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UTILIZATION OF THE US DEPARTMENT OF DEFENSE MEDICAL SURVEILLANCE SYSTEM AND SERUM REPOSITORY FOR ASSESSING LONG-TERM HEALTH CONSEQUENCES OF ACUTE ENTERIC INFECTION

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INTRODUCTION TO DODSR AND DMSS

Second only to randomized controlled trials (RCTs), prospectively designed cohort studies represent the best way to explore the association between exposure and outcome in human populations. However, given practical limitations of sample size requirements, the high frequency of lost-to-follow-up, the relative rarity of some outcomes and other funding and logistical constraints, such epidemiologic investigation is rarely feasible. In absence of this study design, one begins to explore the potential for other, population-based data sets from which cohort studies can be reconstructed. One such available data source is available within the confines of the United States Department of Defense (US DoD). The objective of this paper is to review aspects and elements of the system maintained by the US DoD and how they can be utilized to explore novel associations including the persisting consequences of intestinal infection.

The active duty US military represents a large, uniquely healthy, young, active subset of the general US population and is one amenable to epidemiologic studies. In 1986, the US Army established a data repository with the stated purpose of supporting HIV screening, care and research (*Rubertone* et al., 2002). Seven years later, the scope of this system expanded to include all illness and injuries of importance for public health and/or the DoD. Additionally, self-completed pre- and post-deployment health surveys were initiated in the 1990s to document exposures during deployment as well as general changes in health subsequent to deployment (*Moore* et al., 2010). These data are linked within the Defense Medical Surveillance System by social security number to longitudinal demographic, medical encounter, vaccination and deployment data on all active duty service members.

 There were no financial conflicts of interests among any of the authors. 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. This study was conducted under support of the Military Infectious Disease Research Program.

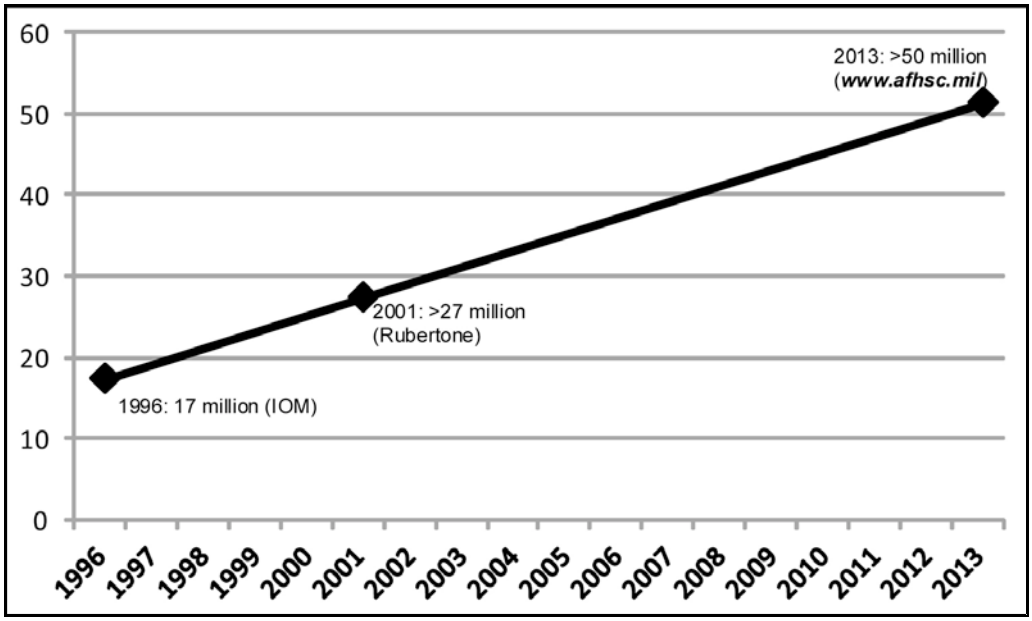

Figure 1: Estimated number of serum samples in DoD serum repository.

Almost simultaneously to the establishment of the serum repository, in 1985, the US DoD implemented a Human Immunodeficiency Virus (HIV) screening program in which remnants of sera collected from recruits that tested negative for HIV was archived (*Moore* et al., 2010). Subsequently, the sera were transported to a single facility and the serum repository was born. In the 1990s, in response to illnesses affiliated with participation in the first Gulf War, the DoD expanded serologic screening by implementing pre- and post-deployment blood draws for serum archival to identify potentially important exposures during deployment. The serum repository has grown exponentially since that time and at present houses over 56 million serum samples from potential recruits, active duty and former active duty service members (Figure 1). These serum samples can be linked (via social security number) to data within the Defense Medical Surveillance System (DMSS).

