richer dataset. The results demonstrate a high prevalence of repeat infections and highlight the need for more vigilant prevention measures which include periodically retesting positive cases and increasing use of EPT. We recommend that the data consolidation and analyses performed be standardized and evaluated for each service branch, independently. Such analyses are a great compliment to the DoD analyses performed and also facilitate more effective service line prevention efforts which are better suited to account for unique differences between the service populations. This practice can also be more broadly applied for non-STI conditions.

Aim 3 analyses showcase case ascertainment for three critical MHS data systems which can inform surveillance enhancements and improve incidence density and burden assessments. A substantial improvement in CT and NG case capture was achieved through data integration over reporting alone. The additional cases identified can serve as a proxy for both under-reporting and under-diagnosis that may be useful in building predictive statistical models such as those used nationally to estimate incidence and prevalence. Additionally, by examining system-specific differences in case capture, particularly at the more granular installation level, reporting and

coding deficiencies identified can be more easily targeted for correction. Our findings show considerable variability and room for improvement across a number of installations. We recommend these types of gap analyses be routinely revisited with more frequent periodicity to assure data quality. As was recommended with multi-sourced surveillance enhancements, doing similar gap analyses within each service can optimize data quality and performance. There are anecdotal reports of NMCPHC successfully using HL7 laboratory data to generate internal auditory reports that reflect reporting completeness and timeliness to improve reporting compliance at Navy MTFs (personal communication, Gosia Nowak, NMCPHC).

Taken together, findings from the research can support surveillance enhancements, facilitate quality assurance initiatives, re-enforce clinical testing guidelines, and direct targeted prevention for high-risk groups within the Army or larger military cohort – all of which have implications for public health policy. Within the STI National Strategic plan, military bases have been identified as a high impact setting because of unique predisposing population characteristics (i.e., the concentration of high-risk members who are disproportionately vulnerable due to a range of social and economic factors) and the efficiencies gained from the military health infrastructure [151]. Thus, we further recommend that the risk analyses performed, which add to the collective empirical evidence, serve to bolster prevention in high-risk groups, most notably in soldiers under 25 years of age.

PATH FORWARD

Although the studies focus on CT and NG surveillance within the Army, the epidemiologic techniques and surveillance enhancements employed are reproducible and warrant standardization across the military service branches. This is particularly important considering the ongoing consolidation of military medical and public health services which was codified

under the 2017 National Defense Authorization Act (NDAA). The recommendations generated from the studies are broadly applicable to all services which can benefit from similar comparative analyses, burden assessments, and gap analyses using multi-sourced surveillance system data as the standard. And the processes may be extended to other conditions of public health interest.

Going forward, other data sources such as pharmacy records should also be considered as another enhancement to maximize case capture. Revisiting the analyses as new data become integrated is important to continually identify and remedy surveillance gaps and to address disparities. Exploration of additional data sources may become increasingly important in light of the observed data loss with MHS GENESIS and potential increases in outsourced laboratory testing and medical care. Further examination of surveillance and prevention standards across the service branches could aid in identification of best practices and deficiencies, and better position the DHA to leverage resources for the collective good (e.g., reduced CT and NG infections, improved reproductive health and well-being, and increased medical readiness).

Because CT and NG reduction can circumvent downstream events such as sequelae from untreated infection, a thorough examination of the incidence, prevalence, and morbidity burden associated with these outcomes is needed to understand the full burden attributable to these infections and potential operational impact. Although there is not a comprehensive assessment of the many attributable sequelae, studies examining specific outcomes such as PID, have shown an elevation within the Army relative to other services which begs the question of what factors may increase risk among soldiers [6, 104]. This question has led researchers to theorize that screening policy differences within the high-risk initial entry training (IET) population are a significant contributing factor given that the Army remains the only service not providing universal

screening for CT and NG to incoming female trainees with additional targeted screening for male trainees. Forging a path forward for the betterment of soldier health means clearing obstacles such as this screening divide. Thus, the DHA would be well served to investigate the impact of these screening disparities, particularly in the under-studied male population.

The need for screening in this age cohort can't be overstated based on the confirmed excess of CT and NG infections among soldiers under 25 – a group which is over-represented in the IET population by a factor of 9 to 1. Although the Army does an excellent job of implementing recommended annual screening for women under 25 within the first year of accession (as do other services), the disparity in IET screening for CT and NG presents a significant screening delay that places soldiers at a disadvantage relative to their military peers [18]. Further studies to include economic modeling are needed to identify an optimal and cost-effective IET screening regimen. Although two studies have demonstrated that CT screening can be cost-effective in the IET setting for both female and male trainees, Army leaders were not swayed to enact policy changes, possibly due to the marginal return on investment relative to that accrued by society which was demonstrated by the studies [84, 114]. As disease burden and antibiotic resistance have increased in the intervening years, it is worth revisiting these studies to incorporate a more thorough accounting of direct and indirect costs associated with sequelae that may be avoided under screening scenarios that employ the more sensitive dual CT and NG testing performed today. Furthermore, standardizing screening across services has the added advantage of increasing the economies of scale (e.g., discounted bulk testing/purchasing) that can maximize returns on investment as resources can then be leveraged to reduce program costs.

Additional studies to address limitations identified are also justified. For example, an examination of provider screening practices regarding compliance with recommended retesting

for identified cases would be beneficial in identifying and correcting deficits. This would necessitate a review of all resulted CT and NG test orders (positive and negative) and not just the positive records we had accessible for our studies. An added advantage of a broader examination is that the more comprehensive dataset could also be used to review paired samples (e.g., urogenital and extra-genital), which in turn could inform burden and incidence estimation which largely rely on urogenital-only testing, a practice that has been shown to miss cases [45, 91].

More comprehensive geospatial analyses to examine age-sex adjusted installation level morbidity burden could also add to our understanding of the epidemiology of infection and heterogeneity in local testing and surveillance practices. And further data integration to include county/state level and service specific STI data could improve our understanding of sexual networks which might also aid in prevention. Such analyses should include when possible differences in community demographics, high-risk subgroups such as MSM, background HIV rates, screening practices, and other preventive or diagnostic resources.

Time-series analyses which examine associations between the length of service and CT/NG infections should also be considered. To date, there is one such assessment, but it was limited to an exploration of diagnosed infections which we found to be the least complete resource for identifying cases [55]. Additionally, advanced statistical modelling that encapsulates probable missed cases, similar to that used nationally, should be explored to elucidate expected and predicted incidence and morbidity burden [96].

Conclusion

STIs such as CT and NG have historically presented operational challenges for the military and continue to be problematic in terms of the sheer volume of service members affected. The Army has the highest infection rates of the military service branches, and studies

examining sequelae associated with untreated infections also show an elevation among Army members. However, burden and risk characterizations specific to the Army are lacking, as are analyses of surveillance practices. Collectively, these studies fill many knowledge gaps that confirm a high disease burden (particularly in those under 25 years of age) and demonstrate the value added of detailed Service level assessments. For example, disaggregation of Army's NG data from the overall DoD NG data revealed uniquely different trends whereby Army incidence rates continued to rise while overall DoD rates declined. The data integration and gap analyses performed also substantially improved incidence and burden estimates, which can be used to advocate for resource allocation and targeted interventions. And the findings offer insight into poorly understood surveillance aspects such as under-reporting and under-coding which can drive corrective action and improved estimation using statistical modeling.

Overall, the studies increase our understanding of the epidemiology of CT and NG infections in a high-risk, high impact population using reproducible and evidence-based analyses. They provide a foundation from which interventions may be developed and evaluated at more tactical levels unique to the service branches (e.g., installations, bases, ships, and camps). Furthermore, the findings may inform standardization of surveillance and prevention practices across the services which align with the NDAA recommended consolidation of public health resources under the auspices of DHA. The findings can have significant impact in terms of guiding public health policy for the Army and larger DoD community, with the goal of improved reproductive health and medical readiness.

Table 1. Data Source Descriptions and Research Aims Supported

Research Aims	Data Source	Description	References
1	CDC Atlas Plus	Dashboard developed by the CDC-NCHHSTP (National Center for HIV, Hepatitis, STD, and TB Prevention) which allows users to create and export customizable data tables and chart/map visualizations of STD data obtained from the NNDSS (see included data source description below).	[42]
1, 2, 3	Defense Manpower Data Center (DMDC)	Data management agency which maintains DoD personnel system for tracking DoD entitlements, benefits, and medical readiness for service members, veterans, and family member beneficiaries. The system is updated monthly to reflect current end of month demographic data (e.g, marital status) and personnel data (e.g., assigned unit).	[150]
1, 2, 3	Disease Reporting System internet (DRSi)	DoD system for recording reportable medical events and outbreaks. A total of 68 conditions which closely align with CDC and Council of State and Territorial Epidemiologists (CSTE) reporting standards for nationally notifiable conditions are monitored based on consensus recommendations from each Service. Conditions included were judged to pose a significant health threat that demands enhanced surveillance.	[10, 113, 145]
2, 3	MHS Health Level 7 (HL7) Laboratory Databases	HL7 formatted chemistry and microbiology records generated from MHS fixed medical treatment facilities (MTFs), managed by the Navy Marine Corps Public Health Center (NMCPHC). Because the MTF source systems allow data collection using free-text fields for key variables (e.g., test name and test results), the information collected is not standardized. NMCPHC uses validated algorithms to process the information for health outcomes such as CT and NG, which are prioritized for health surveillance.	[112, 122, 123]
2,3	MHS Management Analysis and Reporting Tool (MART), a.k.a. M2	DoD relational database accessible through an intuitive Business Intelligence interface that allows users to query and extract administrative claims and personnel data from the MHS Data Repository (MDR). M2 provides access to inpatient and outpatient medical encounter claims submitted from both MHS providers and non-MHS providers submitting claims for reimbursement through the	[53, 54]

Research Aims	Data Source	Description	References
		military health insurer TriCare. The system also houses ancillary MHS data including laboratory test orders and pharmaceutical scripts as well as enrollment and eligibility data for MHS beneficiaries. Data are limited to the most recent 5 fiscal years and the current fiscal year. M2-CAPER (MHS outpatient) and M2-TED-NI (Non-MHS outpatient) tables were used in the analyses.	
1	National Notifiable Disease Surveillance System (NNDSS)	CDC system for reporting approximately 120 nationally notifiable conditions including infectious diseases, bioterrorism agents, and noninfectious conditions. In collaboration with 7 different national health centers and the CSTE, conditions are selected and defined to ensure standardized reporting processes from nearly 3,000 health departments.	[39, 41, 43]
1	US Census Bureau Data	Publicly available population tables that are aggregated by demographic and economic variables of interest. The data are based on census surveys conducted every 10 years. Statistical analyses are performed to generate annual estimates that are informed by trends and data collected from more than 130 annual surveys and programs.	[147, 148]

Table 2. Surveillance Case Definitions for Reporting Confirmed CT and NG Cases

	DoD – DRSi [10]	CDC – NNDSS [30, 36, 41]
CT	A case with any of the following: • <i>C. trachomatis</i> identified by culture from any clinical specimen, or • <i>C. trachomatis</i> positive antigen from any clinical specimen, or • <i>C. trachomatis</i> nucleic acid (DNA) detected (example: PCR, sequencing, NAAT, probe) from any clinical specimen	A case with the following laboratory criteria: • Demonstration of <i>C. trachomatis</i> in a clinical specimen by detection of antigen or nucleic acid, or • Detection of LGV-specific antigen or nucleic acid in a clinical specimen, or • Isolation of <i>C. trachomatis</i> by culture
NG	A case with any of the following: • <i>N. gonorrhoeae</i> identified by culture from any clinical specimen, or • <i>N. gonorrhoeae</i> positive antigen from any clinical specimen, or • <i>N. gonorrhoeae</i> nucleic acid (DNA) detected (example: PCR, sequencing, NAAT, probe) from any clinical specimen	A person with laboratory isolation of: • Typical gram-negative, oxidase-positive diplococcic by culture (presumptive <i>Neisseria gonorrhoeae</i>) from a clinical specimen, or • Demonstration of <i>N. gonorrhoeae</i> in a clinical specimen by detection of antigen or detection of nucleic acid via nucleic acid amplification (e.g., Polymerase Chain Reaction [PCR]) or hybridization with a nucleic acid probe.

Table 3. Aim 1 Sample Size Computation, Army and US Comparison

Annual Population ¹				Reported Cases per 100 person-years ¹		Sample Size ²	
		Army AC	US Adults	Army AC	US Adults	Army AC	US Adults
80% Power	CT	461,000	200,449,000	2.15	0.75	1,303	566,694
	NG			0.35	0.24	4,171	1,814,322
90% Power	CT	461,000	200,449,000	2.15	0.75	1,867	811,914
	NG			0.35	0.24	5,976	2,599,550
¹ Based on averaged case and population data reported from 2015-2019, population rounded to the nearest thousand.							
² Derived from Open Epi Sample size calculation for cohort studies, 95%, two-sided significance level, and Fleiss methodology described in ‘Statistical Methods for Rates and Proportions’, formulas 3.18 & 3.19							

Table 4. Aim 1 Sample Size Computation, Within Army Comparison

		Annual Population ¹		Reported Cases per 100 person-years ¹		Sample Size ²	
		Female	Male	Female	Male	Female	Male
80% Power	CT	68,000	394,000	5.04	1.65	731	4,386
	NG			0.50	0.19	6,481	38,883
90% Power	CT	68,000	394,000	5.04	1.65	1,025	6,149
	NG			0.50	0.19	9,097	54,577
¹ Based on averaged case and population data reported from 2015-2019; population rounded to nearest thousand							
² Derived from Open Epi Sample size calculation for cohort studies, 95%, two-sided significance level, and Fleiss methodology described in ‘Statistical Methods for Rates and Proportions’, formulas 3.18 & 3.19							

Table 5. Variables Selected/Derived from MHS Datasets

Variable*	Description
ID	Patient SSN [Common Field]
DOB*	Date of Birth [Common Field]
D_event	Date of Event • Onset Date [DRSi] • Outpatient Visit Date [M2] • Specimen Collection Date [HL7]
Year	Year of Event (derived from D_event or DMDC file date in the absence of an event)
Incident_CT, Incident_NG	Derived per case definitions: 1=Incident (i.e., new event), 0=Non-incident
CT_count, NG_count	Derived chronological count of new CT infections Derived chronological count of new NG infections
Repeat CT, Repeat NG	Derived from CT_count or NG_count variables (0=Non-Case; 1=Single Case; 2+=Reinfection)
Concurrent	Derived: 1=Yes; 0=No; based on CT and NG infections recorded within a shared 30 day window
Age (years)	Derived: based on date subtraction (D_event – DOB); in the absence of an event date, the mid-year was used per CY (e.g., 07/01/YYYY – DOB)
AgeCat	Derived: <25, 25-34, 35+
Sex*	Female, Male
Race*	American Indian/Alaskan Native, Asian, Black, Native Hawaiian/Pacific Islander, White, Other/Unknown
Ethnicity*	Hispanic, Non-Hispanic
Race_eth	Derived: Hispanic or Non-Hispanic (NH) categories: American Indian/Alaskan Native-NH, Asian-NH, Black-NH, Native Hawaiian/Pacific Islander-NH, White-NH, Other/Unknown-NH)
MarStat*	Marital Status: Single, Married, Other (Divorced, Annulled, Separated, Widowed). Unknown
Edu_Level*	Highest educational level: ≤High School (HS) Diploma, Some College, College degree (Undergraduate or Graduate Degree)
HOR_state*	Home of record – US State of residence upon service entry
Region_HOR	Derived (US Census regions): Northeast, South, Midwest, West, Other/Unknown
DTYLOC_state*	Duty Location – US State where the service member physically reports for Duty

Variable*	Description
DTYLOC_country*	Country where the service member physically reports for Duty
DTY_Region*	Derived (US Census regions and non-US country groups): US regions: Northeast, South, Midwest, West; Non-US Regions: Europe (e.g., Germany, Italy, UK), Pacific (e.g., Japan, Korea), and Central Command (e.g., Afghanistan, Kuwait); Other/Unknown include US states/territories, and non-US countries
Rank*	Includes Enlisted (e.g., E1), Officers (e.g., O1), and Warrant Officers (e.g., W1) of all ranks
RankCat	Derived: Junior Enlisted (E1-E4), Senior Enlisted (E5+), Junior Officer (O1-O3), Senior/Warrant Officer (O4+, W1+)
S_cat	Derived soldier category: Enlisted, Officer
Source	File source: DRSi, M2-CAPER, M2-TED-NI, HL7, DMDC
Case-Source	Derived for CT and NG cases: DRSi Only, M2 Only, HL7 Only, DRSi and HL7, DRSi and M2, HL7 and M2, All sources
Person-Years	Derived from DMDC monthly record counts; summed person-months were converted to person-years
DMISID	Four-digit code that corresponds to the MTF where the soldier medical encounter occurred, the lab test was requested, and/or the case was reported
Installation	Derived for cases using DMISID codes in the clinical data and for non-cases using assigned unit zip codes in the DMDC data; codes were mapped to installations included in USAPHC annual reports using furnished look-up tables
Visit_count_yr	Derived for CT/NG cases with medical encounter data using unique encounter d_event dates per person per year
*Demographic variables used in analyses were obtained from DMDC using the soldier's last recorded record entry per calendar year.	

