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Vaccination of active component US military personnel against Salmonella Typhi

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ABSTRACT

Introduction: Vaccination against Salmonella Typhi is one of the leading public health interventions reducing the risk of typhoid fever. There are two available licensed vaccines, Vivotif, oral live-attenuated, and Typhim Vi, intramuscular Vi capsular polysaccharide. The US military is a high risk travel population commonly vaccinated for S. Typhi. We describe the use of S. Typhi vaccination in this population and the acute reactogenicity profile of these vaccines.
Methods: Data were obtained from the Defense Medical Surveillance System and vaccination identified between 1998 and 2011 from vaccination codes. Clinical outcomes were assessed for four weeks post vaccination. Adverse event rates and odds ratios were estimated across the two vaccine types.
Results: A total of 1.9 million predominately male military personnel received 3.6 million S. Typhi vaccinations with 94.3% of vaccinees receiving the Vi capsule vaccine though variability in the vaccine administered was observed. Receipt of other vaccinations in the 6 months surrounding the S. Typhi vaccine was common. Rates of nausea (195 per 100,000 vaccinations), headache (13 per 100,000 vaccinations) and fever (40 per 100,000 vaccinations) were significantly higher following Vi capsule vaccination compared to receipt of Vivotif (130, 2, 10 per 100,000 vaccinations, respectively). In contrast the rates of rash and non-infectious diarrhea (186 and 426 per 100,000 vaccinations, respectively) were increased in those receiving Vivotif compared to the Vi capsule vaccine.
Discussion: The US military is a major consumer of S. Typhi vaccines. The parenterally administered vaccine appears to be more amenable, though we were limited in our ability to assess the reasons for its higher usage. While we observed a higher rate of several adverse events in subjects receiving the intramuscular vaccination, the overall rate of these events was low. Future studies assessing more long-term health outcomes are warranted.

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1. Introduction

Infection with *Salmonella enterica*, serovar Typhi (hereafter referred to as *S. Typhi*) and the resulting illness known as typhoid fever has been a major cause of morbidity and mortality globally throughout history [1]. The bacterium is spread through consumption of contaminated food and water and is generally associated with poor public sanitation conditions and/or practices [2]. Water chlorination has significantly reduced the incidence of *S. Typhi* in the developed world with fewer than 400 cases in the United States annually [3]. Nonetheless, typhoid fever remains endemic in much of the developing world where it affects approximately 21.5 million people annually [2]. The United States military has targeted vaccination against *S. Typhi* as one key effort in primary disease prevention.

Presently, there are two licensed typhoid vaccines available in the United States; a live-attenuated strain of *S. Typhi*, Ty21a (Vivotif; PaxVax Inc.) and a Vi capsular polysaccharide vaccine (Typhim Vi; Sanofi Pasteur Inc.) administered parenterally as a single shot with a 2 year booster. Product inserts for both vaccines indicate the occurrence of relatively non-specific adverse events such as abdominal pain, nausea, headache, fever, diarrhea, vomiting, skin rash, urticaria and anaphylactic shock [5,6]. Additionally, post-marketing reports of glomerulonephritis, neutropenia, bilateral retinitis, and polyarthritis has been reported in patients who had also received other vaccines, though a causal association is unclear

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[6]. Additionally, the Vaccine Adverse Event Reporting System (VAERS) estimated 0.3 and 0.6 serious adverse events per 100,000 doses for the parenteral Vi vaccine and the Ty21a vaccine, respectively [7].

Current US Department of Defense (DoD) policy regarding typhoid fever and typhoid vaccines states "Vaccination is required (either in oral or injectable form) for alert forces during deployment or travel to typhoid-endemic areas and other areas with poor sanitation systems. Typhoid immunization is generally required for members of units designated to be ready to deploy outside of the US within 10 days of notification" [8]. Given the increased rate of deployments over the past decade with Operations Iraqi Freedom and Enduring Freedom and New Dawn, this policy has resulted in a significant proportion of active component personnel receiving one of the available vaccines.

While numerous studies on the safety of the two vaccines available to the US military have been conducted [5,6], post-marketing safety studies are limited. Additionally, given current US DoD policy on typhoid fever vaccination, it is anticipated that a large number of active duty service members have received one of the two vaccines, and sometimes multiple doses, available in the US. We aimed to take advantage of the US military's electronic medical encounter data system and vaccination of a young and healthy population to describe the distribution of vaccinations with Ty21a and with Vi capsule, the number of vaccination series received, the relation of vaccination timing to deployment, other vaccinations received and specific health outcomes following vaccination.

2. Methods

We utilized a retrospective cohort study to identify typhoid vaccinations among active component U.S. military population from 1998 and 2011. Vaccinated subjects were defined as individuals immunized with either the live-attenuated or capsular typhoid vaccines. Ty21a vaccine recipients were identified as those who had a vaccine administered (CVX) code of 025 and Vi capsule recipients were identified with CVX code of 101.