While these are invaluable resources with fairly limited access, it is useful to explore how these data and samples have begun to be utilized to explore the association between acute infection and chronic gastrointestinal (GI) sequelae, what additional questions are pending and how archives within the US DoD can be utilized to answer some of these questions. Additionally, full acknowledgement and evaluation of the strengths and limitations of the DMSS and the Department of Defense serum Repository (DODSR) related to assessing the link between acute enteric infection and post-infectious sequelae is necessary to identify knowledge gaps that need filling with supplementary data and other data/repository systems available. The objective of this report is to summarize the key findings to date utilizing the DMSS/DODSR, to outline expanded areas of research in which they can be utilized to explore novel hypotheses on infection and chronic GI sequelae and begin to frame the mechanism(s) by which these studies could be conducted.

Table 1: List of gastrointestinal conditions that do not meet the standard for appointment, enlistment or induction with relevant ICD-9 and CPT codes (DOD instruction 6130.03)

Site/Condition:	**Exclusionary conditions:**
Oesophageal Disease:	(1) Current or history of oesophageal disease (530.0-530-9), including but not limited to ulceration, varices, fistula, or achalasia. (2) Gastro-Oesophageal Reflux Disease (GERD) (530.81), with complications. (a) Stricture or B-ring. (b) Dysphagia. (c) Recurrent symptoms or esophagitis despite maintenance medication. (d) Barrett's esophagitis. (e) Extra-oesophageal complications; reactive airway disease; recurrent sinusitis or dental complications. (3) History of surgical correction (fundoplication or dilation) for GERD within 6 months (45.89). (4) Current or history of dysmotility disorders, to include diffuse oesophageal spasm, nutcracker oesophagus, non-specific motility disorder, and achalasia. (5) Eosinophilic oesophagitis. (6) Other oesophageal strictures, for example lye or other caustic ingestion
Stomach and Duodenum:	(1) Current dyspepsia requiring medication; or history of dyspepsia lasting 3 or more consecutive months and requiring medication within the preceding 12 months. (2) Gastric or duodenal ulcers: (a) Current ulcer or history of treated ulcer within the last 3 months. (b) Recurrent or complicated by bleeding, obstruction, or perforation within preceding 5 years confirmed by endoscopy. (3) History of surgery for peptic ulceration or perforation (533.0-599.9). (4) History of gastroparesis. (5) History of bariatric surgery of any type (e.g., lap-band or gastric bypass surgery for weight loss). (6) History of gastric varices.
Small and Large Intestine:	(1) Current or history of inflammatory bowel disease, including but not limited to indeterminate (558.9), Crohn's disease (555), ulcerative colitis (556), or ulcerative proctitis (556.2). (2) Current infectious colitis not otherwise specified (009.1). (3) Current or history of intestinal malabsorption syndromes (579.9), including but not limited to celiac sprue, pancreatic insufficiency, post-surgical and idiopathic (579). Lactase deficiency does not meet the standard only if of sufficient severity to require frequent intervention, or to interfere with normal function. (4) Current or history of gastrointestinal functional and motility disorders within the past 2 years, including but not limited to pseudo-obstruction, megacolon, history of volvulus, or chronic constipation (564.0) and or diarrhoea (787.91), regardless of cause, persisting or symptomatic in the past 2 years.

Table 1 (continued): List of gastrointestinal conditions that do not meet the standard for appointment, enlistment or induction with relevant ICD-9 and CPT codes (DOD instruction 6130.03)