Table 6. ICD Codes Used to Identify CT and NG Cases from Medical Encounter Records

STI[^]	ICD9 codes	ICD10 codes
CT	099.41, 099.5*	A56*
NG	098*	A54*
[^] Based on primary (first-listed) or secondary (second-listed) diagnosis codes per outpatient encounter, 30 day gap-in-care rule applied to detect incident cases *Includes all trailing digits in the ICD code		

Table 7. Aim 2 Covariates included in Risk Analyses

Covariate	Data Type	Categories
Age Group	Categorical	18-24, 25-34, 35+ (ref)
Sex	Categorical	Female, Male (ref)
Race-ethnicity	Categorical	Hispanic, and Non-Hispanic racial groups: American Indian/Alaskan Native, Asian, Black, Native Hawaiian/ Pacific Islander, White (ref)
Region_Duty	Categorical	US: Northeast (ref), Midwest, West, South; Non-US: Pacific (Korea, Japan), Europe (e.g., Germany, and Italy), Central (e.g., Kuwait, Afghanistan, Iraq); Other/Unknown
Region_HOR	Categorical	US: Northeast (ref), Midwest, West, South, Other/Unknown
Education Level	Categorical	≤High School (HS), Some College, Undergraduate or Graduate degree (ref)
Soldier Type	Categorical	Enlisted, Officer (ref)
Marital status	Categorical	Single (Never Married), Previously Married (Divorced/Widowed/Separated), Married (ref)
Year	Categorical	2015 (ref), 2016, 2017, 2018, 2019
Rank[^]	Categorical	Junior Enlisted (E1-E4), Senior Enlisted (E5-E9), Junior Officer (O1-O3), and Senior Officer (O4+, including Warrant Officers; [ref])
^Excluded from multivariate analyses due to multicollinearity with age and education		

Table 8. Aim 2 Sample Size and Power Computation

		Population (Thousands)	IR per 100 p-years ¹	Sample Size (70% Power) ²	Sample size (80% Power) ²	Sample size (90% Power) ²
CT	Sex:					
	Female	68	5.54	492	655	917
	Male *	394	1.82	2,952	3,925	5,502
	Age:					
	18-24	181	4.54	58,069	70,630	90,082
	25-34	178	1.53	58,069	70,630	90,082
	35-44	84	0.34	30,270	37,198	47,985
	45-64 *	21	0.17	7,568	9,300	11,997
	Age:					
	18-24	181	4.54	8,448	10,577	13,925
	25-34	178	1.53	8,448	10,577	13,925
	35-64 *	105	0.31	4,900	6,135	8,077
NC	Sex:					
	Female	68	0.55	2,606	3,469	4,870
	Male*	394	0.35	15,636	20,813	29,216
	Age:					
	18-24	181	0.68	164,274	199,781	254,770
	25-34	178	0.28	164,274	199,781	254,770
	35-44	84	0.09	85,624	105,210	135,707
	45-64*	21	0.06	21,406	26,303	33,927
	Age:					
	18-24	181	0.68	33,142	41,498	54,639
	25-34	178	0.28	33,142	41,498	54,639
	35-64 *	105	0.08	19,223	24,069	31,691
¹ Based on case and population data reported from 2015-2019; a 10% increase in case detection above reported case rates (Aim 1) was assumed						
² Derived from Open Epi Sample size calculation for cohort studies, Fleiss methodology described in ‘Statistical Methods for Rates and Proportions’, formulas 3.18 & 3.19						
* Unexposed or reference group used in computations						

Table 9. Reported CT Case Rates and Relative Risk (Crude and Adjusted), AC Soldiers, 2015-2019

	Case rates/100,000 p-yrs	Crude RR (95% CI)^	Adjusted RR (95% CI)^^
2019	2,482	1.40 (1.36-1.44)	1.21 (1.14-1.29)
2018	2,391	1.35 (1.31-1.39)	1.18 (1.11-1.26)
2017	2,144	1.21 (1.17-1.24)	1.11 (1.04-1.18)
2016	1,953	1.10 (1.07-1.13)	1.09 (1.02-1.15)
2015	1,775	1.00 (ref)	1.00 (ref)
Female	5,037	3.05 (3.00-3.11)	2.42 (2.32-2.52)
Male	1,650	1.00 (ref)	1.00 (ref)
<25	4,127	14.77 (14.04-15.55)	13.70 (12.85-14.62)
25-34	1,391	4.98 (4.72-5.25)	4.61 (4.32-4.92)
35+	279	1.00 (ref)	1.00 (ref)
Asian	1,340	1.00 (0.95-1.05)	0.97 (0.90-1.04)
AI/AN	2,101	1.57 (1.41-1.74)	1.32 (1.17-1.49)
Black	4,334	3.23 (3.16-3.29)	2.52 (2.40-2.65)
Hispanic	2,370	1.77 (1.72-1.81)	1.49 (1.42-1.57)
NH/PI	3,242	2.42 (2.25-2.59)	2.07 (1.89-2.26)
White	1,343	1.00 (ref)	1.00 (ref)
Non-US			
Europe	2,307	1.19 (1.12-1.27)	1.41 (1.26-1.59)
Pacific	3,576	1.85 (1.74-1.96)	2.08 (1.84-2.34)
US			
Midwest	2,066	1.07 (1.01-1.14)	1.20 (1.06-1.36)
South	2,110	1.09 (1.04-1.15)	1.18 (1.06-1.31)
West	2,611	1.35 (1.28-1.42)	1.45 (1.30-1.62)
Northeast	1,934	1.00 (ref)	1.00 (ref)
^Based on univariate conditional MLE Exact RR and CI Estimation with the Byar approximation			
^^Based on multivariate GLM with Negative Binomial Distribution (log-link function and MLE)			
*Geographic region based on Soldier duty assignment with states mapped to US census regions; results for soldiers in other or unknown regions (8%) are included in the models but not displayed			

Table 10. Unadjusted Reported CT Case Rates and Relative Risk, AC Soldiers and US Adults 18-64 years, 2015-2019

Age		Case Rate per 100,000 p-years (95% CI)		Unadjusted RR (95% CI)^
		Army	US	Army : US
TOTAL	18-24	4,127 (4,085-4,170)	2,913 (2,910-2,915)	1.42 (1.40-1.43)
	25-34	1,391 (1,366-1,415)	1,015 (1,014-1,016)	1.37 (1.35-1.40)
	35-64	279 (265-294)	124 (123.8-124.4)	2.25 (2.14-2.37)
	Total	2,149 (2,130-2,168)	750.4 (749.9-751)	2.86 (2.84-2.89)
FEMALE	18-24	10,404 (10,230-10,580)	4,257 (4,252-4,262)	2.44 (2.40-2.49)
	25-34	2,320 (2,240-2,403)	1,206 (1,204-1,208)	1.92 (1.86-1.99)
	35-64	371 (328-417)	112 (111.6-112.3)	3.31 (2.94-3.73)
	Total	5,037 (4,962-5,113)	969 (968-970)	5.20 (5.12-5.28)
MALE	18-24	2,996 (2,956-3,036)	1,633 (1,630-1,636)	1.84 (1.81-1.86)
	25-34	1,227 (1,202-1,252)	829 (828-831)	1.48 (1.45-1.51)
	35-64	265 (251-280)	137 (136.3-137.1)	1.94 (1.84-2.05)
	Total	1,650 (1,632-1,668)	530 (530-531)	3.11 (3.08-3.15)
^Calculated from univariate analyses using the exact method (OpenEpi Byar approximation)				

Table 11. Unadjusted Reported NG Case Rates and Relative Risk, AC Soldiers and US Adults 18-64 years, 2015-2019

Age		Case Rate per 100,000 p-years (95% CI)		Unadjusted RR (95% CI)^
		Army	US	Army : US
TOTAL	18-24	625 (608-642)	660 (659-661)	0.95 (0.92-0.97)
	25-34	248 (237-258)	405 (404-406)	0.61 (0.59-0.64)
	35-64	78 (70-85)	81.5 (81.3-81.7)	0.96 (0.87-1.05)
	Total	348 (341-356)	243 (242.3-242.9)	1.44 (1.40-2.43)
FEMALE	18-24	1,014 (959-1,068)	694 (692-696)	1.46 (1.38-1.54)
	25-34	227 (201-252)	300 (299-301)	0.76 (0.68-0.85)
	35-64	66 (48-85)	40 (39.9-40.4)	1.65 (1.25-2.18)
	Total	498 (474-521)	195 (194-195)	2.56 (2.44-2.68)
MALE	18-24	555 (538-572)	628 (626-629)	0.88 (0.86-0.91)
	25-34	251 (240-263)	506 (505-508)	0.50 (0.47-0.52)
	35-64	80 (72-88)	124 (123.9-124.7)	0.64 (0.58-0.71)
	Total	322 (314-330)	291 (290.4-291.4)	1.11 (1.08-1.13)
^Calculated from univariate analyses using the exact method (Byar approximation)				

Table 12. Reported NG Case Rates and Relative Risk (Crude and Adjusted), AC Soldiers, 2015-2019

Covariate	Case rates/100,000 p-yrs	Crude RR (95% CI) [^]	Adjusted RR (95% CI) ^{^^}
Year:			
2019	417	1.57 (1.46-1.69)	1.39 (1.24-1.56)
2018	401	1.51 (1.41-1.63)	1.38 (1.23-1.55)
2017	348	1.31(1.22-1.41)	1.24 (1.10-1.39)
2016	310	1.17 (1.09-1.26)	1.16 (1.03-1.30)
2015	265	1.00 (ref)	1.00 (ref)
Sex:			
Female	498	1.54 (1.46-1.63)	1.10 (1.02-1.19)
Male	322	1.00 (ref)	1.00 (ref)
Age:			
<25	625	8.03 (7.28-8.86)	6.93 (6.17-7.80)
25-34	248	3.18 (2.87-3.53)	3.00 (2.66-3.39)
35+	78	1.00 (ref)	1.00 (ref)
Race/eth:			
Asian	151	1.08 (0.92-1.27)	1.09 (0.91-1.31)
AI/AN	344	2.47 (1.89-3.22)	2.22 (1.66-2.91)
Black	1019	7.31 (6.93-7.71)	5.84 (5.34-6.38)
Hispanic	260	1.86 (1.72-2.02)	1.65 (1.48-1.84)
NH/PI	332	2.38 (1.92-2.96)	2.30 (1.81-2.89)
White	139.5	1.00 (ref)	1.00 (ref)
Duty Region			
Europe	236	1.43 (1.17-1.74)	1.48 (1.14-1.94)
Pacific	255	1.54 (1.25-1.91)	1.41 (1.07-1.86)
Midwest US	309	1.87 (1.54-2.26)	1.80 (1.38-2.36)
South US	407	2.46 (2.08-2.91)	2.19 (1.74-2.77)
West US	386	2.33 (1.96-2.77)	2.27 (1.79-2.90)
Northeast US	165	1.00 (ref)	1.00 (ref)
[^] Based on univariate conditional MLE Exact RR and CI Estimation with the Byar approximation			
^{^^} Based on multivariate GLM with Negative Binomial Distribution (log-link function and MLE)			

Table 13. Population Demographics, AC 2015-2019

		<i>Chlamydia trachomatis</i> (CT) N=45,895*						<i>Neisseria gonorrhoeae</i> (NG) N=8,923*					
		Non-Cases		Single Cases		Recurrent Cases		Non-Cases		Single Cases		Recurrent Cases	
N=840,138 ^		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age	<25	414776	52.2	28182	78.1	8413	85.8	444581	53.5	5842	75.8	948	78.0
	25-34	247283	31.1	6951	19.3	1257	12.8	253693	30.5	1568	20.3	230	18.9
	35+	132184	16.6	959	2.7	133	1.4	132941	16.0	297	3.9	38	3.1
	Mean +/- std dev	26.4 +/- 8.0		22.2 +/- 4.6		21.2 +/- 3.9		26.2 +/- 7.9		22.5 +/- 5.0		22.3 +/- 4.7	
Sex	F	114986	14.5	10690	29.6	4001	40.8	127671	15.4	1771	23.0	235	19.3
	M	679257	85.5	25402	70.4	5802	59.2	703544	84.6	5936	77.0	981	80.7
Race-Eth	AI/AN	5815	0.7	250	0.7	66	0.7	6066	0.7	57	0.7	8	0.7
	Asian	36250	4.6	1044	2.9	278	2.8	37377	4.5	168	2.2	27	2.2
	Black	159819	20.3	14124	39.3	4708	48.2	173292	21.0	4508	58.7	851	70.2
	Hispanic	117047	14.9	5796	16.1	1553	15.9	123429	15.0	852	11.1	115	9.5
	NH/PI	7837	1.0	513	1.4	178	1.8	8440	1.0	77	1.0	11	0.9
	White	460674	58.5	14246	39.6	2990	30.6	475690	57.7	2019	26.3	201	16.6
Married	Never Married	406326	51.2	25387	70.3	7435	75.8	432872	52.1	5394	70.0	882	72.5
	Previously Married	31693	4.0	1605	4.4	333	3.4	33275	4.0	307	4.0	49	4.0
	Married	356168	44.8	9097	25.2	2035	20.8	365009	43.9	2006	26.0	285	23.4
Rank	Jr Enlisted (E1-E4)	474275	59.7	29470	81.7	8583	87.6	505004	60.8	6315	81.9	1009	83.0
	Sr Enlisted (E5-E9)	197230	24.8	4840	13.4	921	9.4	201738	24.3	1095	14.2	158	13.0
	Jr Officer (O1-O3)	73492	9.3	1537	4.3	260	2.7	75020	9.0	233	3.0	36	3.0
	Sr Officer (O4+)	49246	6.2	245	0.7	39	0.4	49453	5.9	64	0.8	13	1.1
Education	HS or Less	537754	68.0	30723	85.4	8742	89.4	569482	68.8	6693	87.0	1044	85.9
	Some College	92182	11.7	2519	7.0	537	5.5	94657	11.4	503	6.5	78	6.4
	Undergrad/ Grad Degree	160868	20.3	2743	7.6	504	5.2	163524	19.8	497	6.5	94	7.7
HOR Region	South	364652	45.9	19262	53.4	5566	56.8	384012	46.2	4681	60.7	787	64.7
	Midwest	133675	16.8	5070	14.0	1211	12.4	138828	16.7	986	12.8	142	11.7
	Northeast	98859	12.4	3939	10.9	997	10.2	102915	12.4	767	10.0	113	9.3
	Other/Unk	22350	2.8	886	2.5	272	2.8	23322	2.8	160	2.1	26	2.1
	West	174707	22.0	6935	19.2	1757	17.9	182138	21.9	1113	14.4	148	12.2
TOTAL		794243	94.5	36092	4.3	9803	1.2	831215	98.9	7707	0.9	1216	0.1
^Number of unique soldiers – data are based on end of year demographics for the soldier’s first year of observation; 2.8 +/- 1.7 person-years of observation per soldier, on average *Total number of infections (58,935 total CT cases and 10,524 total NG cases; range of infections per infected person: CT=1-9; NG=1-14)													

Table 14. CT and NG Morbidity Burden Metrics, AC Soldiers, 2015-2019

	Metric	2015	2016	2017	2018	2019	Total
Chlamydia (CT)	IR per 100K person-years	2,085	2,331	2,539	2,753	2,844	2,510
	New Cases	10,121	10,932	11,764	12,785	13,333	58,935
	Individuals Affected	9,088	9,781	10,462	11,348	11,831	45,895
	Medical Encounters^	12,632	13,987	14,542	16,341	17,273	74,775
Gonorrhea (NG)	IR per 100K person-years	352	409	460	504	517	448
	New Cases	1,709	1,916	2,133	2,340	2,426	10,524
	Individuals Affected	1,574	1,762	1,974	2,164	2,242	8,923
	Medical Encounters^	2,188	2,520	2,744	3,116	3,273	13,841
Total	IR per 100K person-years	2,310	2,572	2,822	3,059	3,163	2,787
	New Cases	11,347	12,061	13,072	14,209	14,828	65,517
	Individuals Affected	10,100	10,698	11,519	12,496	13,004	49,743
	Medical Encounters^	14,043	15,295	16,019	17,976	19,022	82,356

^Based on average annual
encounters/affected individual:

1.39 1.43 1.39 1.44 1.46 1.42

Table 15. Crude and Adjusted CT and NG Incidence, AC Soldiers 2015-2019

	Rate per 100,000 person-years		RR (95% CI), Crude		RR (95% CI), Adjusted		
	CT	NG	CT	NG	CT	NG	CT/NG
Year:							
2019	2844	517	1.36 (1.32-1.39)	1.5 (1.4-1.6)	1.3 (1.22-1.28)	1.4 (1.29-1.46)	1.3 (1.23-1.29)
2018	2753	504	1.3 (1.28-1.35)	1.4 (1.3-1.5)	1.2 (1.19-1.25)	1.3 (1.26-1.4)	1.2 (1.20-1.26)
2017	2539	460	1.2 (1.18-1.24)	1.3 (1.2-1.4)	1.2 (1.12-1.18)	1.2 (1.16-1.3)	1.2 (1.12-1.18)
2016	2331	409	1.1 (1.08-1.14)	1.16 (1.1-1.2)	1.1 (1.06-1.12)	1.1 (1.05-1.2)	1.1 (1.05-1.10)
2015	2085	352	1.0	1.0	1.0	1.0	1.0
Age:							
<25	4823	795	13.9 (13.3-14.6)	7.4 (6.7-8.0)	8.4 (8.0-8.9)	4.6 (4.1-5.0)	7.7 (7.4-8.1)
25-34	1613	325	4.9 (4.7-5.2)	3.1 (2.9-3.5)	4.0 (3.8-4.2)	2.7 (2.4-3.0)	3.7 (3.5-3.9)
35+	323	101	1.0	1.0	1.0	1.0	1.0
Sex							
F	5851	657	2.9 (2.9-3.0)	1.5 (1.47-1.61)	2.4 (2.3-2.4)	1.0 (0.98-1.08)	2.3 (2.2-2.3)
M	1929	412	1.0	1.0	1.0	1.0	1.0
Race-ethnicity:							
AI/AN	2423	451	1.5 (1.4-1.7)	2.4 (1.9-3.0)	1.3 (1.1-1.4)	2.3 (1.8-2.9)	1.3 (1.2-1.5)
Asian	1522	202	1.0 (0.92-1.02)	1.1 (1.0-1.3)	1.0 (0.93-1.03)	1.2 (1.1-1.4)	1.0 (0.95-1.05)
Black	5058	1297	3.1 (3.07-3.2)	6.8 (6.5-7.1)	2.3 (2.35-2.44)	6.0 (5.8-6.3)	2.7 (2.66-2.76)
Hispanic	2748	327	1.7 (1.69-1.77)	1.8 (1.6-1.9)	1.4 (1.33-1.40)	1.6 (1.4-1.7)	1.4 (1.36-1.43)
NH/PI	3696	423	2.3 (2.19-2.49)	2.3 (1.9-2.7)	1.8 (1.7-2.0)	2.2 (1.8-2.7)	1.9 (1.8-2.1)
White	1573	185	1.0	1.0	1.0	1.0	1.0
Marital Status:							
Never Married	4124	724	2.8 (2.71-2.81)	2.6 (2.5-2.8)	1.4 (1.36-1.42)	1.5 (1.40-1.53)	1.4 (1.38-1.43)
Previously Married	3213	582	2.2 (2.17-2.32)	2.2 (2.1-2.4)	2.1 (1.98-2.12)	2.1 (2.0-2.3)	2.1 (2.02-2.15)
Married	1414	259	1.0	1.0	1.0	1.0	1.0
Rank^:							
Jr Enl (E1-E4)	4424	765	22.7 (20.5-25.0)	12.9 (10.7-15.4)	NA	NA	NA
Sr Enl (E5-E9)	1414	282	7.8 (7.0-8.6)	5.1 (4.2-6.1)	NA	NA	NA
Jr Off (O1-O3)	879	130	4.8 (4.3-5.4)	2.3 (1.9-2.9)	NA	NA	NA
Sr Off (O4+)	180	55	1.0	1.0	NA	NA	NA
Rank Category:							
Enlisted	2978	533	5.2 (5.0-5.4)	5.4 (4.9-6.0)	1.4 (1.36-1.52)	1.5 (1.34-1.73)	1.4 (1.37-1.52)
Officer	550	95	1.0	1.0	1.0	1.0	1.0
Education:							
HS or Less	3566	632	4.8 (4.7-5.0)	4.5 (4.2-4.8)	1.7 (1.62-1.78)	1.6 (1.4-1.7)	1.7 (1.6-1.8)
Some College	1344	246	1.9 (1.8-2.0)	1.8 (1.6-2.0)	1.3 (1.22-1.35)	1.1 (1.0-1.2)	1.3 (1.2-1.3)
Undergrad/ Grad Degree	707	136	1.0	1.0	1.0	1.0	1.0

	Rate per 100,000 person-years		RR (95% CI), Crude		RR (95% CI), Adjusted		
	CT	NG	CT	NG	CT	NG	CT/NG
HOR_Region:							
West	2157	283	1.0 (0.99-1.05)	0.8 (0.7-0.9)	0.9 (0.89-0.95)	0.9 (0.79-0.94)	0.9 (0.89-0.94)
South	2986	600	1.4 (1.36-1.44)	1.7 (1.6-1.8)	1.0 (1.00-1.05)	1.1 (1.0-1.15)	1.0 (1.0-1.06)
Midwest	2013	339	0.95 (0.92-0.98)	1.0 (0.9-1.04)	1.0 (0.94-1.01)	1.0 (0.9-1.1)	1.0 (0.95-1.01)
Northeast	2116	352	1.0	1.0	1.0	1.0	1.0
Duty_Region^^:							
West	2930	475	1.5 (1.39-1.53)	2.2 (1.9-2.5)	1.4 (1.32-1.45)	2.1 (1.86-2.45)	1.4 (1.38-1.51)
South	2396	495	1.2 (1.12-1.22)	2.2 (2.0-2.5)	1.1 (1.06-1.16)	2.1 (1.8-2.4)	1.2 (1.13-1.23)
NonUS_Pacific	3448	370	1.7 (1.63-1.82)	1.7 (1.4-2.0)	1.4 (1.32-1.48)	1.3 (1.1-1.6)	1.4 (1.34-1.49)
NonUS_Europe	2527	310	1.3 (1.20-1.34)	1.4 (1.2-1.7)	1.2 (1.17-1.31)	1.3 (1.1-1.6)	1.3 (1.19-1.33)
NonUS_Central	1066	164	0.6 (0.43-0.70)	0.8 (0.4-1.5)	0.6 (0.50-0.81)	0.8 (0.4-1.4)	0.6 (0.51-0.81)
Midwest	2262	345	1.1 (1.04-1.16)	1.5 (1.3-1.8)	1.1 (1.01-1.13)	1.5 (1.3-1.8)	1.1 (1.05-1.16)
Northeast	2001	217	1	1	1	1	1
^Rank 'Enl'=Enlisted and 'Off'=Officer; excluded from multivariate model due to multicollinearity with age and education level ^^NonUS Central=Central Command countries (e.g., Afghanistan, Kuwait); Non-US Europe includes Germany and Italy; Non-US Pacific includes Korea and Japan; Other/Unknown region results not displayed							