Data were supplied by the Armed Forces Health Surveillance Branch (AFHSB; previously the Armed Forces Health Surveillance Center) which oversees the Defense Medical Surveillance System (DMSS), the main data repository for all US Armed Forces medical data [9]. Medical encounter data were obtained from ambulatory and inpatient data for care obtained within the Military Health Services and outsourced care paid for by the military and the Tri-Service Reportable Events System data. Demographic information was obtained from personnel data. Deployment data were derived from deployment rosters and post-deployment health assessments. Immunization data were obtained from the Defense Enrollment Eligibility Reporting System (DEERS) which houses records of all administrated vaccines for a service member as part of readiness assessment and accountability. Service member rank was characterized as either enlisted or officer.

To estimate the utilization of either typhoid vaccine we calculated the number of dosing series administered annually relative to the number of active component US military personnel during the same time period. For each vaccine, we identified (based on CVX codes) the most common vaccines co-administered. We estimated and compared the risk of specific medically-attendant clinical outcomes following vaccination with either the live-attenuated or Vi capsule typhoid vaccines. Specifically, in the 4 weeks post-vaccination, we utilized International Classification for Disease edition 9 – clinical modification (ICD9-CM) codes to assess for medical encounters of fever (ICD9-CM: 780.60, 780.64, 780.63), headache (ICD9-CM: 784.6, 339.00-339.89), nausea (ICD9-CM: 787.x), abdominal pain (ICD9-CM: 789.0), non-infectious diarrhea (ICD9-CM: 558), skin rashes (ICD9-CM: 782.1, 691.0, 216, 782.8) and syncope (ICD9-CM: 780.2) given their inclusion in the product inserts for these vaccines [5,6]. The four week limit was applied to minimize non-specificity of outcomes and to maximize the temporal relationship with vaccination.

The incidence of medically attendant clinical outcomes in the four weeks post-vaccination was estimated based on the number of medical encounters with an outcome of interest divided by the total number of vaccine doses administered and reported per 100,000 vaccinations. We estimated the odds ratio of each outcome of interest following initial vaccination using multivariate logistic regression models to control for potentially important demographic variables. All statistical analyses were performed using SAS v. 9.2 for Windows (SAS Institute, Cary, NC). Two-tailed statistical significance was evaluated using an *alpha* = 0.05.

The study protocol was approved by the Naval Medical Research Center Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

3. Results

Between 1998 and 2011 over 1.9 million active component US military personnel received 3.6 million vaccinations for S. Typhi. The vaccinated population (Table 1) was reflective of the general deployable military population and predominately male (85.9%), enlisted (86.0%), and Army (44.9%) personnel with a high school education or equivalent (69.1%). The majority of vaccine recipients received only the Vi capsule vaccine (94.3%); however, 112,175 individuals received either the Ty21a vaccine only or in series (prior to or after) with the Vi capsule vaccine per interval booster recommendations. Demographics were comparable across the vaccine type administered with the exception of the higher proportion of Air Force personnel receiving the Ty21a vaccine ($p < 0.001$). As shown in Table 2, the majority of vaccinees (51.7%) received more than one S. Typhi vaccine series though multiple vaccinations with Ty21a were less common than with the Vi capsule vaccine (5.7% vs 52.1%, respectively).

In 1998, the Ty21a vaccine accounted for 82.9% of the total typhoid vaccinations administered (Fig. 1). Subsequently, utilization dropped significantly by 2000 and beyond after which it accounted for less than 4% of all typhoid vaccines administered. Concurrently, the number of S. Typhi vaccines administered increased sharply from just over 50,000 doses in 2001 (4.3% of the active component population) to approximately 200,000 in 2002 (13.5% of the active component population). The number of S. Typhi vaccines administered increased over the study period and peaked in 2010 with just over 28% of the active component population being vaccinated that year. Simultaneous with increasing typhoid vaccination rates, the number of annual operational deployments increased from less than 8000 in 2001 to over 200,000 from 2007 through 2011. In total, 45.3% ($N = 1,625,128$) of the typhoid vaccinations were followed by an operational deployment within 6 months.

In addition to receiving S. Typhi vaccines, subjects also received additional vaccines in the six months before and after typhoid vaccination (Fig. 2); however, co-vaccinations were more common among subjects receiving the Vi capsule vaccine compared to those receiving Ty21a (approximately 90% and 50%, respectively within six months). Among those receiving non-typhoid vaccines, the mean number of additional vaccinations ranged from approximately one, within one month of typhoid vaccination, to over six vaccines within six months. The additional vaccines received were comparable across the two studied typhoid vaccines and most

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