Site/Condition:	Exclusionary conditions:
Small and Large Intestine:	(5) History of gastrointestinal bleeding (578), including positive occult blood (792.1), if the cause has not been corrected. Meckel's diverticulum (751.0), if surgically corrected more than 6 months prior DOES meet the standard. (6) Current or history of irritable bowel syndrome (564.1) of sufficient severity to require frequent intervention or prescription medication or to interfere with normal function. (7) History of bowel resection (CPT 44202-44203). (8) Current or history of symptomatic diverticular disease of the intestine (562). (9) Personal or family history of familial adenomatous polyposis syndrome or hereditary non-polyposis colon cancer syndrome.
Hepatic-Biliary Tract:	(1) Current acute or chronic hepatitis, hepatitis carrier state (070), hepatitis in the preceding 6 months or persistence of symptoms after 6 months, or objective evidence of impairment of liver function. (2) Current or history of cirrhosis (571), hepatic cysts (573.8), abscess (572.0), or sequelae of chronic liver disease (571.3). (3) Current or history of symptomatic cholecystitis (575.10), unless successfully surgically corrected; postcholecystectomy syndrome; or other disorders of the gallbladder and biliary system (576). Cholecystectomy DOES meet the standard if performed more than 6 months prior to examination and patient remains asymptomatic. Endoscopic procedure to correct choledocholithiasis, if performed more than 6 months prior to examination and patient remains asymptomatic, MAY meet the standard. (4) History of sphincter of Oddi dysfunction. (5) Choledochocyst. (6) Primary biliary cirrhosis or primary sclerosing cholangitis. (7) Current or history of pancreatitis, acute (577.0) or chronic (577.1). (8) Pancreatic cyst. (9) History of pancreatic surgery. (10) Current or history of metabolic liver disease, including but not limited to hemochromatosis (275.0), Wilson's disease (275.1), or alpha-1 anti-trypsin deficiency (273.4). Gilbert's syndrome DOES meet the standard. (11) Current enlargement of the liver from any cause (789.1).
Anorectal:	(1) Current anal fissure or anal fistula (565). (2) Current or history of anal or rectal polyp (569.0), prolapse (569.1), stricture (569.2), or faecal incontinence (787.6), within the last 2 years. History of removal of juvenile or inflammatory polyp DOES meet the standard. (3) Current haemorrhoid (internal or external), when large, symptomatic, or with a history of bleeding (455) within the last 60 days.

Table 1 (continued): List of gastrointestinal conditions that do not meet the standard for appointment, enlistment or induction with relevant ICD-9 and CPT codes (DOD instruction 6130.03)

Site/Condition:	Exclusionary conditions:
Abdominal Wall:	(1) Current hernia (except for small or asymptomatic umbilical hernias), including but not limited to uncorrected inguinal (550) and other abdominal wall hernias (553). (2) History of open or laparoscopic abdominal surgery (CPT 22900-22999, 43500-49999) during the preceding 6 months (P54). Uncomplicated laparoscopic appendectomies (CPT 44970) meet the standard after 3 months.
Obesity:	History of any gastrointestinal procedure for the control of obesity (CPT 43644-43645, 43770-43775, 43842-43848, 43886-43888) or artificial openings, including but not limited to ostomy (V44).

POPULATION DEMOGRAPHICS

One of the most unique attributes of the Department of Defense repository is the population from which the data are obtained. As of February 28, 2013, there were 1.39 million active duty service members with an average age of 28.8 years (Defense Manpower Data Center; DMDC). This very healthy, physically active subset of the general population is one in which assessment of the risk of chronic GI sequelae following from infection is beneficial as it is generally free of oftentimes confounding co-morbidities. Specifically, all United States Department of Defense recruits are subject to detailed physical exams and medical history prior to being processed for recruit training. The specific requirements are outlined in the Department of Defense Medical Standards for Appointment, Enlistment, or Induction. The current list of gastrointestinal conditions that do not meet the standard for appointment, enlistment or induction, updated 28 April 2010 under Department of Defense Instruction 6130.03 are included in Table 1 and highlight the differences between this and the general population. Conversely, studies in this population often lack external validity to the general population which may limit extrapolation of data to other dissimilar populations.

Age is a known risk factor for many of the chronic GI outcomes currently linked to IGE including IBS, IBD and coeliac disease. With the overwhelming majority (approximately 80%) of active duty personnel aged 18-35 (DMDC), estimates of relative risks may be confounded by age. Specifically, risk of PI-IBS has been shown to decrease with increasing age (*Marshall* et al., 2006; *Neal* et al., 1997). Studies to date are too limited to assess whether age serves as a confounder or an effect modifier of the risk associated with antecedent exposure and studies of active duty personnel have included age as a matching variable between cases and controls. However, matching on this potential important covariate precludes any assessment of its impact on the association between infection and outcome among this uniquely young population.

The overwhelming majority (85.4% as of Sept 2012) (DMDC) of active duty military personnel are male compared to an estimated 50.2% of the general US population (2010 US census). Importantly, being of female gender has been repeatedly associated with an increased risk of FGD including IBS, functional dyspepsia and functional constipation (*Mearin*, 2011). Incidence of these functional outcomes in military populations based on these data is lower than what has been reported elsewhere using similar methodology. As such, studies should ensure matching on gender for assessment of most PI-FGD. Furthermore, stress has a role in IBS risk and may confound or modify the effect of enteric infection on FGD risk in a population that is frequently deployed into what are likely broadly considered to be stressful environments (*Drossman*, 2011). Additionally, gender has been indicated as a risk factor for more pathological conditions such as IBD and coeliac disease (*Green* and *Cellier*, 2007; *Karlinger* et al., 2000). Despite the potential lack of external validity, numerous large cohort studies have elucidate novel findings of public health importance; examples include the Framingham Heart Study (*Dawber* et al., 1951) and those of smoking and mortality among a cohort of physicians (*Doll* and *Hill*, 1954; *Doll* and *Pike*, 1972).