Table 16. Odds of Single Occurrence and Recurrent CT and NG Infections, AC Soldiers, 2015-2019

	CT (Adjusted OR, 95% CI)		NG (Adjusted OR, 95% CI)	
	Single Case	Recurrent Cases	Single Case	Recurrent Cases
Age:				
<25	7.11 (6.63-7.64)	13.26 (11.06-15.90)	4.11 (3.60-4.70)	6.18 (4.30-8.89)
25-34	3.54 (3.30-3.80)	4.34 (3.62-5.20)	2.52 (2.21-2.86)	3.21 (2.26-4.57)
35+	1.0	1.0	1.0	1.0
Sex:				
Female	2.12 (2.07-2.17)	3.32 (3.18-3.46)	1.17 (1.10-1.23)	0.84 (0.72-0.97)
Male	1.0	1.0	1.0	1.0
Race-ethnicity:				
AI/AN	1.23 (1.08-1.40)	1.43 (1.12-1.83)	2.12 (1.62-2.76)	3.16 (1.56-6.42)
Asian	0.95 (0.89-1.01)	1.18 (1.04-1.33)	1.18 (1.00-1.38)	1.91 (1.27-2.87)
Black	2.48 (2.42-2.55)	3.55 (3.38-3.73)	5.58 (5.28-5.90)	11.21 (9.55-13.16)
Hispanic	1.36 (1.31-1.40)	1.58 (1.48-1.68)	1.46 (1.35-1.59)	2.06 (1.63-2.60)
NA/PI	1.83 (1.66-2.03)	2.54 (2.13-3.03)	2.04 (1.60-2.61)	2.94 (1.53-5.65)
White	1.0	1.0	1.0	1.0
Marital status:				
Never Married	1.32 (1.28-1.36)	1.46 (1.38-1.54)	1.33 (1.25-1.41)	1.45 (1.25-1.69)
Previously Married	2.04 (1.92-2.15)	1.90 (1.68-2.14)	1.68 (1.49-1.90)	2.02 (1.48-2.75)
Married	1.0	1.0	1.0	1.0
Soldier category:				
Enlisted	1.21 (1.13-1.30)	1.34 (1.15-1.58)	1.27 (1.08-1.48)	1.35 (0.93-1.96)
Officer	1.0	1.0	1.0	1.0
Education level:				
High school or less	1.61 (1.52-1.70)	1.98 (1.74-2.25)	1.78 (1.56-2.02)	1.15 (0.87-1.54)
Some college	1.41 (1.32-1.50)	1.59 (1.37-1.83)	1.35 (1.17-1.56)	1.00 (0.71-1.41)
Undergrad/advanced degree	1.0	1.0	1.0	1.0
Home of record, region				
Midwest	0.98 (0.94-1.02)	0.95 (0.88-1.04)	1.02 (0.93-1.12)	1.05 (0.82-1.35)
South	1.03 (0.99-1.06)	1.04 (0.97-1.12)	1.10 (1.02-1.19)	1.16 (0.95-1.42)
West	0.94 (0.91-0.98)	0.93 (0.86-1.01)	0.92 (0.82-1.00)	0.88 (0.69-1.13)
Northeast	1.0	1.0	1.0	1.0
Duty location, region				
Midwest	0.96 (0.89-1.03)	1.04 (0.89-1.21)	1.33 (1.11-1.60)	1.06 (0.65-1.73)
South	1.03 (0.96-1.10)	1.18 (1.03-1.35)	1.62 (1.38-1.90)	1.75 (1.14-2.67)
West	1.28 (1.19-1.36)	1.63 (1.42-1.87)	1.79 (1.51-2.12)	2.27 (1.47-3.52)
Non-US, Europe	1.30 (1.20-1.41)	1.75 (1.49-2.06)	1.55 (1.27-1.89)	1.79 (1.08-2.96)
Non-US, Pacific	1.60 (1.48-1.73)	2.10 (1.80-2.44)	1.87 (1.55-2.26)	1.60 (0.97-2.63)
Northeast	1.0	1.0	1.0	1.0

Table 17. Frequency of CT and NG Cases Captured by Data Source, AC Soldiers, 2015-2019

Identifying Data Source [^]			CT Cases ^{^^} (N=58,935)		NG Cases ^{^^} (N=10,524)	
Reporting (DRSI)	Laboratory (HL7)	Medical Encounter (M2)*	Frequency	%	Frequency	%
1	1	1	26,459	44.9	3,239	30.8
1	1	0	18,759	31.8	2,667	25.3
1	0	1	712	1.2	876	8.3
1	0	0	3,237	5.5	1,169	11.1
0	1	1	2,949	5.0	545	5.2
0	1	0	2,919	4.9	603	5.7
0	0	1	3,900	6.6	1,425	13.6
Reporting System Capture			49,167	83.4	7,951	75.6
Laboratory System Capture			51,086	86.7	7,054	67.0
Medical Encounter System Capture			34,020	57.7	6,085	57.8
[^] 1=Case Identified by data source, 0=Case Not Identified by data source ^{^^} N=65,403; 4,056 cases (6.2%) identified had concurrent CT and NG infections *387 (1.1%) of CT cases and 376 (6.2%) of NG cases identified from M2 medical encounters were exclusively from non-MHS MTFs						

Table 18. Agreement between Surveillance Systems used to Identify CT and NG Cases, AC Soldiers 2015-2019

Data system	CT	NG
	Kappa (95% CI)	Kappa (95% CI)
All Systems[^]	0.76 (0.756-0.757)	0.67 (0.665-0.666)
DRSi & HL7^{^^}	0.90 (0.898-0.902)	0.79 (0.779-0.794)
DRSi & M2^{^^}	0.65 (0.647-0.655)	0.60 (0.592-0.611)
HL7 & M2^{^^}	0.69 (0.686-0.694)	0.59 (0.582-0.602)
Color coding: Green=Near perfect; Blue=Substantial; Gray=Moderate		
[^] Agreement based on Fleiss Kappa		
^{^^} Agreement based on Cohen's Kappa		
All values were statistically significant (p<<0.05)		

Table 19. Installation System-Specific Case Capture, AC Soldier CT cases, 2015-2019

	Reporting					Medical					Laboratory				
	2015	2016	2017	2018	2019	2015	2016	2017	2018	2019	2015	2016	2017	2018	2019
Installation 1	83%	85%	87%	78%	88%	50%	56%	63%	69%	54%	93%	90%	90%	80%	91%
Installation 2	59%	86%	89%	84%	92%	59%	46%	44%	43%	38%	91%	89%	90%	91%	94%
Installation 3	79%	86%	85%	90%	88%	50%	53%	62%	93%	93%	90%	89%	89%	92%	91%
Installation 4	84%	69%	84%	87%	89%	73%	79%	73%	79%	81%	89%	85%	87%	90%	87%
Installation 5	72%	35%	49%	72%	74%	43%	59%	53%	53%	51%	91%	92%	93%	93%	42%
Installation 6	54%	89%	86%	80%	89%	31%	51%	49%	49%	56%	96%	96%	87%	91%	92%
Installation 7	85%	76%	80%	91%	86%	42%	60%	38%	51%	53%	92%	82%	85%	94%	91%
Installation 8	85%	85%	89%	86%	90%	55%	57%	58%	55%	50%	89%	96%	91%	94%	95%
Installation 9	92%	94%	90%	92%	88%	33%	57%	60%	61%	58%	92%	95%	93%	95%	89%
Installation 10	81%	85%	80%	89%	82%	63%	66%	48%	49%	26%	93%	92%	88%	79%	87%
Installation 11	71%	70%	33%	88%	69%	48%	47%	64%	60%	49%	88%	94%	83%	91%	90%
Installation 12	89%	89%	82%	87%	95%	67%	71%	68%	73%	57%	93%	92%	92%	91%	95%
Installation 13	81%	94%	86%	76%	78%	51%	67%	70%	85%	73%	94%	96%	89%	90%	15%
Installation 14	97%	88%	89%	84%	82%	70%	79%	81%	69%	57%	97%	84%	83%	84%	80%
Installation 15	94%	91%	91%	85%	87%	80%	80%	82%	83%	73%	90%	91%	86%	84%	93%
Installation 16	89%	84%	78%	91%	86%	42%	64%	55%	54%	53%	91%	87%	74%	93%	86%
Installation 17	100%	93%	95%	81%	89%	85%	70%	65%	79%	61%	96%	91%	89%	81%	91%
Installation 18	97%	97%	94%	97%	94%	32%	38%	40%	52%	49%	95%	96%	94%	98%	97%
Installation 19	80%	88%	92%	91%	96%	67%	55%	61%	49%	61%	82%	93%	93%	95%	96%
Installation 20	96%	94%	88%	86%	86%	30%	53%	40%	53%	40%	93%	94%	90%	94%	88%
Installation 21	85%	84%	76%	87%	88%	50%	71%	58%	37%	34%	91%	88%	87%	90%	92%

	Reporting					Medical					Laboratory				
	2015	2016	2017	2018	2019	2015	2016	2017	2018	2019	2015	2016	2017	2018	2019
Installation 22	79%	81%	80%	81%	68%	40%	48%	53%	56%	51%	89%	94%	87%	89%	93%
Installation 23	88%	43%	79%	75%	76%	50%	70%	62%	71%	65%	94%	70%	89%	78%	78%
Installation 24	92%	89%	87%	88%	89%	48%	56%	61%	63%	64%	92%	91%	90%	92%	90%
Installation 25	72%	72%	90%	86%	94%	38%	65%	48%	66%	45%	92%	91%	88%	89%	96%
Installation 26	72%	88%	89%	92%	95%	52%	50%	48%	44%	49%	90%	88%	87%	95%	97%
Installation 27	83%	79%	82%	90%	90%	53%	65%	66%	63%	71%	87%	88%	88%	96%	87%
Installation 28^	93%	91%	93%	97%	99%	51%	77%	72%	14%	10%	95%	94%	79%	0%	0%
Installation 29	96%	89%	93%	89%	100%	74%	91%	79%	74%	71%	92%	89%	92%	89%	100%
Installation 30	82%	79%	74%	51%	64%	56%	69%	79%	77%	72%	92%	81%	87%	90%	90%
Installation 31	87%	81%	90%	77%	86%	54%	49%	28%	38%	51%	83%	84%	97%	98%	91%
Installation 32	89%	90%	88%	88%	88%	41%	51%	63%	60%	54%	89%	88%	85%	91%	92%
Installation 33	96%	91%	84%	82%	86%	56%	61%	85%	84%	68%	94%	94%	91%	95%	97%
Installation 34	88%	91%	97%	91%	86%	62%	67%	72%	49%	34%	91%	93%	97%	99%	95%
Installation 35	95%	91%	89%	89%	88%	53%	51%	49%	50%	32%	91%	94%	93%	95%	98%
Installation 36	48%	78%	91%	95%	100%	100%	57%	59%	57%	35%	43%	83%	91%	95%	95%
Installation 37	74%	63%	87%	73%	92%	68%	65%	55%	71%	68%	78%	69%	83%	85%	97%
Installation 38	71%	70%	75%	70%	88%	77%	67%	43%	63%	41%	69%	85%	82%	86%	90%
Installation 39	80%	83%	83%	76%	55%	73%	77%	70%	66%	71%	87%	85%	93%	94%	82%
Installation 40	81%	86%	79%	78%	77%	60%	71%	66%	62%	61%	90%	93%	93%	96%	94%

Red cells denote significant negative deviation between the installation and the Army Average (z-scores < -2); yellow cells denote moderate negative deviation (z-scores -1.0 to -1.9).

^Installation 28 transitioned to MHS GENESIS for medical encounter and lab records in the fall of 2017.

Table 20. Installation System-Specific Case Capture, AC Soldier NG cases, 2015-2019

	Reporting					Medical					Laboratory				
	2015	2016	2017	2018	2019	2015	2016	2017	2018	2019	2015	2016	2017	2018	2019
I-1	58%	88%	80%	76%	82%	51%	31%	42%	48%	38%	81%	96%	87%	89%	93%
I-2	72%	66%	75%	81%	86%	38%	49%	53%	77%	77%	91%	83%	75%	70%	84%
I-3	61%	57%	68%	79%	83%	83%	88%	81%	82%	81%	72%	78%	69%	73%	77%
I-4	72%	55%	49%	69%	75%	54%	59%	47%	48%	48%	90%	95%	89%	95%	40%
I-5	65%	85%	70%	76%	82%	44%	44%	42%	37%	48%	88%	88%	82%	87%	88%
I-6	68%	59%	64%	81%	73%	53%	51%	45%	58%	51%	68%	51%	72%	84%	70%
I-7	79%	62%	61%	78%	67%	55%	71%	52%	49%	42%	89%	85%	94%	90%	86%
I-8	83%	89%	88%	90%	83%	48%	53%	50%	52%	52%	51%	1%	1%	1%	3%
I-9	77%	68%	70%	76%	59%	54%	71%	70%	73%	67%	86%	89%	85%	94%	70%
I-10	100%	89%	91%	85%	92%	19%	39%	36%	43%	36%	94%	89%	82%	88%	78%
I-11	95%	89%	89%	89%	91%	39%	45%	61%	45%	49%	95%	89%	91%	93%	91%
I-12	93%	77%	58%	77%	77%	69%	65%	67%	38%	47%	86%	92%	84%	83%	83%
I-13	64%	65%	79%	82%	68%	39%	48%	50%	45%	47%	81%	82%	85%	92%	89%
I-14	87%	72%	74%	74%	79%	59%	73%	61%	54%	66%	86%	78%	85%	87%	85%
I-15	60%	79%	90%	82%	84%	40%	50%	27%	45%	48%	80%	79%	77%	88%	84%
I-16^	68%	83%	92%	90%	87%	79%	83%	85%	36%	40%	76%	83%	66%	0%	0%
I-17	50%	73%	77%	42%	63%	77%	91%	92%	78%	76%	62%	88%	69%	81%	86%
I-18	81%	82%	84%	86%	77%	25%	46%	56%	59%	42%	81%	82%	84%	91%	73%
I-19	96%	86%	100%	64%	84%	50%	61%	41%	50%	60%	93%	86%	95%	86%	88%
I-20	63%	79%	63%	71%	68%	56%	83%	47%	63%	75%	69%	83%	89%	93%	93%
Red cells denote significant negative deviation between the installation and the Army Average (z-scores < -2); yellow cells denote moderate negative deviation (z-scores -1.0 to -1.9).															
^Installation (I) 16 transitioned to MHS GENESIS for medical encounter and lab records in the fall of 2017.															

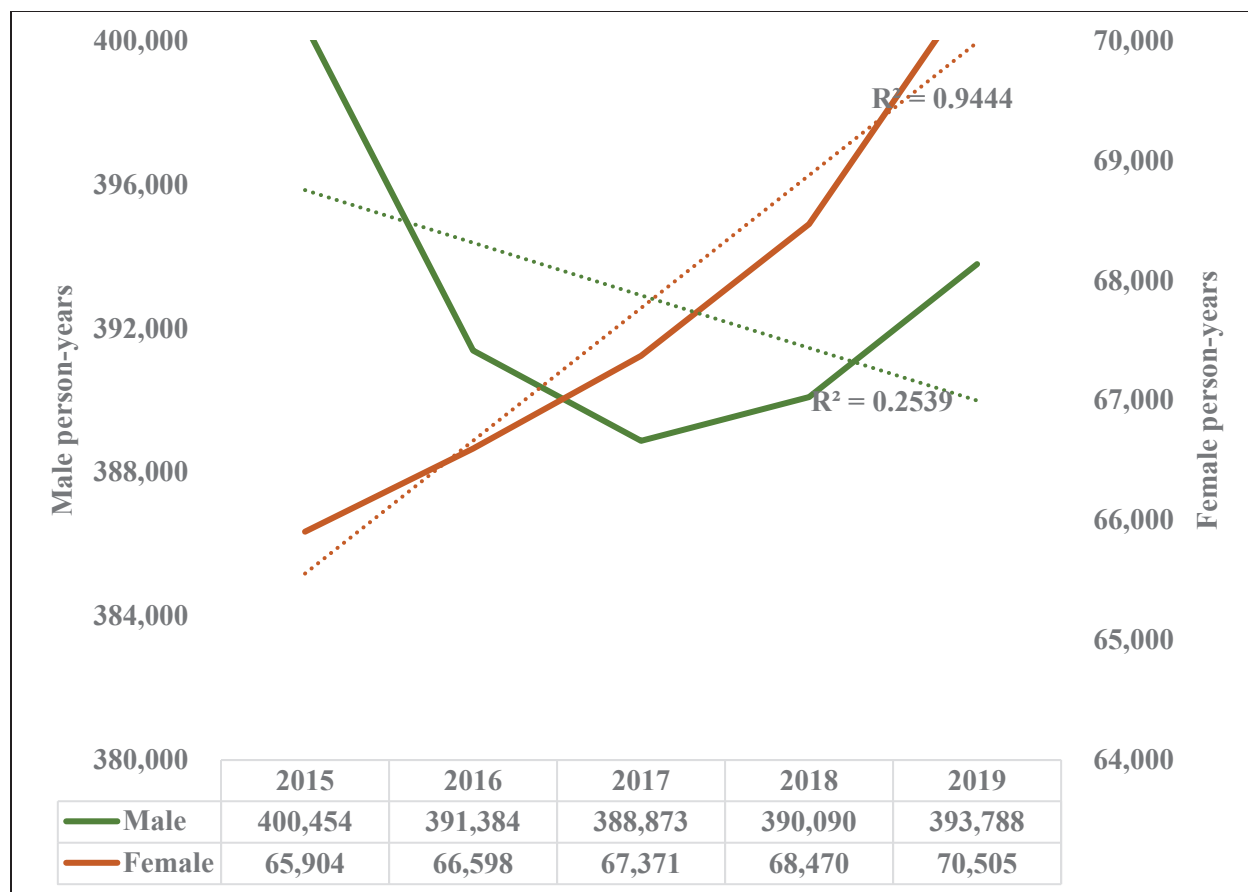


Figure 1. Trends in Annual Population by Sex, AC Soldiers, 2015-2019

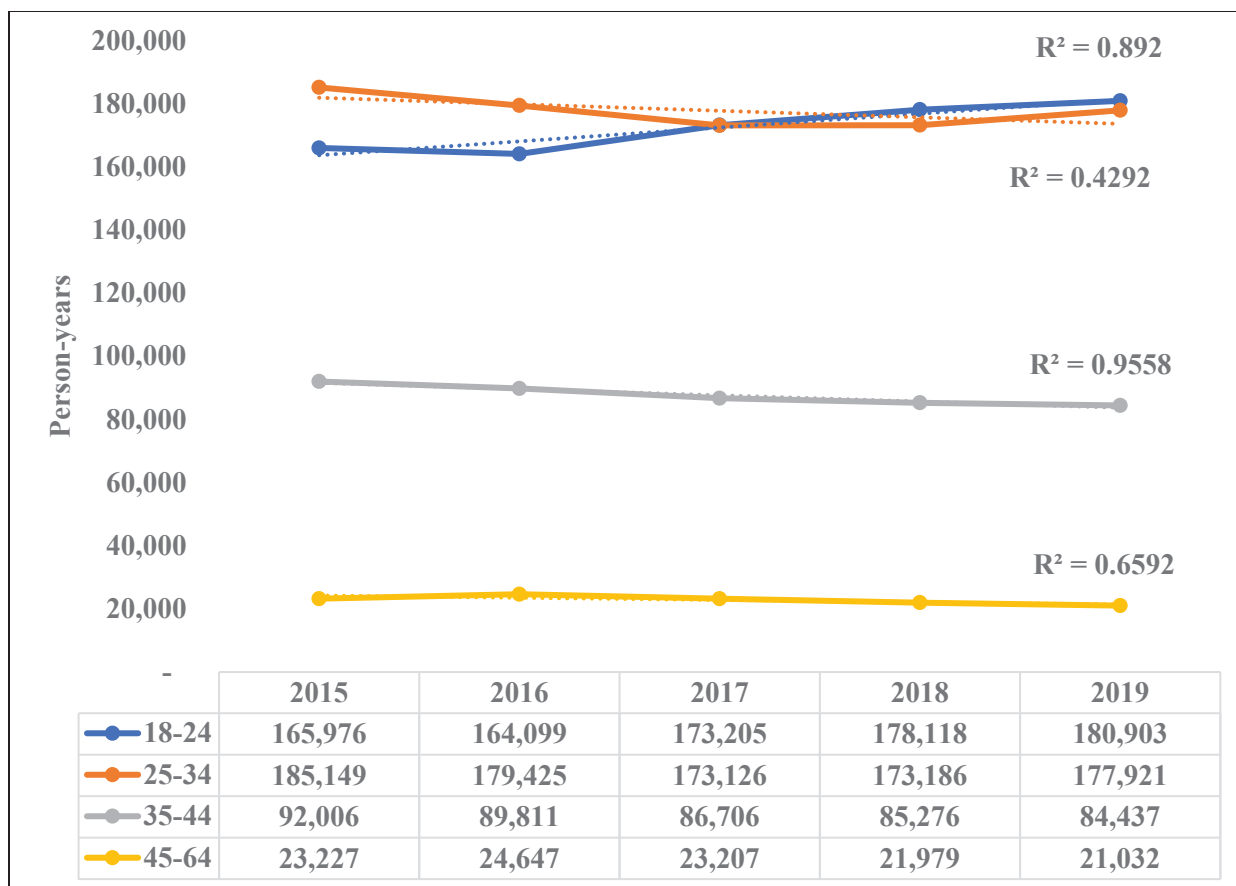


Figure 2. Trends in Annual Population by Age, AC Soldiers 2015-2019

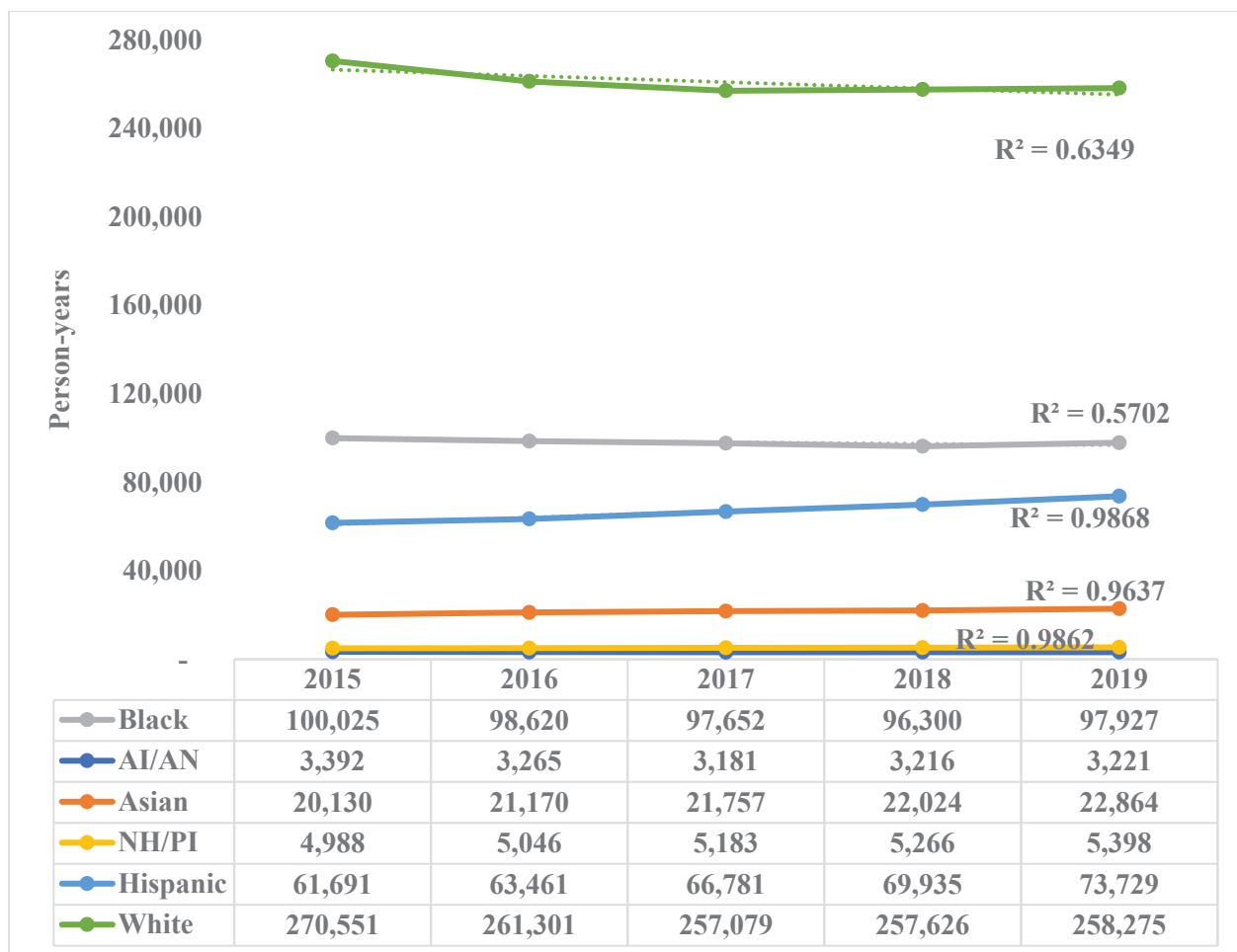


Figure 3. Trends in Annual Population by Race-ethnicity, AC Soldiers, 2015-2019

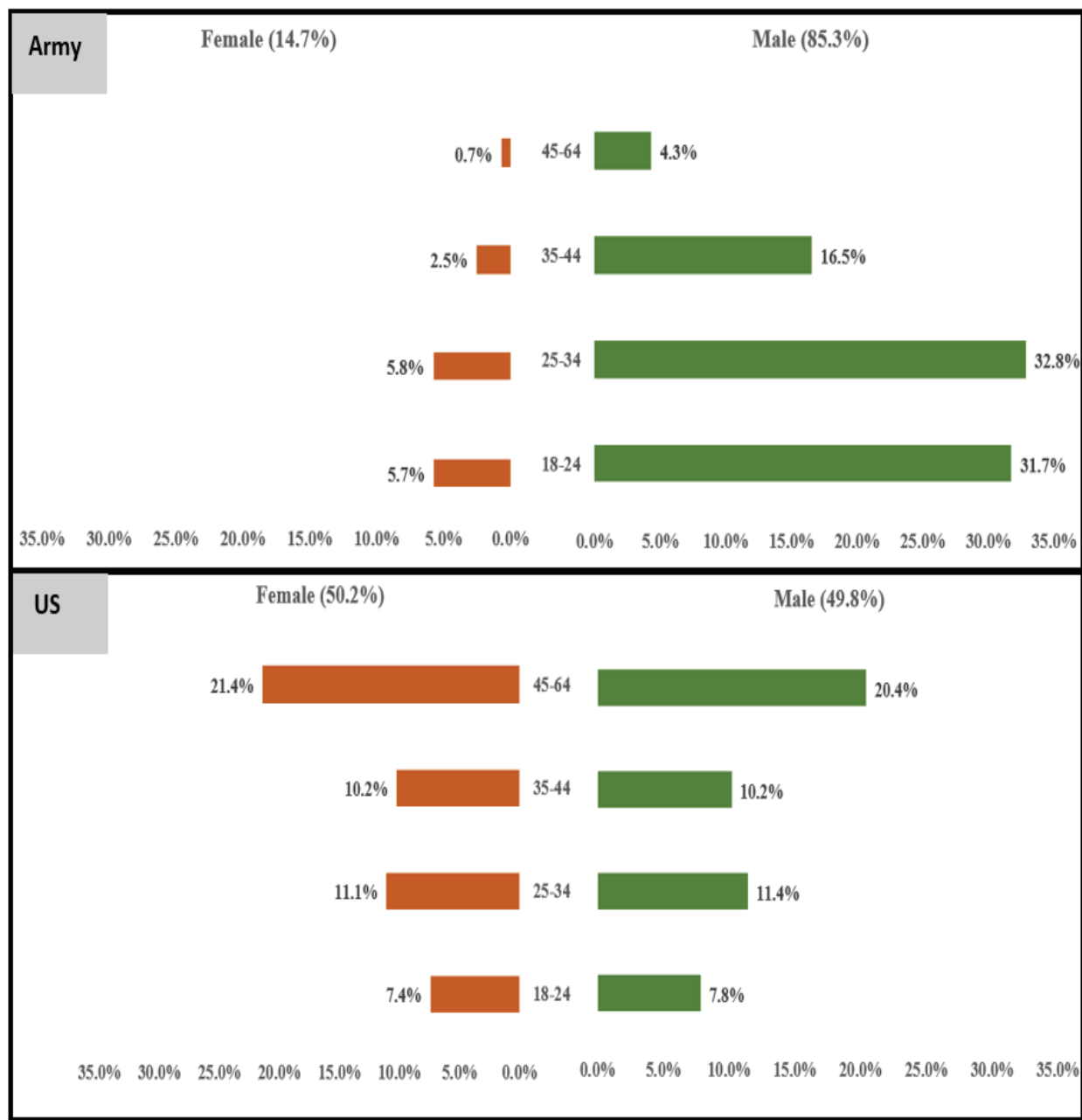


Figure 4. Population Pyramids by Sex and Age, AC Soldiers and US Adults 18-64 years, 2015-2019

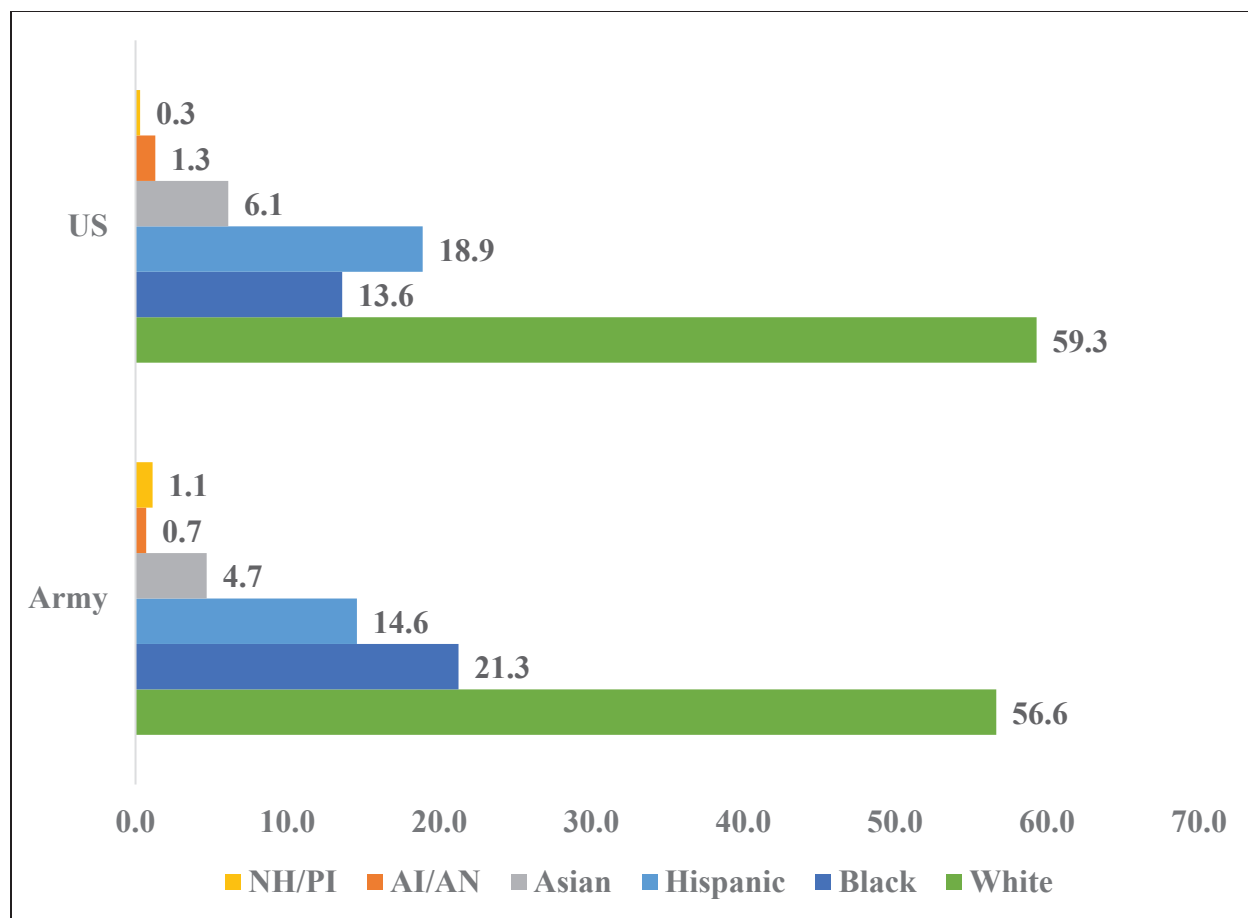


Figure 5. Race and ethnicity among US Army AC Soldiers and US Adults 18-64 years of age, 2015-2019

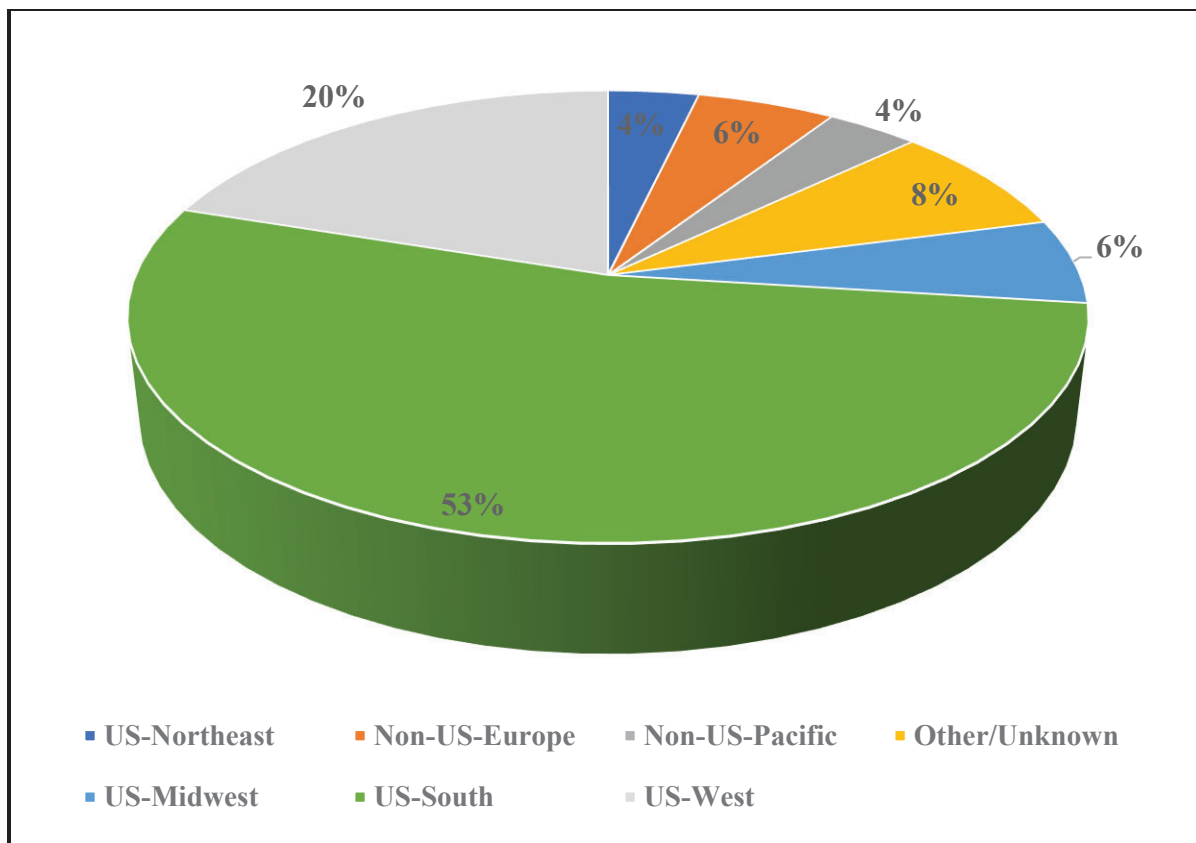


Figure 6. AC Soldier Assignment, US Census Region, 2015-2019

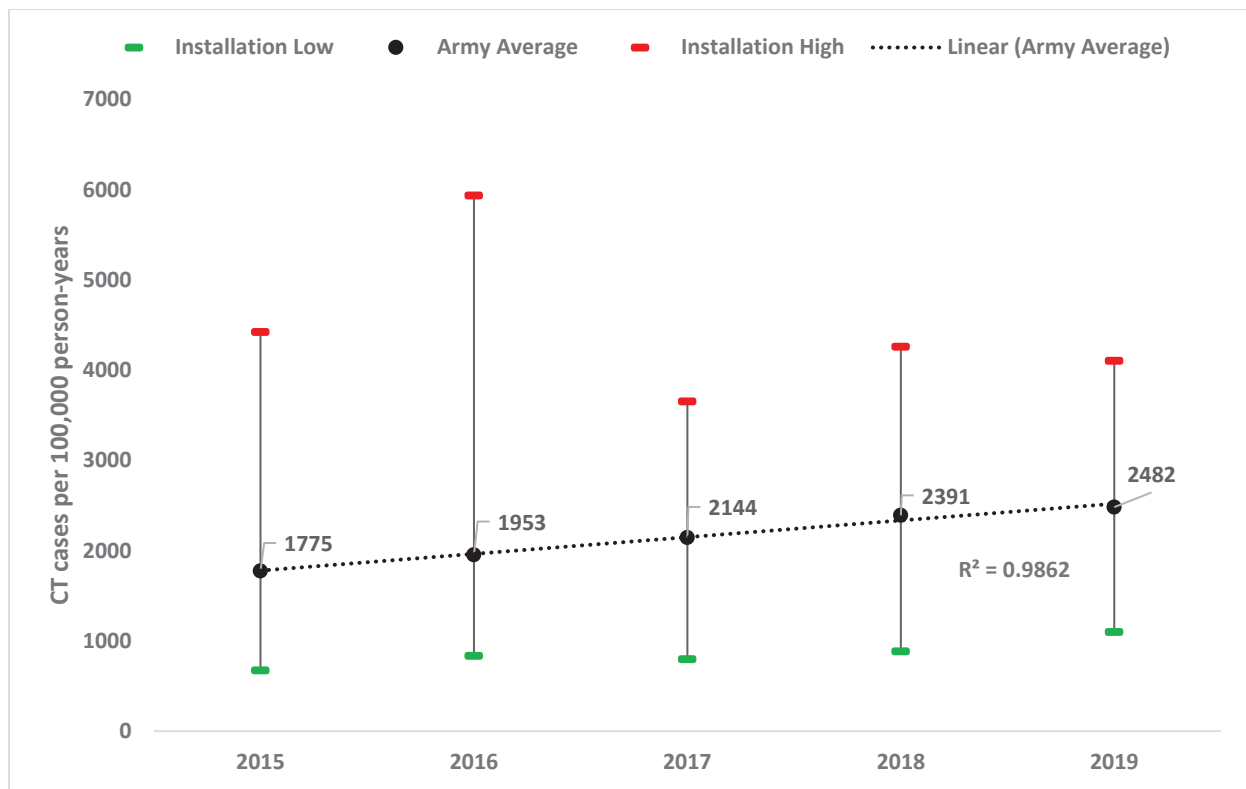


Figure 7. Annual CT Reported Case Rates with Installation Case Rate Ranges, AC Soldiers, 2015-2019