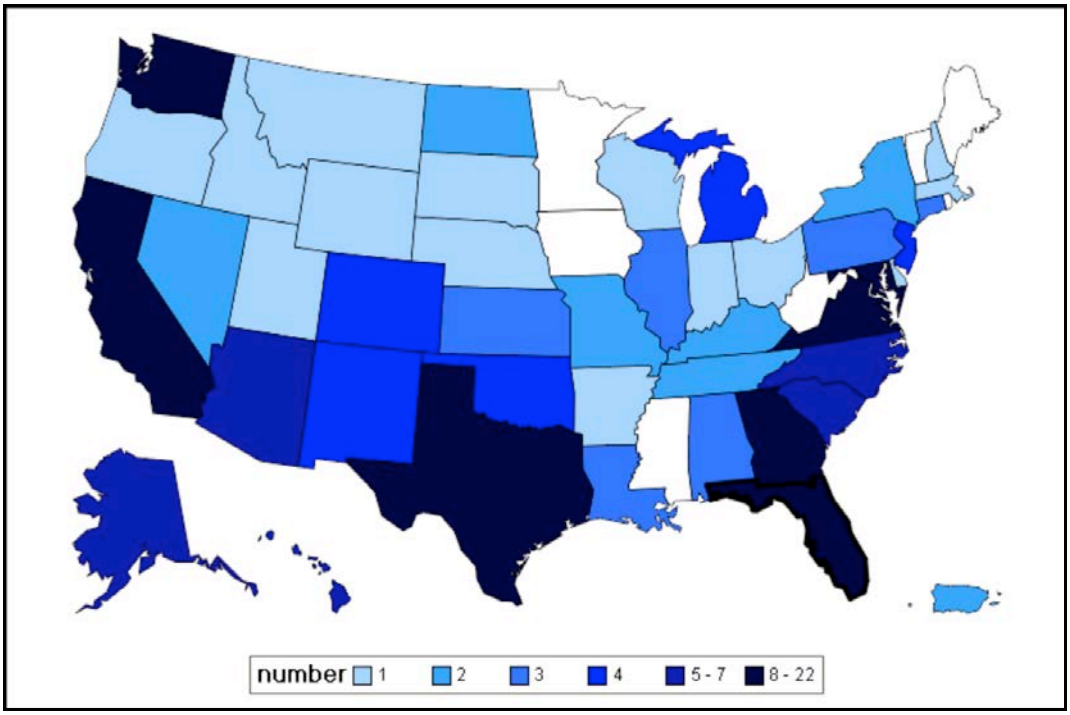

Figure 2: Map of the Number of Military Treatment Facilities in the US and Puerto Rico.

ACCESS TO CARE

One of the factors limiting the utilization of medical encounter databases in other populations is variability in access to medical care. For example, studies within large provider networks (Kaiser, Aetna, etc.) within the United States have frequently reported findings within their covered population; however, it is unclear if the covered and non-covered populations in those regions are comparable or whether covered individuals sought care outside of their provider network (*Koebnick* et al., 2012; *Stephenson* et al., 2005). In contrast, active duty military personnel have equal and unfettered access to healthcare at any one of the 184 US- (and Puerto Rico-) based military treatment facilities (MTFs) (Figure 2) or the 31 locations internationally (http://www.tricare.mil/mtf/main1.aspx; accessed 5/10/13). In a reference population followed for an average of 3.7 years, the median number of outpatient medical encounters per subject was 29 (interquartile range: 14, 56) for just under an estimated 8 outpatient medical encounters annually per active duty service member (*Porter* et al., 2012). These encounters included general health physicals, vaccinations, procedures, illness and injuries handled in an ambulatory setting. As expected, the number of inpatient visits was much lower (annually <1 per service member).