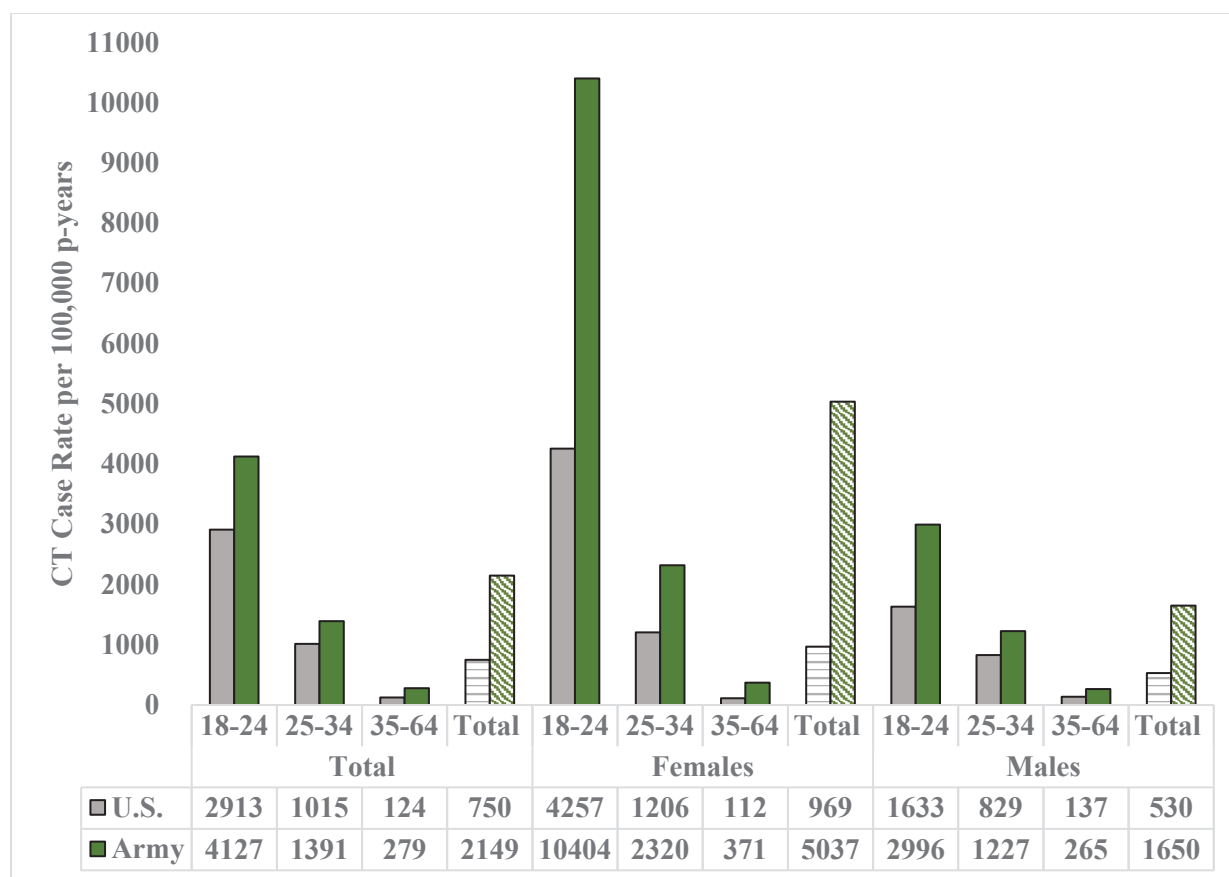


Figure 8. Reported CT Case Rates by Age and Sex, AC Soldiers and US Adults, 2015-2019

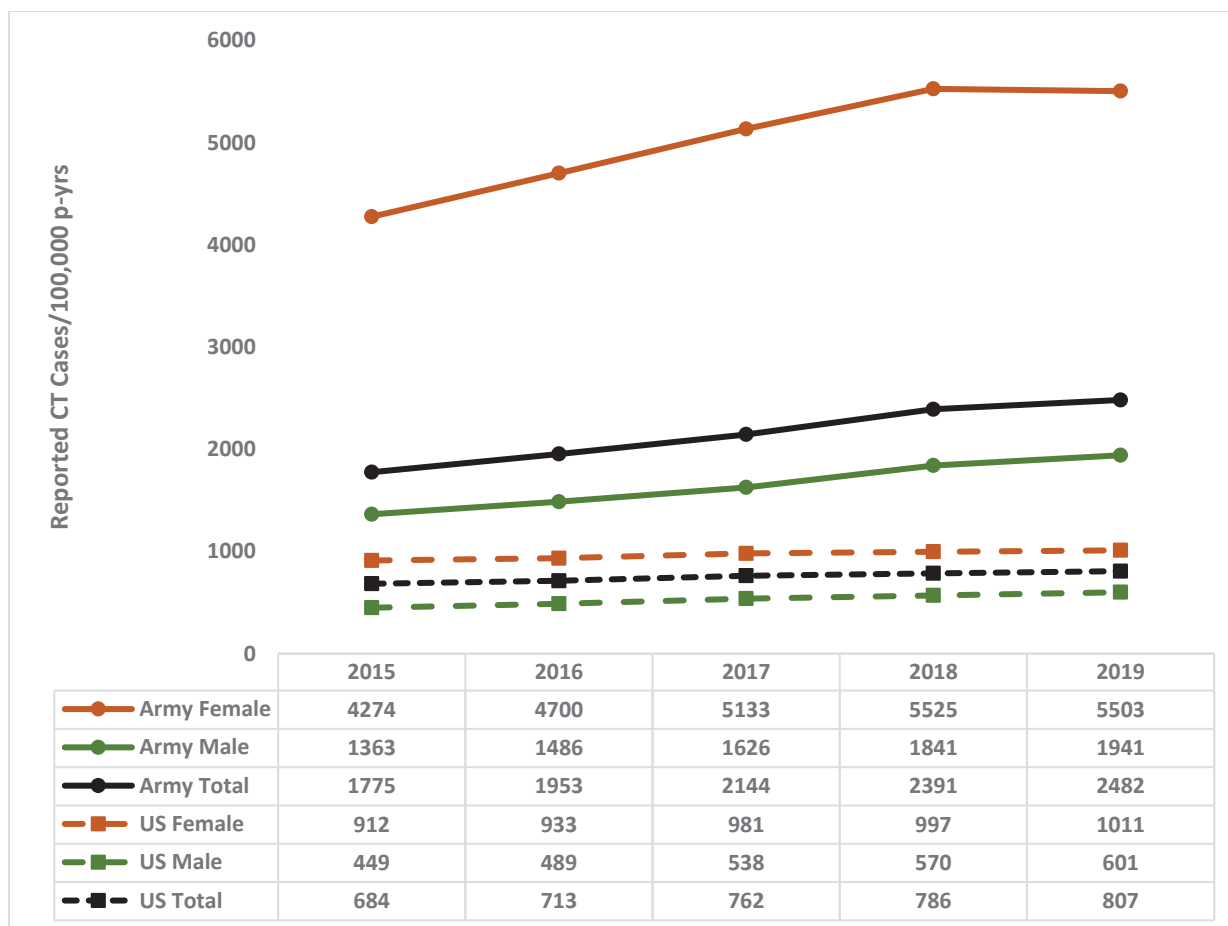


Figure 9. Reported CT Case Rates by Sex and Year, AC Soldiers and US Adults 18-64 years, 2015-2019

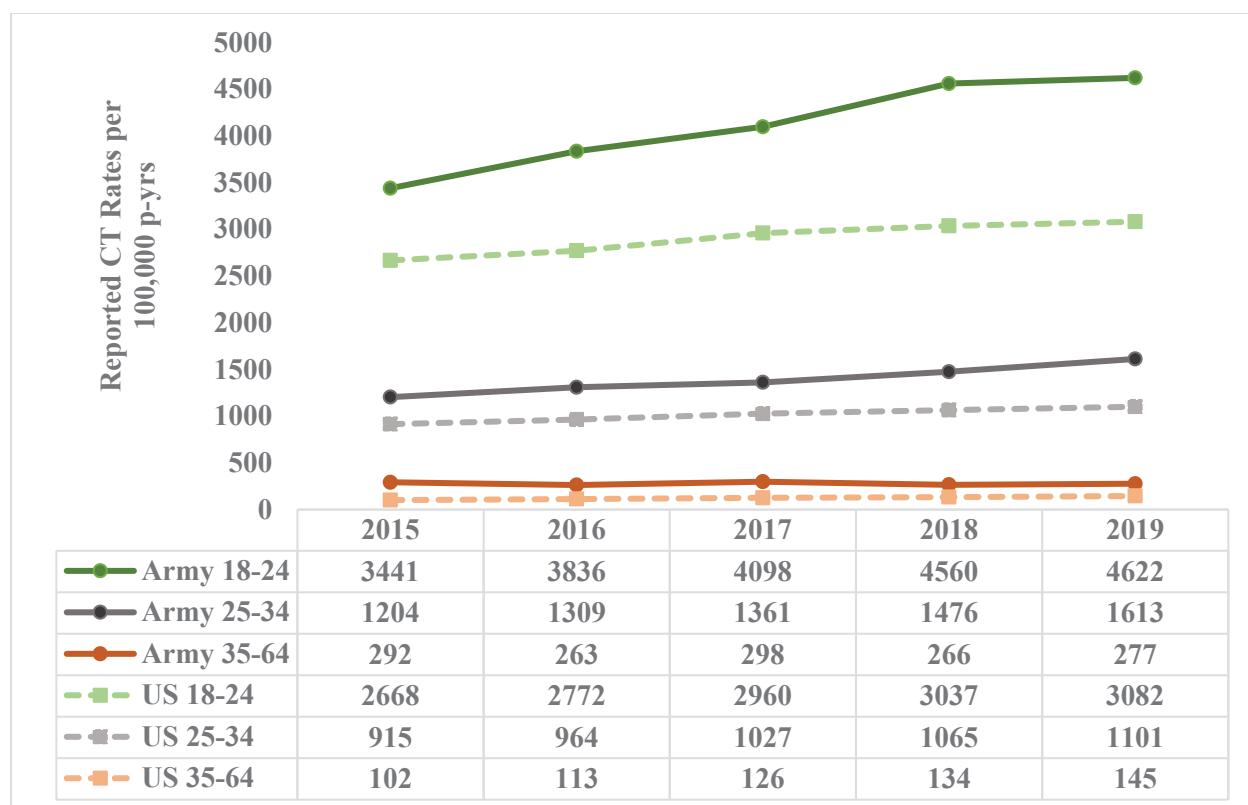


Figure 10. Reported CT Case Rates by Age and Year, AC Soldiers and US Adults 18-64 years, 2015-2019

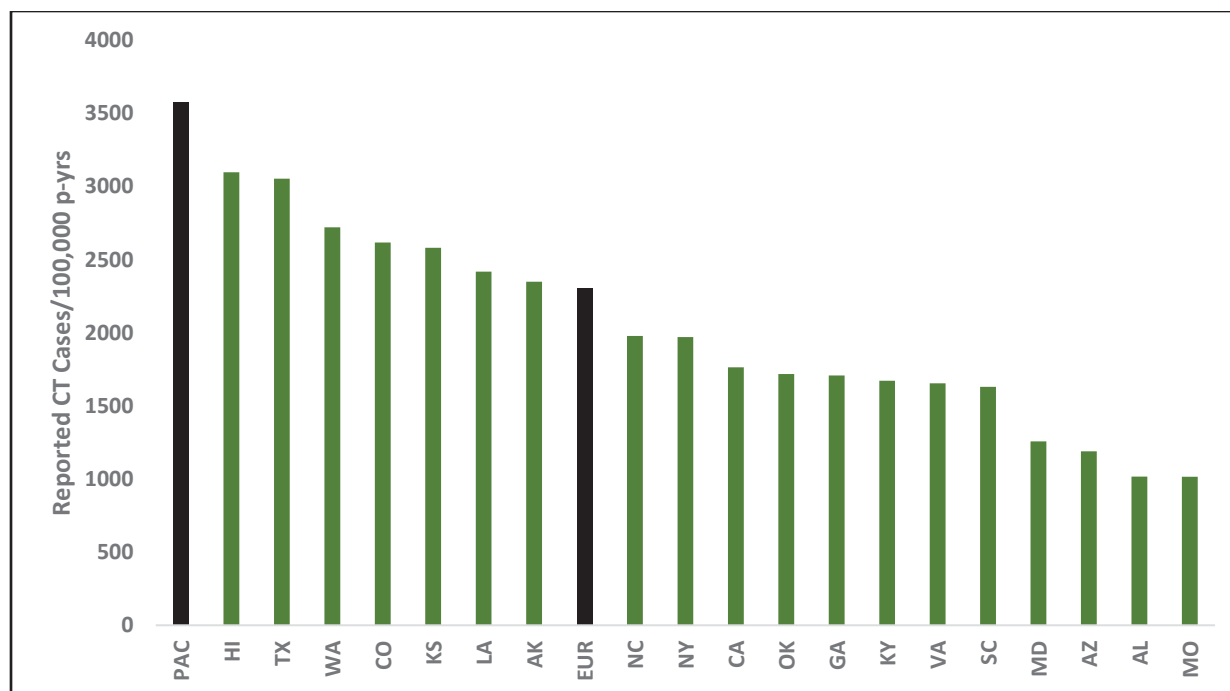


Figure 11. Unadjusted Reported CT Case Rates by Duty Location, AC Soldiers, 2015-2019

^Location based on US state abbreviations; PAC=Pacific countries, EUR=European countries

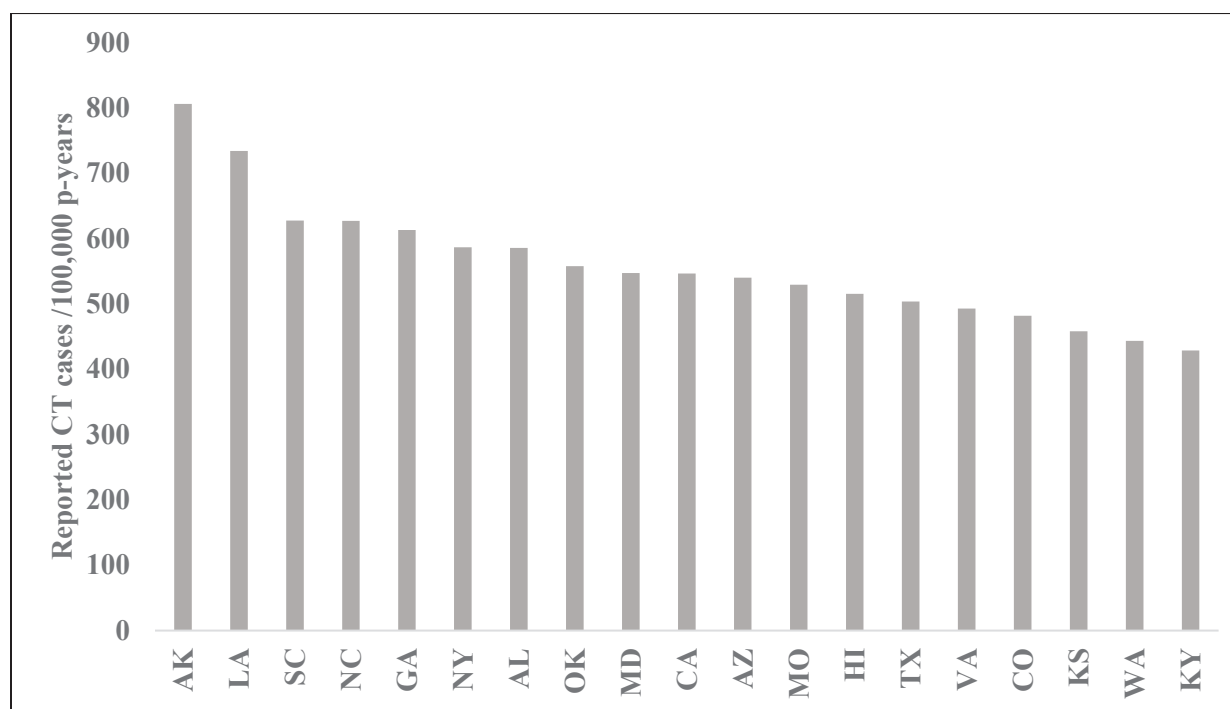


Figure 12. Unadjusted Reported CT Case Rates by Reporting Location, US Adults 18-64 years, 2015-2019

^CDC STD Atlas DATA; states without an Army installation were excluded.

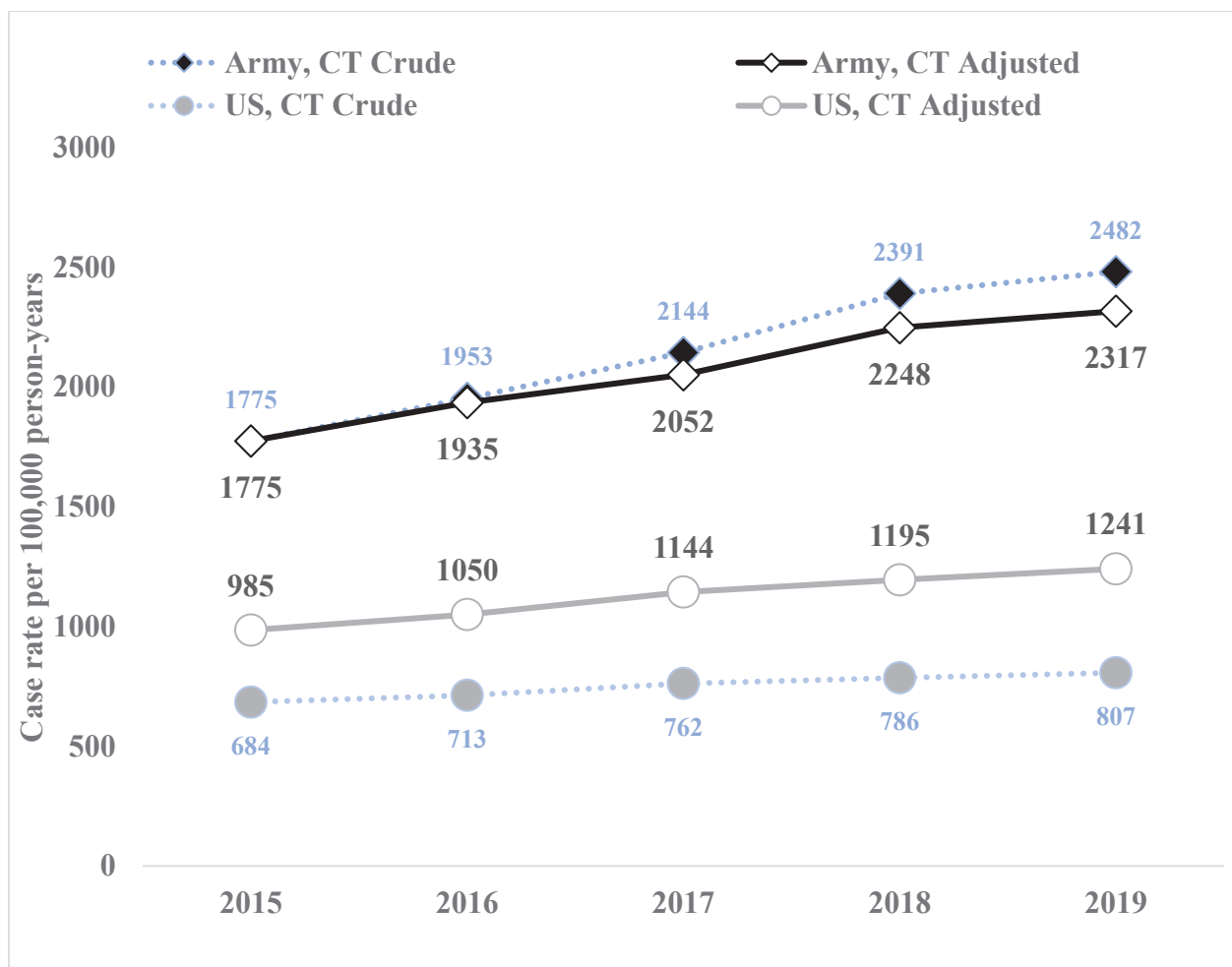


Figure 13. Crude and Age-sex Adjusted CT Rates Reported among AC Soldiers and US Adults 18-64 years, 2015-2019