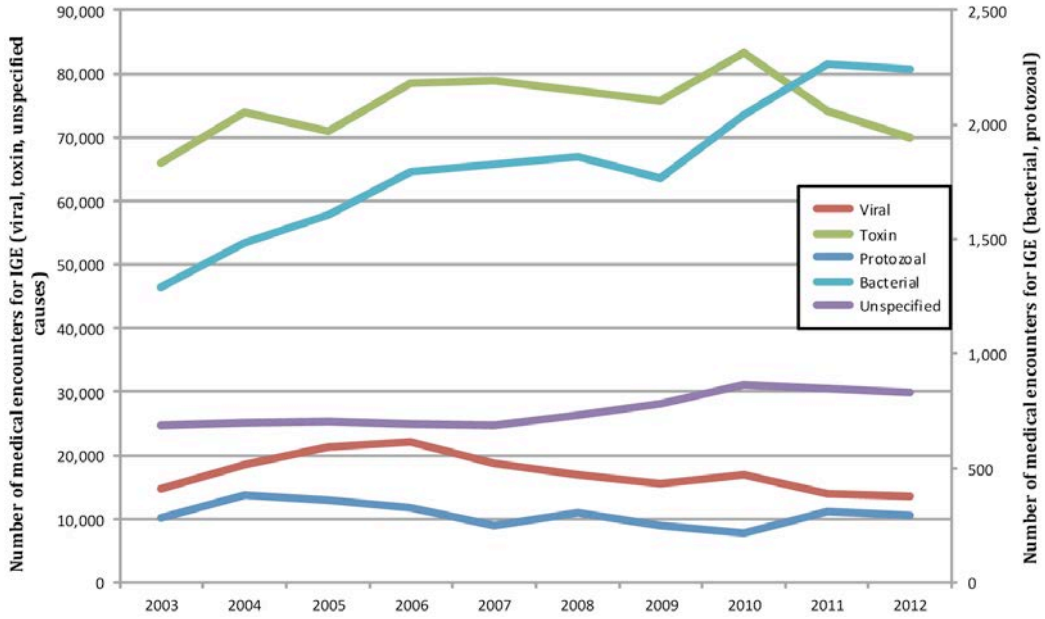

Figure 3: Number of medical encounters for infectious gastroenteritis among active duty US military personnel 2003-2012.

EXPOSURES OF INTEREST

The under-reporting phenomenon of acute gastroenteritis is well-appreciated and has been documented by the US Centers for Disease Control and Prevention (CDC) most recently in estimates of foodborne-related illness in the US (*Scallan*, 2011a,b). The DMSS is no different from other passive reporting systems and it is anticipated that estimates of infectious (and/or toxin-mediated) gastroenteritis rates significantly underestimate true incidence. Nonetheless, over the past 10 years (2003-2012), there have been 1.8 million documented medical encounters for acute gastroenteritis of presumed infectious/toxin-mediated origin (Figure 3), the overwhelming majority (99.2%) of which occurred in an outpatient setting. Current studies of the post-infectious consequences of acute infection have most frequently focused on specific bacterial pathogens including Campylobacter, Salmonella, Shigella and entero-haemorrhagic *E. coli*; thus an assessment of the estimated minimum number of available relevant exposures for these pathogens is warranted. As shown in Figure 4, medical encounters associated with these 4 pathogens have remained relatively stable over the past 10 years with a total number of just under 3,000 total encounters. Importantly, these documented medical encounters are likely to greatly underestimate the actual population exposed to these pathogens (*Porter* et al., 2012a).

Importantly, the above events are limited to those occurring at a MTF and do not include the numerous exposures that occur during military deployment and/or assignment in regions of the globe with high rates of travellers' diarrhoea. While deployment to those regions may serve as a surrogate of exposure, prior studies have been limited in their ability to link increased

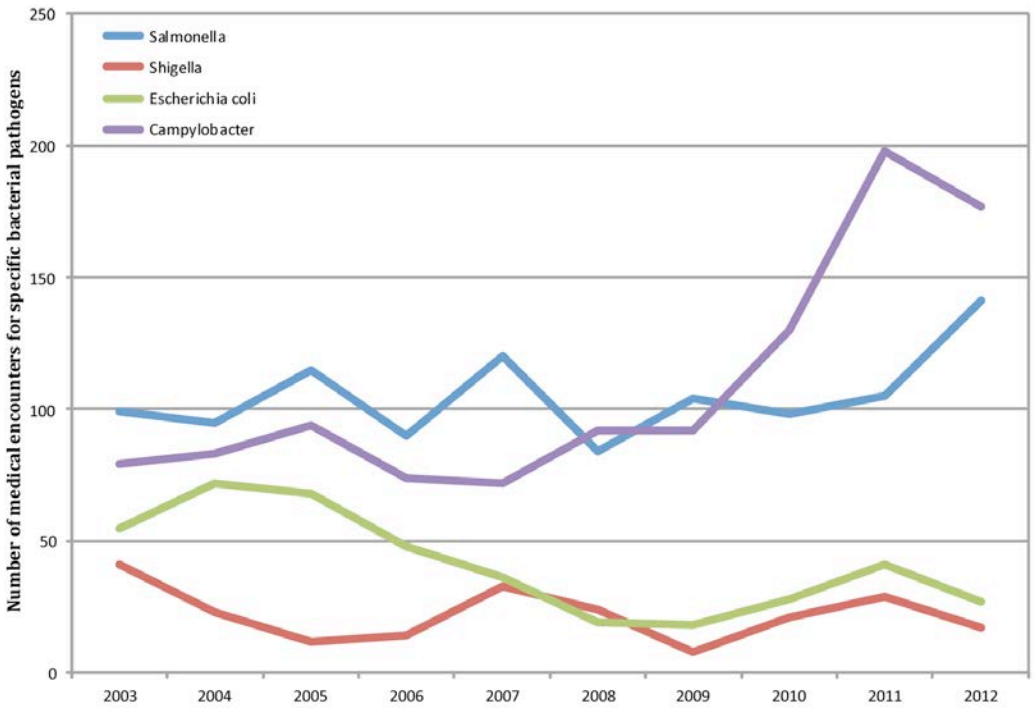

Figure 4: Number of medical encounters for Salmonella, Shigella, Campylobacter and *E. coli* O157:H7 among active duty US military personnel 2003-2012.

sequelae risk with deployment to high TD regions (*Porter* et al., 2011a, 2012b, 2013a). This may be due to a potential healthy worker effect or non-specific in the exposure (or in this case the exposure surrogate) thus biasing effect estimates toward the null hypothesis of no association.

A potential mechanism to circumvent this limitation is to utilize deployment health assessments designed to document exposures occurring during deployment. US Department of Defense policy mandates the collection and maintenance of deployment health data (DoDI 6490.03, Deployment Health, 11 Aug. '06). One mechanism utilized to facilitate these mandates is the pre- and post-deployment health assessments (DD 2795 and 2796, respectively). These self-assessments are completed electronically, maintained by the AFHSC and can be linked with the serum specimens as well as demographic and medical encounter data. Data obtained as part of these forms include deployment information (e.g., country, duration), general assessments of in-theatre and post-deployment health and exposures of interest during deployment. While this form has undergone several iterations, most recently in SEPT 2012, the version preceding the current edition collected data on potential IGE. In 2011, Porter et al described an increased odds of self-reported diarrhoea/vomiting among FGD cases compared to matched controls both of whom were first-time deployers with only one deployment during the surveillance period (*Porter* et al., 2011b). While lacking sensitivity and specificity, these data sources open the door for obtaining important deployment-specific exposures.

Table 2: Epidemiologic studies of post-infectious sequelae conducted utilizing data obtained from DMSS

Reference	Exposure(s)	Outcome(s) and estimated relative risk/odds ratio	
Curry et al., 2010	Infectious gastroenteritis	Reactive arthritis: Nonspecific arthropathy:	4.4 (2.2, 8.7) 1.8 (1.5, 2.1)
Porter et al., 2008	Infectious gastroenteritis	Crohn's disease: Ulcerative colitis:	1.5 (1.2, 2.0) 1.4 (1.1, 1.7)
Porter et al., 2011a	Infectious gastroenteritis	Constipation: Dyspepsia: Functional diarrhea: Irritable bowel syndrome:	2.2 (2.0, 2.3) 2.4 (2.1, 2.7) 6.3 (4.4, 8.9) 3.7 (3.4, 4.1)
Porter et al., 2011b	Diarrhea/vomiting during deployment	Constipation: Dyspepsia: Irritable bowel syndrome: Any FGD:	1.9 (0.9, 3.9) 6.8 (2.9, 15.4) 6.3 (2.5, 15.4) 2.9 (1.8, 4.8)
Porter et al., 2012a	Infectious gastroenteritis[a]	Crohn's disease Ulcerative colitis	1.5 (0.4, 6.3) 3.5 (1.4, 9.0)
Porter et al., 2012b	Norovirus	Constipation: Dyspepsia: IBS: GERD:	1.3 (0.9, 1.8) 1.4 (0.8, 2.5) 0.7 (0.3, 1.5) 1.4 (1.1, 1.8)
Porter et al., 2013c	Campylobacter Salmonella Shigella Yersinia	Constipation: Dyspepsia: IBS: GERD:	1.6 (1.3, 2.0) 1.3 (1.0, 1.9) 2.9 (2.2, 3.8) 1.6 (1.4, 1.8)
Riddle et al., 2012	Infectious gastroenteritis	Celiac disease:	2.1 (1.4, 3.0)
Riddle et al., 2013	Campylobacter[b]	Celiac disease:	3.5 (0.7, 18.0)

IBS=Irritable bowel syndrome; FGD=Functional gastrointestinal disorder
[a] Among personnel with IBS
[b] No increased risk observed following Shigella, Salmonella or Yersinia

Importantly, deployment not only increases the potential risk of exposure, but also likely increases the risk of psychological stressors, independent risk factors of functional bowel disorders. It has been hypothesized that stressful events, such as deployment and/or combat situations may modify the effect of infection of FGD risk (*Drossman*, 2011). This was corroborated by the 2011 study by Porter et al (although not statistically significant) (*Porter* et al., 2011b). Further supporting the link between military exercises and functional symptoms are the results of a recent study of Singapore military personnel in which increased intestinal permeability during combat training corresponded to an increase in post-training GI complaints (*Li* et al., 2013). Recognition of this potential effect modification and development of methods to accurately capture levels of deployment-related stress are important to ensure appropriate interpretation of results in this population.