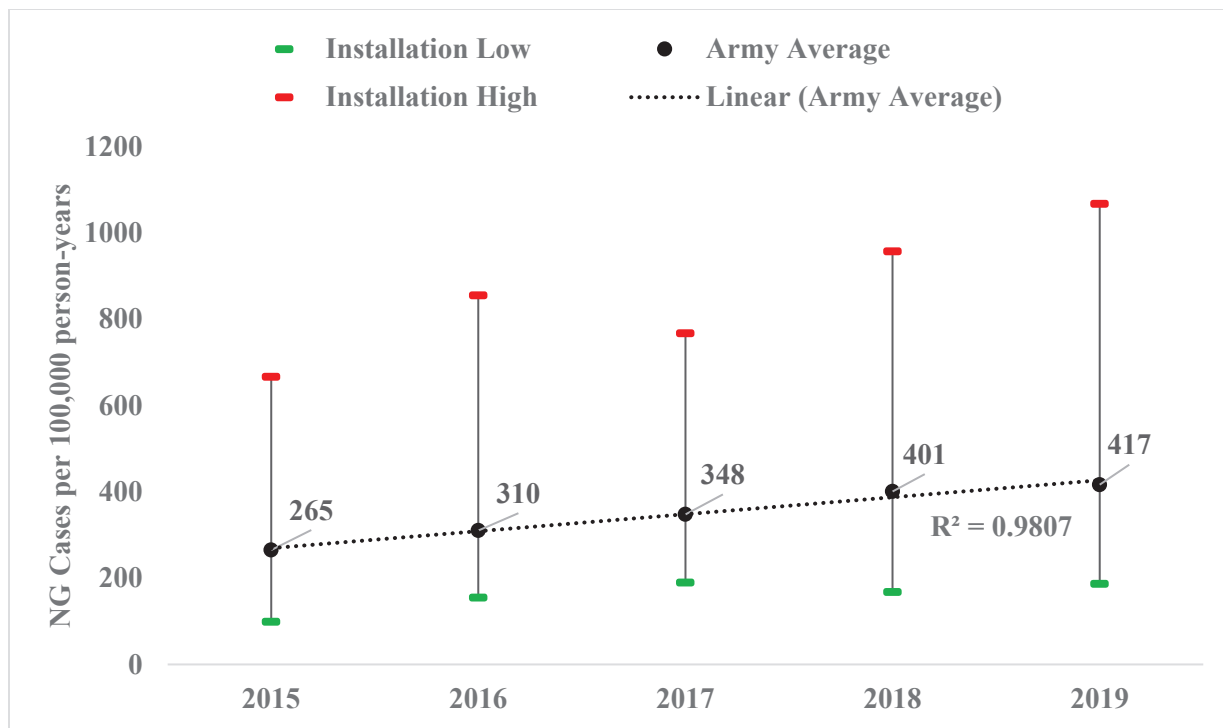


Figure 14. Annual Reported NG Case Rates with Installation Case Rate Ranges, AC Soldiers, 2015-2019

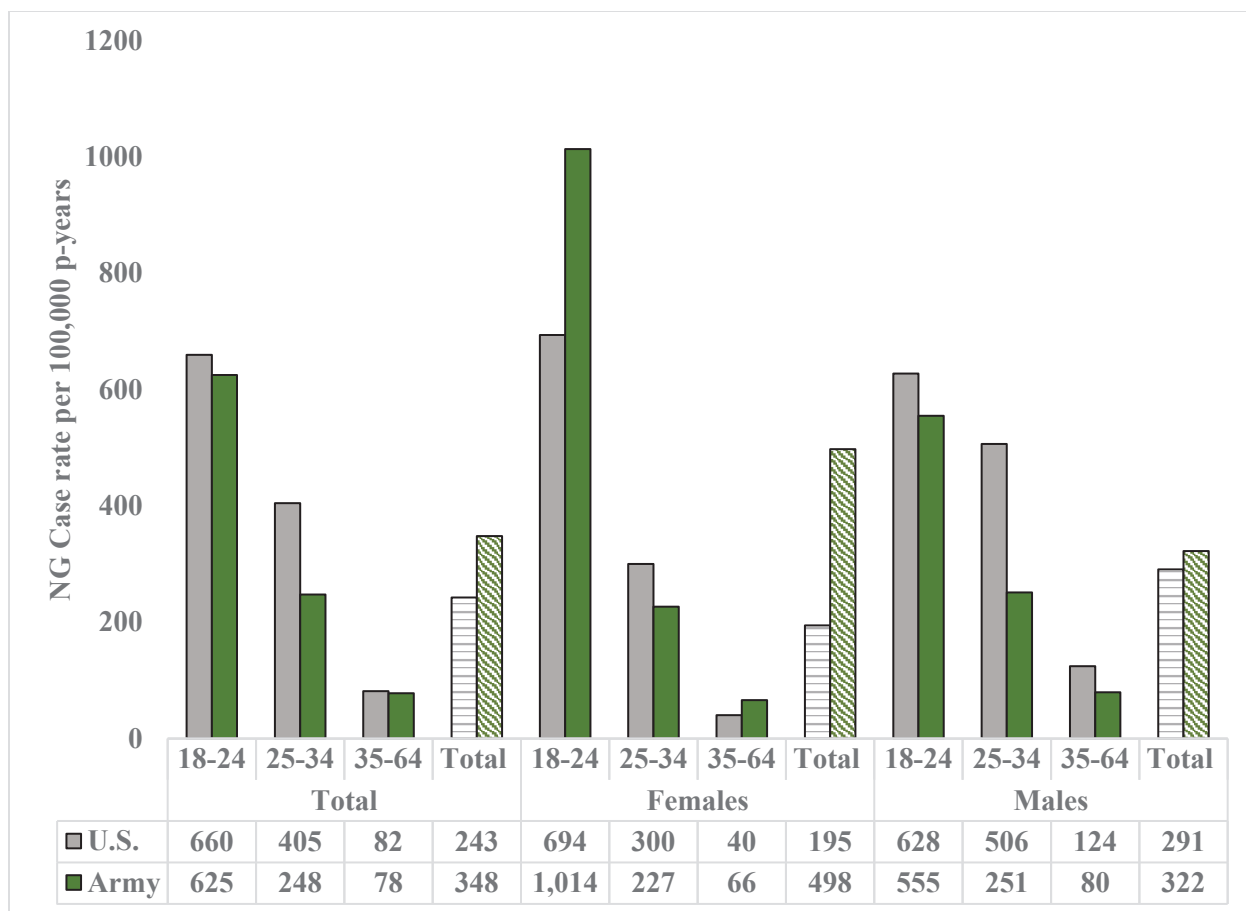


Figure 15. Reported NG Case Rates by Age and Sex, AC Soldiers and US Adults, 2015-2019

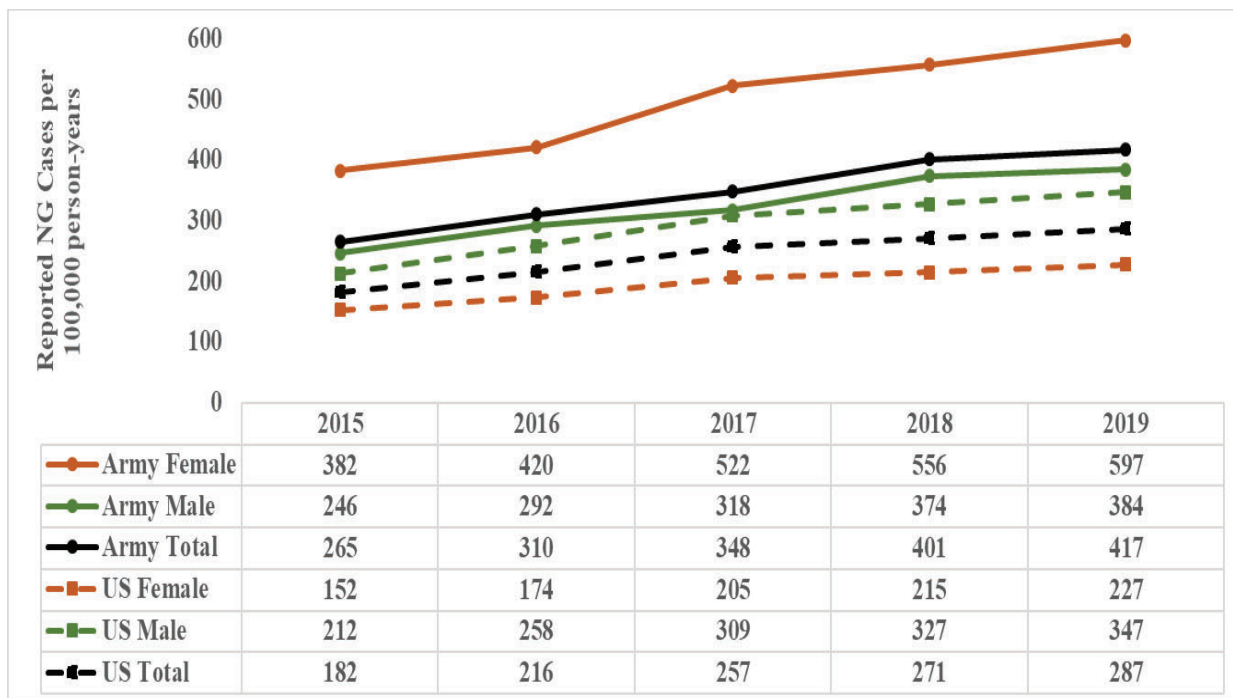


Figure 16. Reported NG Case Rates by Sex and Year, AC Soldiers and US Adults 18-64 years, 2015-2019

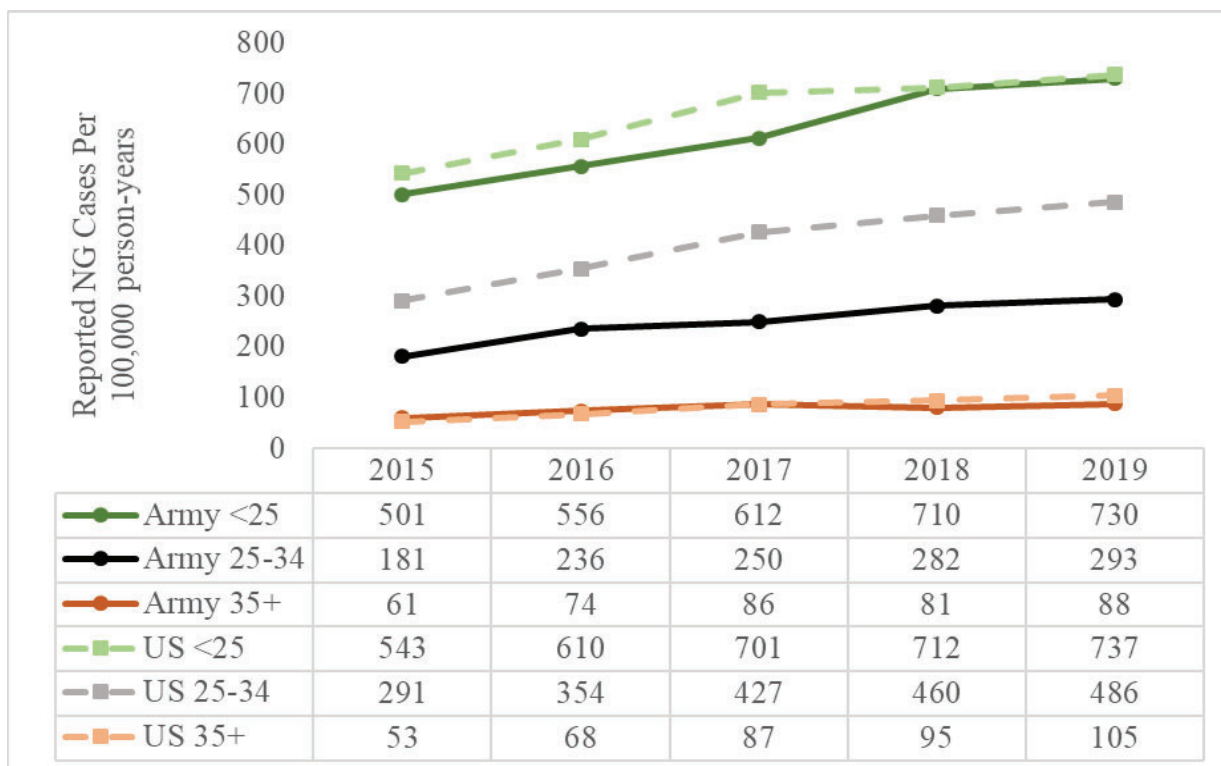


Figure 17. Reported NG Rates by Age and Year, AC Soldiers and US Adults 18-64 years of age, 2015-2019

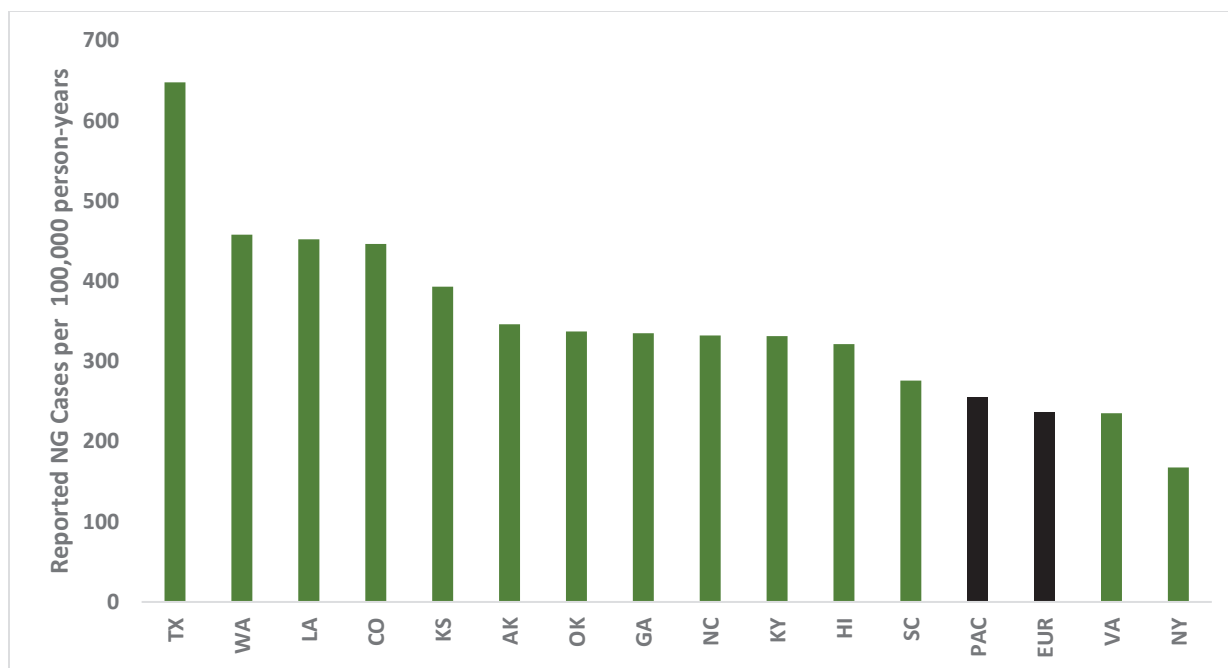


Figure 18. Unadjusted Reported NG Rates by Duty Location, AC Soldiers 2015-2019

^Location based on US state abbreviations; PAC=Pacific countries, EUR=European countries

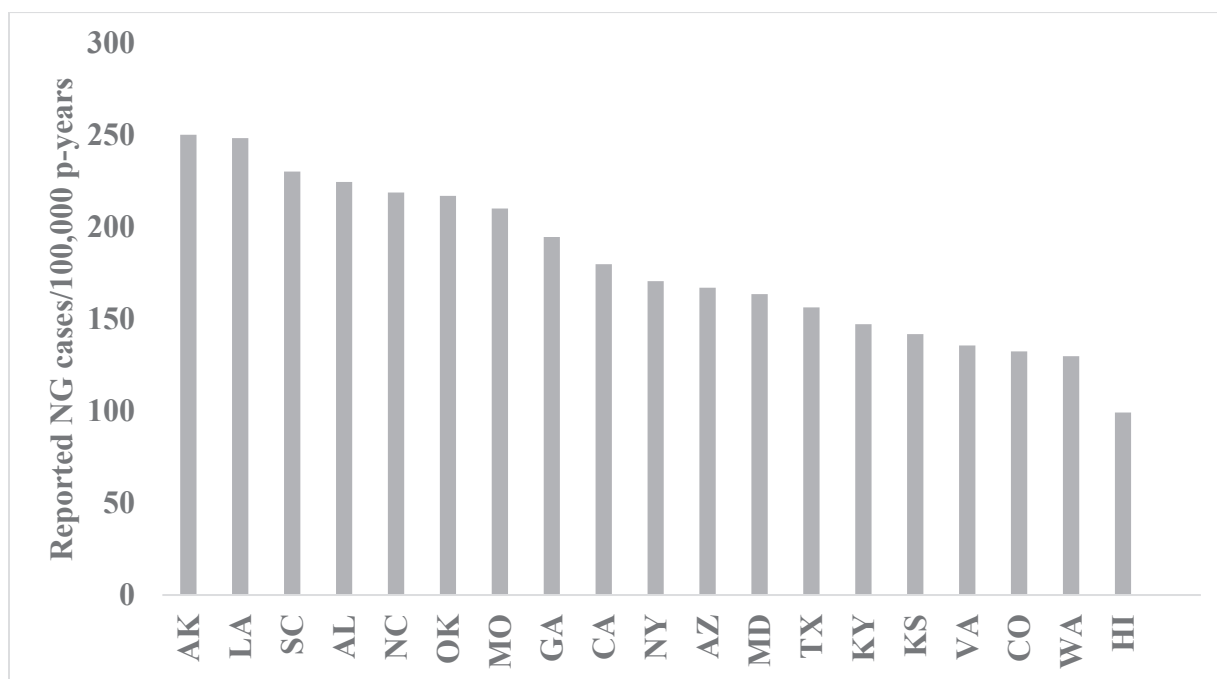


Figure 19. Unadjusted Reported NG Case Rates, US Adults 18-64 years of age, 2015-2019

^CDC STD Atlas DATA; states without an Army installation were excluded.