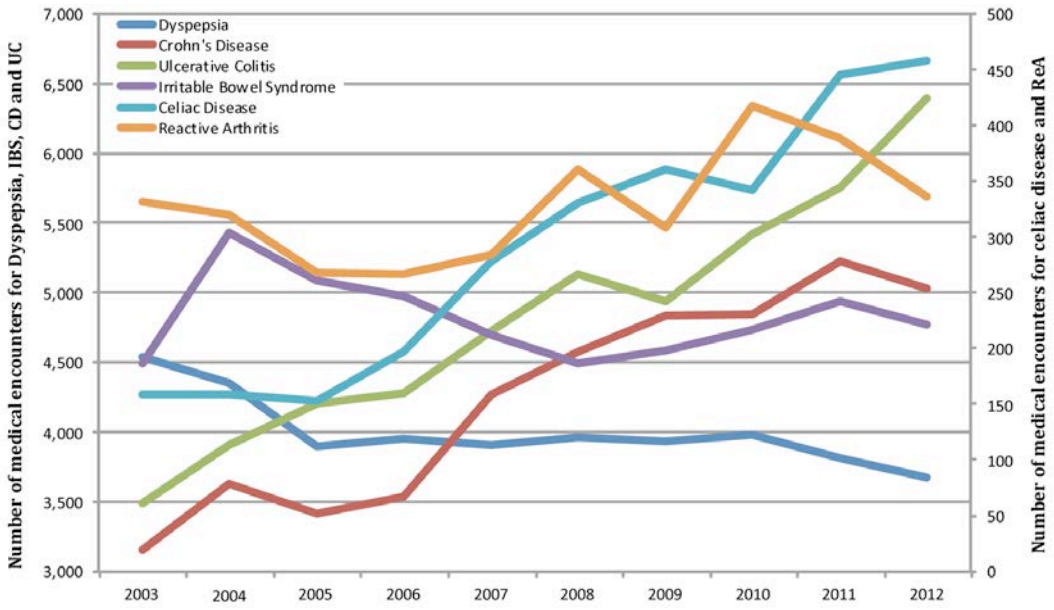

Figure 5: Number of medical encounters for adverse health outcomes associated with enteric infection among US military personnel 2003-2012.

OUTCOMES OF INTEREST

Of equal importance to the numbers of available exposures are the outcomes of interest for studying the long-term impact of acute gastroenteritis. A recent study on the incidence of FGD among this population from 1997-2007 estimated rates of any FGD of approximately 231 per 100,000 person-years (/100K p-y) with the highest rate observed for constipation (127/100K p-y) followed by IBS (66/100K p-y) and dyspepsia (49/100K p-y) and (*Porter* et al., 2011a). Similar estimates over comparable time periods have been made for IBD (29.2/100K p-y) (*Porter* et al., 2008), coeliac disease (3.6/100K p-y) (*Riddle*, 2012) and reactive arthritis (4.1/100K p-y) (*Curry* et al., 2010). Importantly, these outcomes are associated with numerous medical encounters annually (Figure 5). Over the last 10 years, there have been 40,000-50,000 medical encounters each for dyspepsia, CD, UC and IBS and 3,000-4,000 each for coeliac disease and reactive arthritis. This represents as substantial population from which to identify well-defined cases and retrospectively follow the disease progression from pre-onset to present.

LIMITATIONS

The limitations of medical encounter data systems have been described previously and an exhaustive delineation of the limitations specific to the DoD system is beyond the scope of this review. Nonetheless, Table 3 outlines some of the potential areas of bias inherent in generic systems as well as the DMSS. Importantly, studies assessing the quality of medical encoun-

Table 3: Potential sources of bias inherent in generic medical encounter repositories as well as the DMSS (modified from *Schneeweiss* and *Avorn*, 2005)