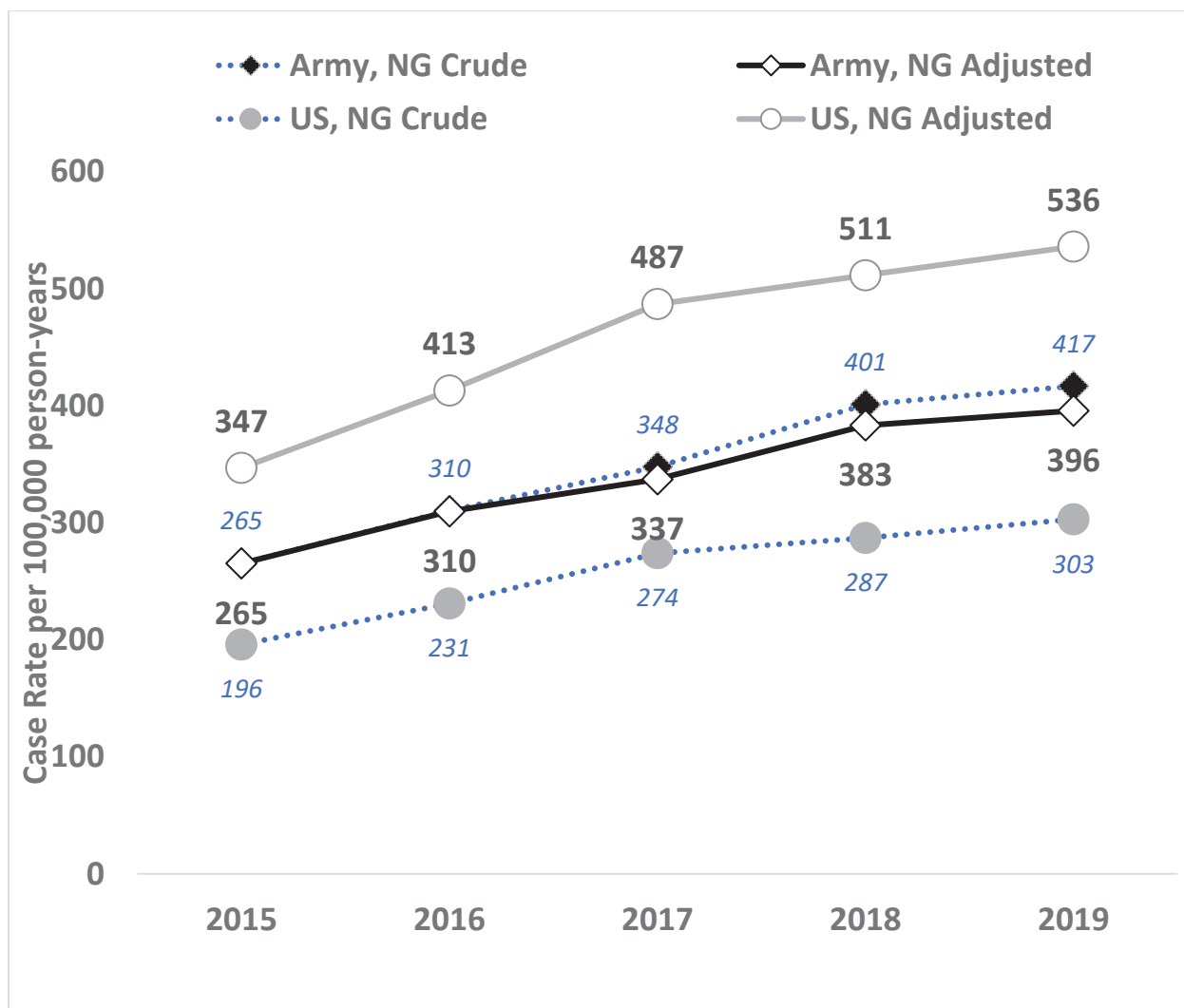


Figure 20. Crude and Age-sex Adjusted NG Rates Reported among AC Soldiers and US Adults 18-64 years, 2015-2019

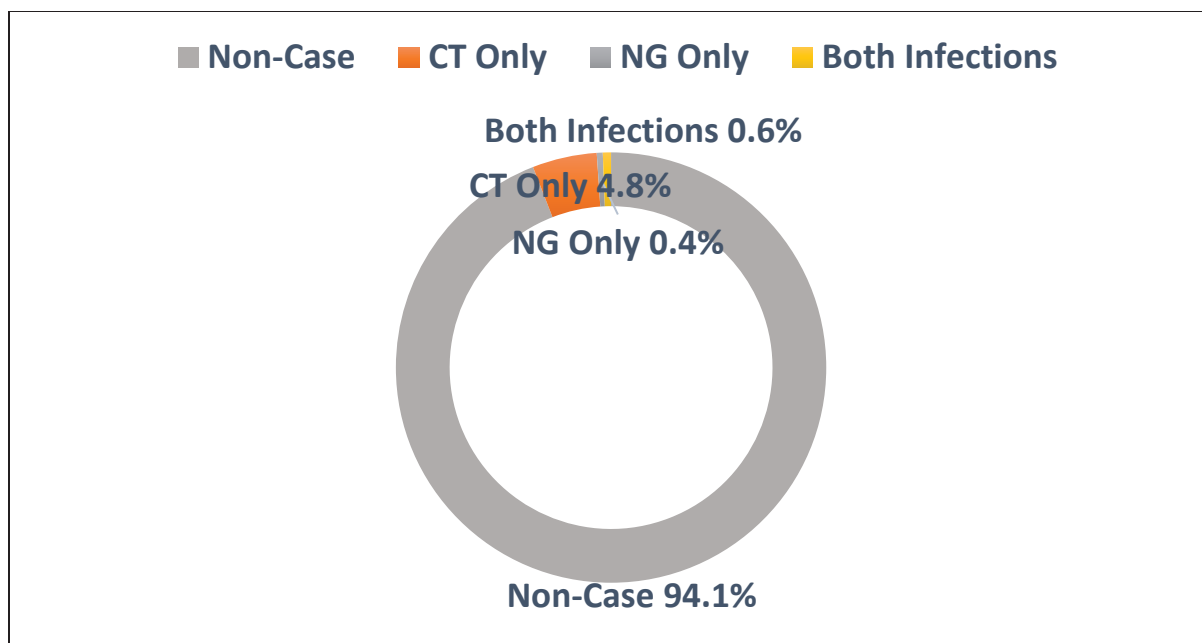


Figure 21. CT and NG Period Prevalence, AC Soldiers, 2015-2019

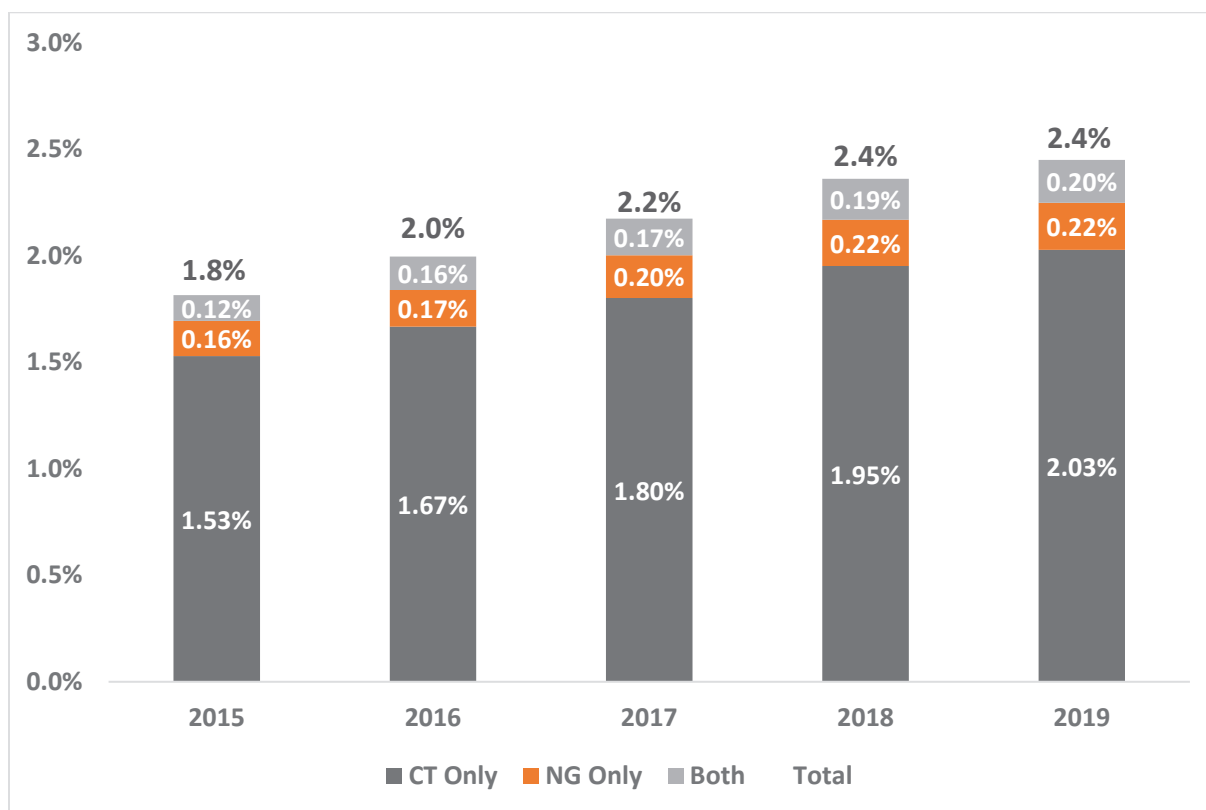


Figure 22. Annual Prevalence of CT and NG, AC Soldiers, 2015-2019

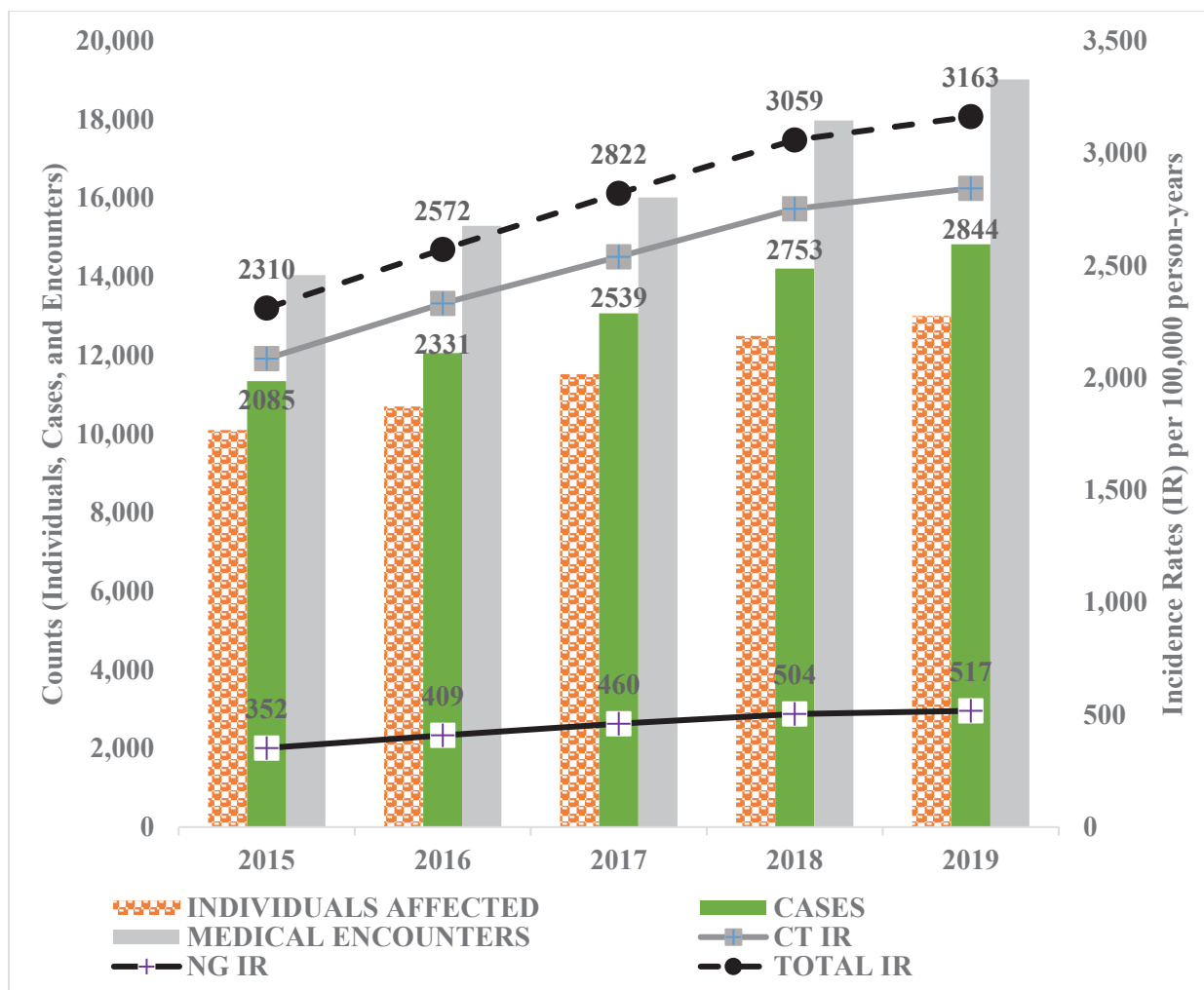


Figure 23. CT and NG Morbidity Burden and Incidence Trends, AC Soldiers, 2015-2019

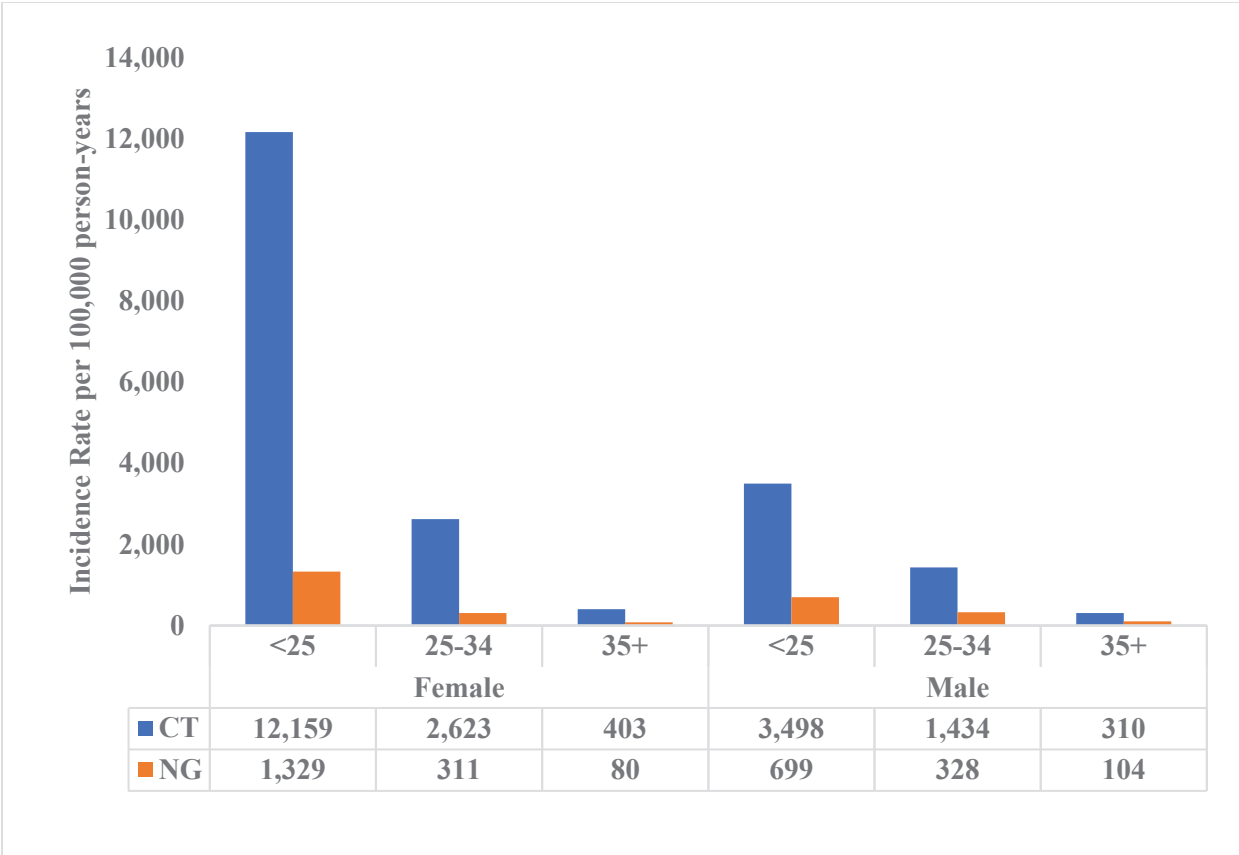


Figure 24. CT and NG Incidence by Age and Sex, AC Soldiers, 2015-2019

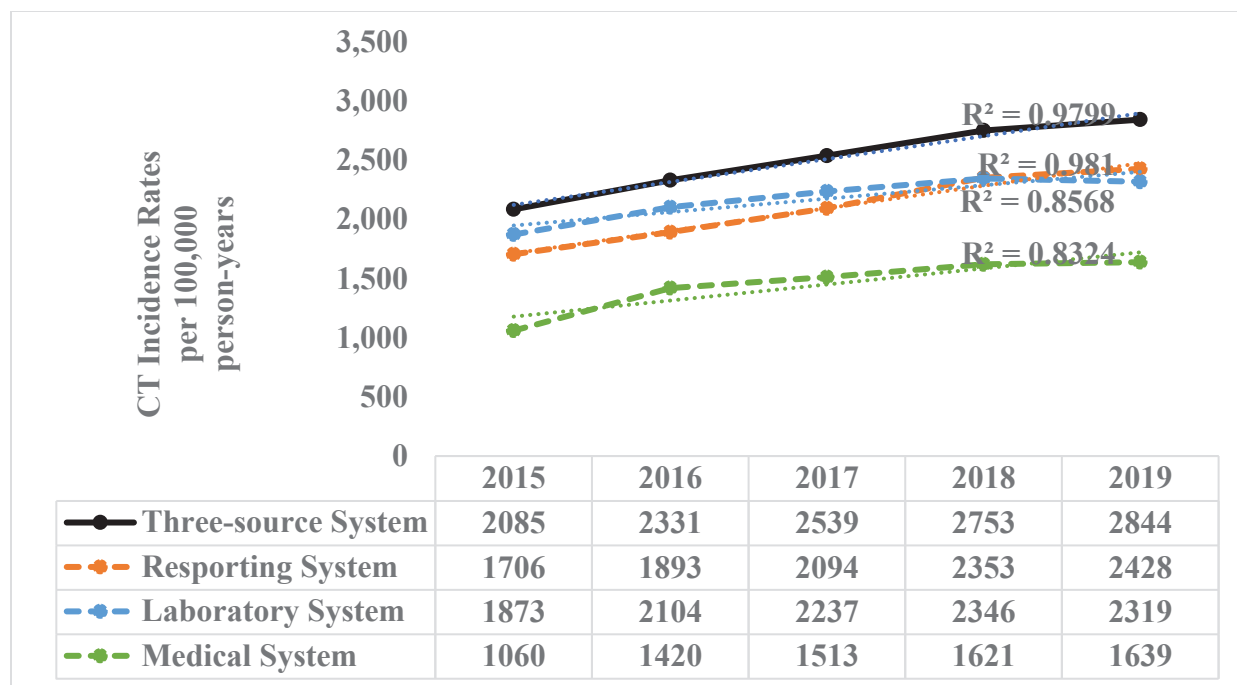


Figure 25. CT Incidence Rate Trends for AC Soldiers by Data System, 2015-2019

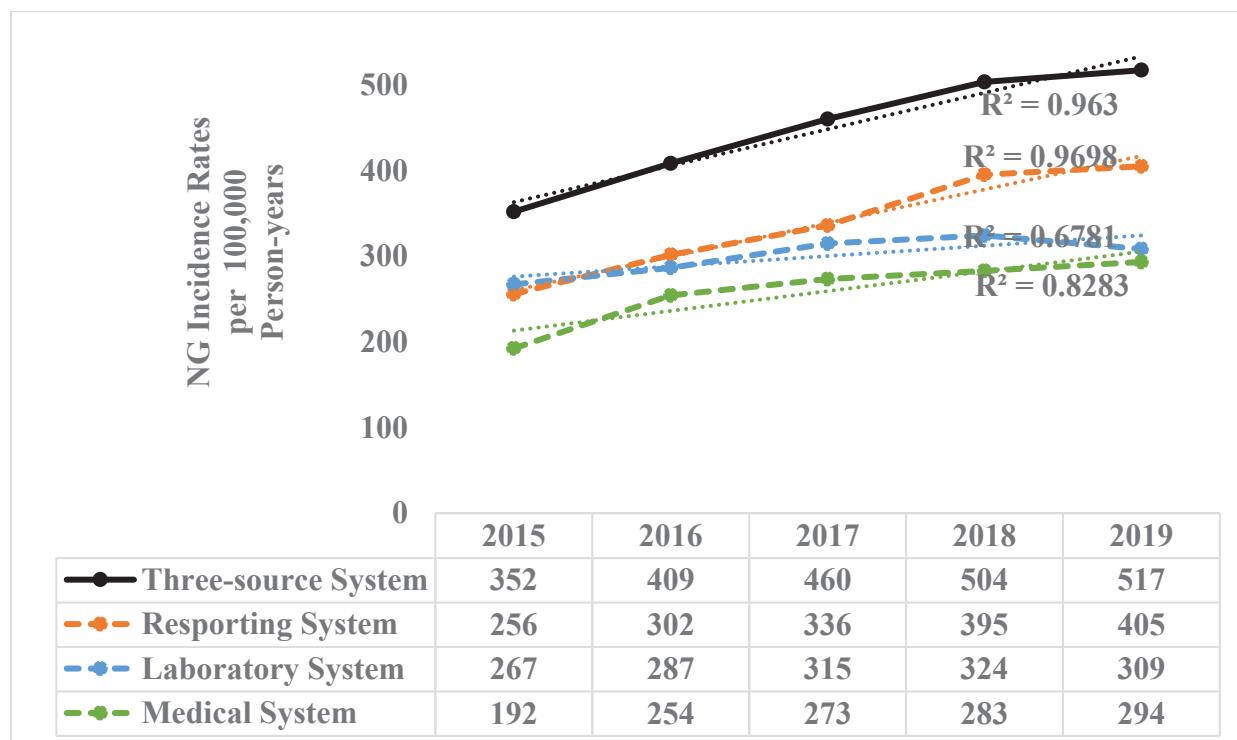


Figure 26. NG Incidence Rate Trends for AC Soldiers by Data System, 2015-2019

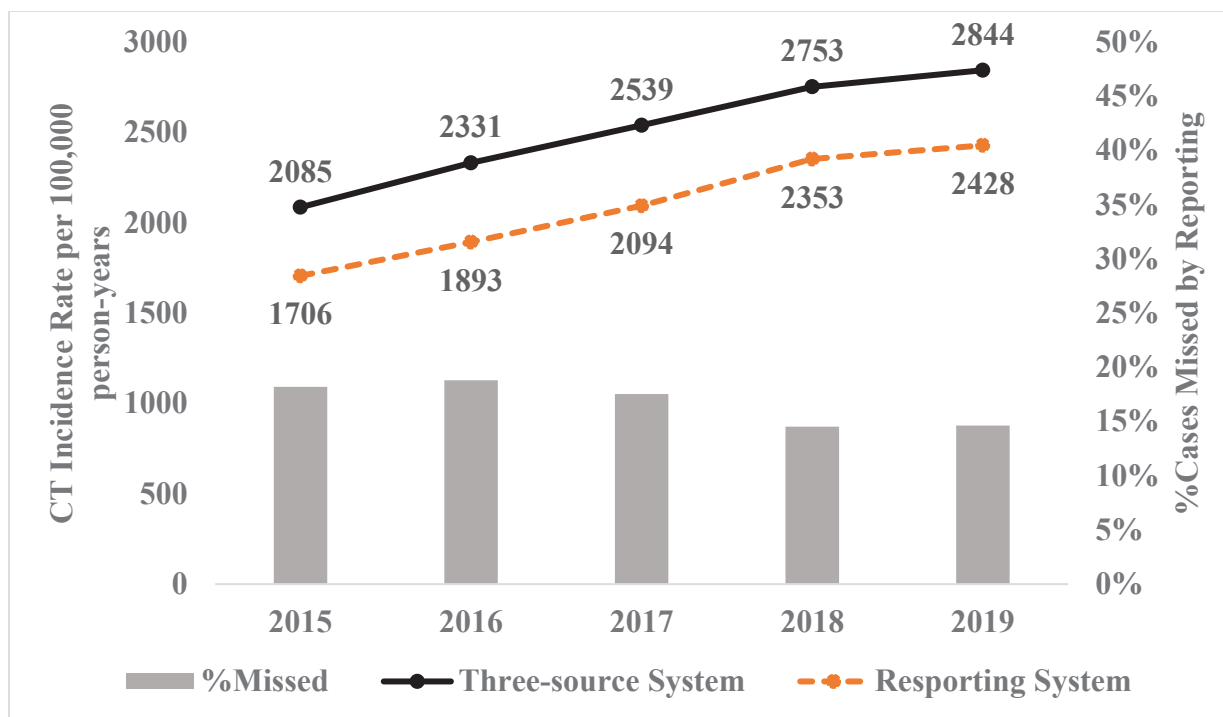


Figure 27. Trends in CT Incidence Rates for AC Soldiers by Surveillance System: Reporting System vs 3-Source System, 2015-2019

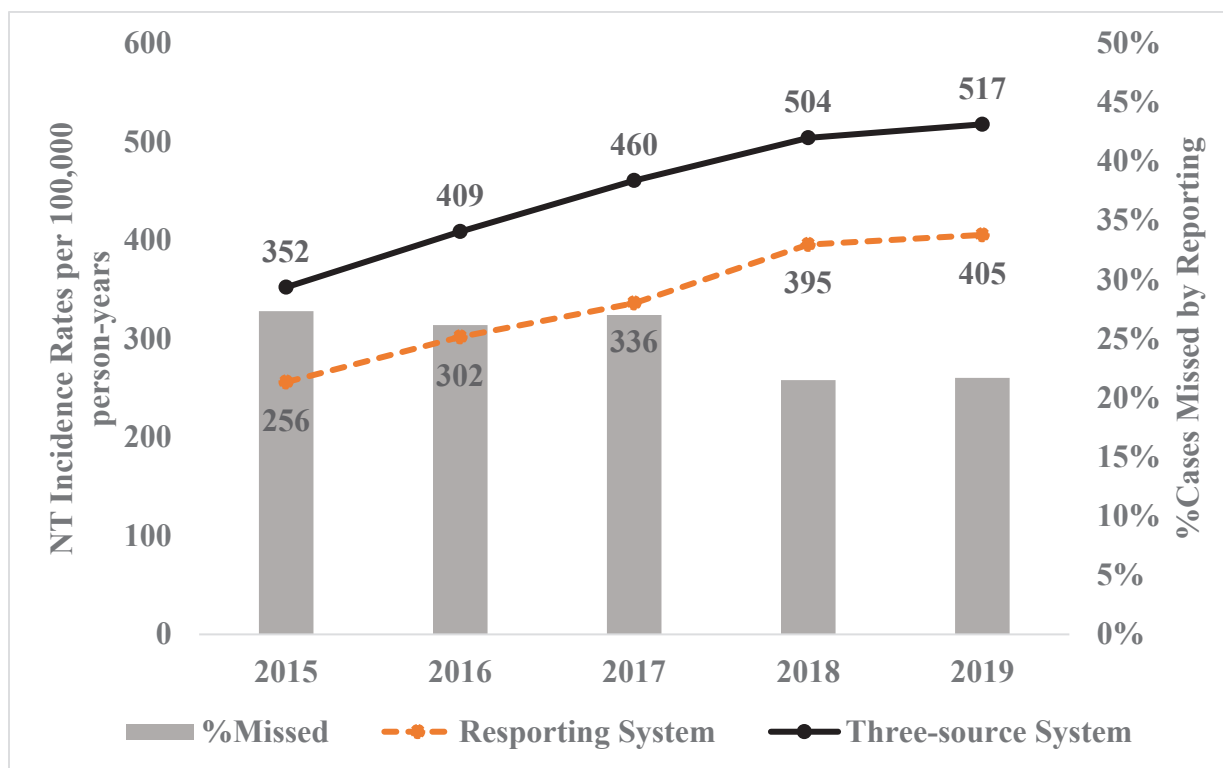


Figure 28. Trends in NG Incidence Rates for AC Soldiers by Surveillance System: Reporting System vs 3-Source System, 2015-2019

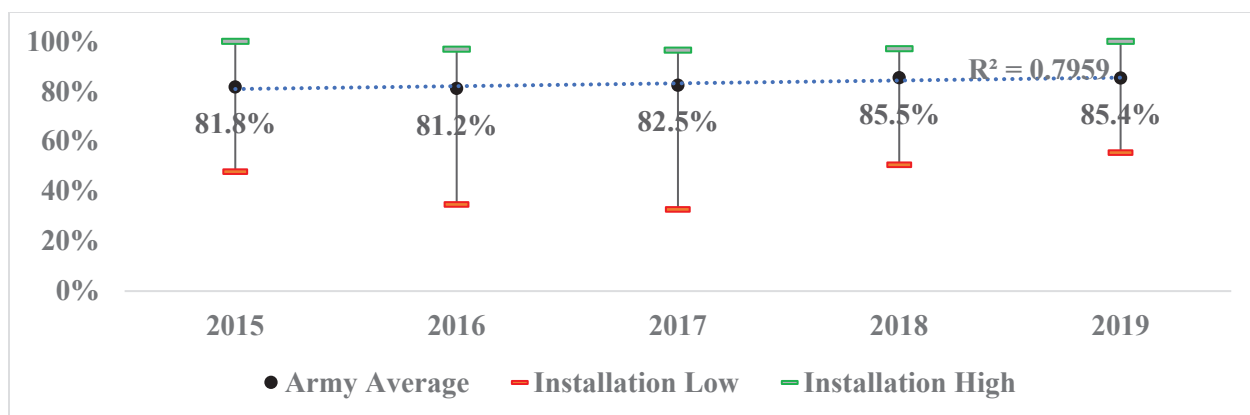


Figure 29. Trends in MHS Reporting System CT Case Capture by Army Installation, AC Soldiers, 2015-2019

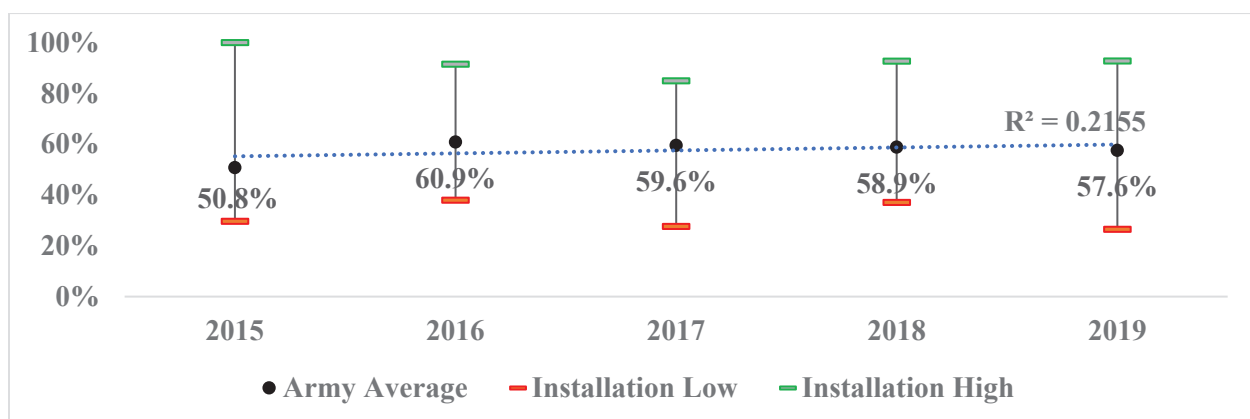


Figure 30. Trends in MHS Medical Record CT Case Capture by Army Installation, AC Soldiers, 2015-2019

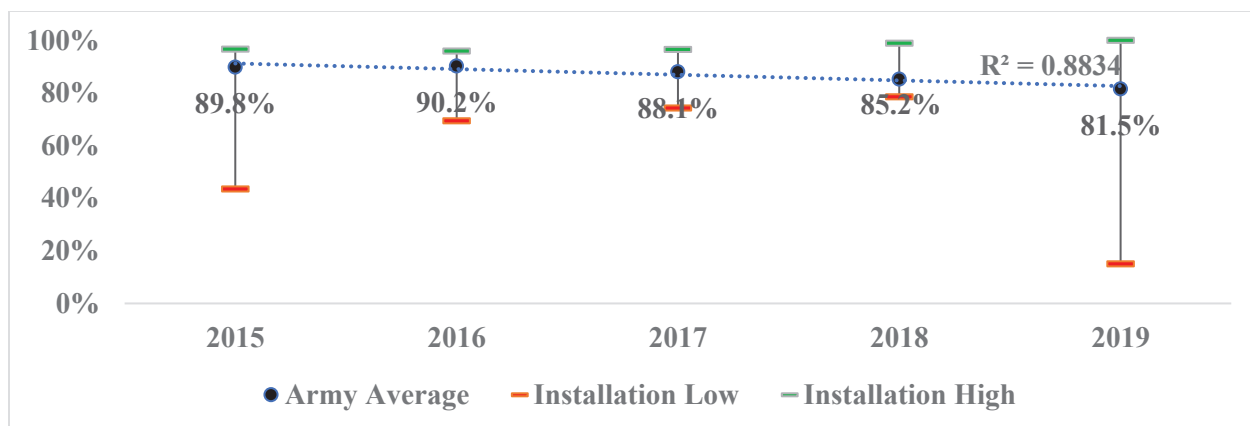


Figure 31. Trends in MHS Laboratory Record CT Case Capture by Installation, AC Soldiers, 2015-2019

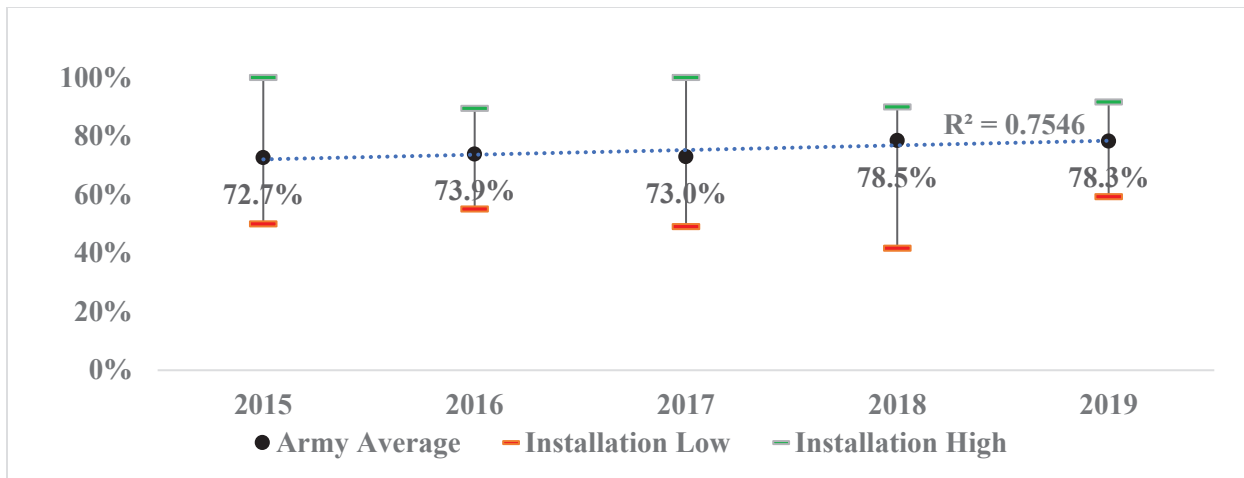


Figure 32. Trends in MHS Reporting System NG Case Capture by Installation, AC Soldiers, 2015-2019

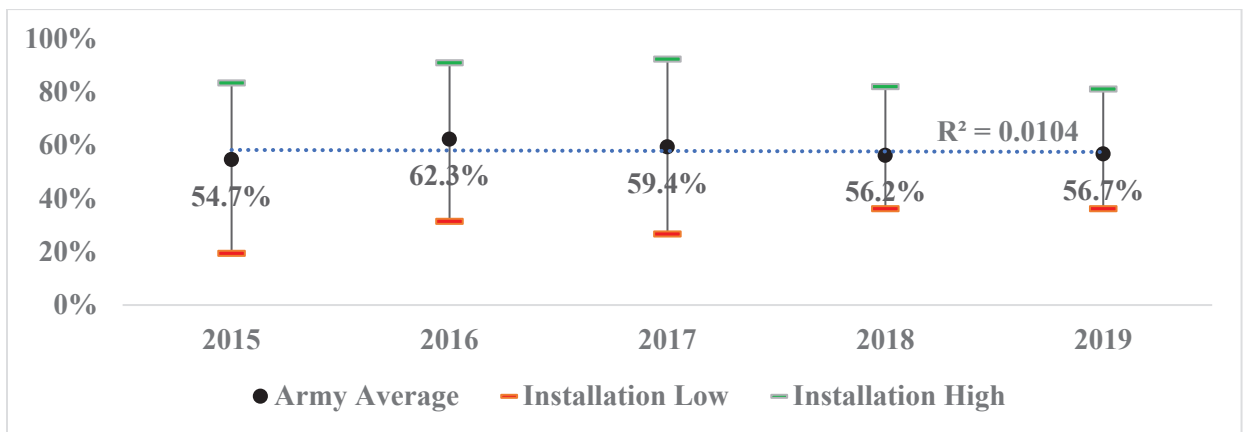


Figure 33. Trends in MHS Medical Record NG Case Capture by Installation, AC Soldiers, 2015-2019

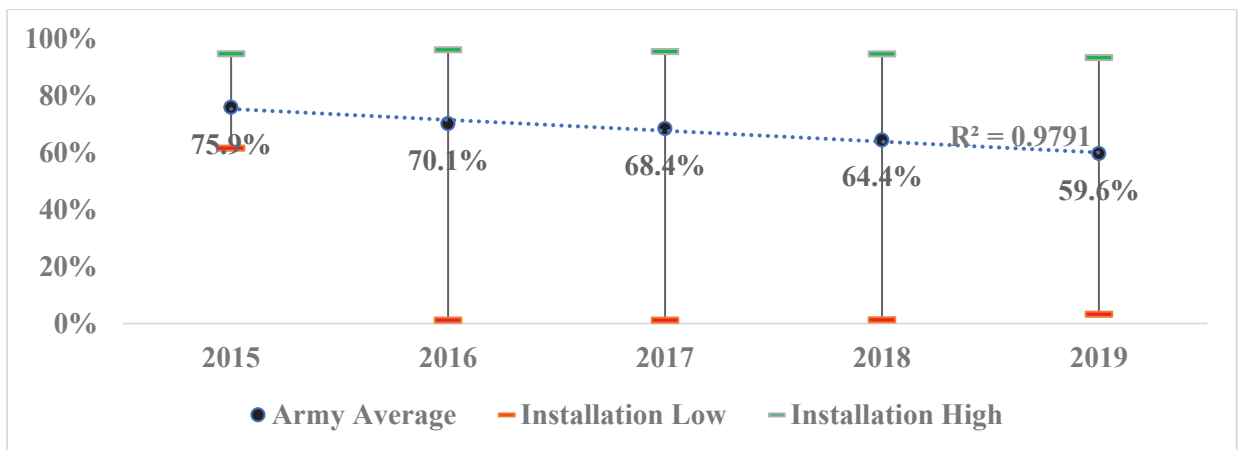


Figure 34. Trends in MHS Laboratory Record NG Case Capture by Installation, AC Soldiers, 2015-2019

Appendix A. USAPHC Data Protection Plan

All work was conducted under the oversight of the US Army Public Health Center (USAPHC) which has a standard data protection plan which analysts adhere to when using Protected Health Information (PHI). As a member of USAPHC's Disease Epidemiology Program (DEP), the doctoral candidate supported the STI projects described herein which were classified by USAPHC's Human Protections Board as IRB exempted surveillance covered under the program's surveillance 'umbrella'. All work was executed in accordance with the data protection planned as outlined below.

All USAPHC DEP personnel involved in activities that fall under this umbrella project are directly involved in public health surveillance as part of their regular responsibilities and have therefore conducted relevant HIPAA and data protection trainings. In accordance with regular work procedures, all data are stored only on designated secure drives. PII and PHI may include: SSNs, date of birth, disease diagnoses (including ICD code}, CPT code, rank, sex, age, marital status, race, first and last name, age, laboratory test orders and/or results, pharmacy orders and/or results, geographic information (e.g., MTF name and DMISID of diagnosis/record creation location, zip code of enrolling site, home of record, state of enrollment), deployment status, etc. Inpatient records will include admission and discharge date and disposition. Outpatient and reportable medical event data will include diagnosis or onset date; pharmacy and laboratory records will include ordering and result/dispensing date. These data elements are necessary to:

- 1) link cases/records across datasets (SSNs, name),
- 2) differentiate disease/health condition type and stage,

- 3) determine incident versus prevalent cases (personal identifiers, date information),
- 4) identify potential duplicate or erroneous records (SSN, name, dates, disease stage, ICD9/10 code, etc.),
- 5) ensure quality assurance steps during data cleaning and processing, and
- 6) create trend information and comparisons to other populations via demographic factors.

Data Use Agreements (DUAs) with data owners are on file; all data is downloaded from appropriate data system(s). Files containing PII and/or PHI are encrypted, password protected, and stored on the designated appropriate drive only. Data will not be de-identified as identification is needed to link records across record/data systems and perform quality control steps after the end of analysis. One year after the project ends/publication, all original data (PII, PHI) will be deleted permanently. Results from analyses in deliverables are de-identified.

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