Generation of typical medical encounter data	**DMSS**	**'Other' systems**
Population:	- Well-defined demographic data for 1.4 million currently active duty service members - Approximately 10 million total service members - Dissimilar to general population - Unique occupational exposures	- Demographic data of total population may be unavailable - System dependent (Kaiser, NHANES, country-wide)
'Ill' patient seeks care:	- Potential variability in care-seeking behaviour across demographic characteristics - Potential use of serum repository to document outcomes among those not seeking care - Frequent well-visits and vaccinations - Data linkable across global MTFs - Lacks medical encounters during deployment • pre-deployment health assessments • Post-deployment health assessments	- Lack of insurance in specific populations may decrease care-seeking behaviour - No ability to document outcomes among those not seeking care - Potential variability in care-seeking behaviour across demographic characteristics - Care 'out of network' • ER visits • During travel
Medical examination/ history:	- Medical history electronically available - Medical examination data not available	- Medical history may/may not be electronically available - Medical examination data may/may not be available
Procedures & testing:	- CPT codes readily available (potential for miscoding)	- CPT codes may/may not be available (potential for miscoding)
Diagnoses:	- ICD9-CM codes readily available (potential for miscoding) - Can be validated by serologic testing for specific outcomes	- ICD9-CM codes readily available (potential for miscoding)

Table 3 (continued): Potential sources of bias inherent in generic medical encounter repositories as well as the DMSS (modified from *Schneeweiss* and *Avorn*, 2005)

Generation of typical medical encounter data	**DMSS**	**'Other' systems**
Interventions (pharmacy):	- Pharmaceutical data not readily linked with medical encounter data - Over the counter medications not routinely available - Free samples not documented	- Over the counter medications not routinely available - Free samples not documented
Outcomes:	- Out of military (theoretically linkable with Veteran's Administration data) - All other administrative changes documented in system	- Lost to follow-up • Provider/network change • Death • Other
Research purposes:	- Supported through AFHSC (with DoD collaborator) - Human subjects' protection - Methods exist to remove patient identifiers	- Limited to those with network-specific access

ter data to identify exposures and outcomes of interest have been conducted to varying degrees of success. Specific to the DMSS, Payne et al validated anthrax vaccination history and found relatively highly levels of positive and negative predictive values (*Payne* et al., 2007). While no studies assessing the PPV of the exposures and outcomes of interests related to post-infectious sequelae of acute enteric infectious have been published to date, efforts are underway by the authors to explore the utility of these ICD-9 codes to identify incident outcomes. The on-going study utilizes a total of 1750 subjects with a medical encounter in which an ICD9-CM code specific for one of a variety (IBS, Crohn's disease, ulcerative colitis, reactive arthritis, non-specific mono-arthropathy, coeliac disease, infectious gastroenteritis) of clinical outcomes is documented (250 patients/outcome). The medical chart of each identified patient is then obtained and data elements extracted to allow for adjudication by a third party. Completion of the adjudication process will enable the estimation of a positive predictive value associated with each ICD9-CM code with $^{+}/_{-}$ 5%. The results of this study will support on-going efforts within and external to the DoD regarding outcomes of interest and the utilization of electronic medical records to identify novel associations.

UTILIZATION OF SERUM REPOSITORY

Perhaps one of the greatest strengths of the DoD system and an element that sets it apart from other medical encounter systems is the availability of sequential serum samples that can be linked to the demographic, deployment, vaccination and medical encounter data. A quick PubMed® search indicates that investigators have utilized the serum repository to identify serologic risk factors for disease (*Levin* et al., 2012; *Munger* et al., 2013), genotypic factors associated with disease (*Scher* et al., 2011) and temporal changes in antibody profiles preceding disease onset (*Arbuckle* et al., 2003). Despite these significant advancements in disease understanding brought about through utilization of the serum repository, these, and similar studies have only begun to scratch the surface of the potential utility of these serum samples. Specifically, revolutionary advances in genomics, proteomics and metabolomics have ushered in the systems' biology era and utilization of the DoD's serum repository, has the potential to transform our understanding of disease processes and, related to post-infectious sequelae of enteric infection, sample testing may elucidate novel mechanisms by which acute infection may lead to prolonged adverse health outcomes.

Specifically related to potential sequelae of enteric infection, genomic analyses have identified that genes associated with intestinal barrier and responses to enteric pathogens were associated with an increased risk of PI-IBS among subjects with affected by a waterborne outbreak of entero-haemorrhagic *E. coli* and *Campylobacter* (*Villani* et al., 2010). Metabolomics have been utilized to identify baseline differences in IBS patients compared to controls and to subsequently measure the impact of probiotics on the metabolome and subsequent clinical improvement of IBS patients (*Hong* et al., 2011). Genetic biomarkers have shown

similar importance for Crohn's disease with CARD15/NOD2 combined with bacterial infection shown to increase disease risk (*Vaiopoulou* et al., 2012). While not specific to post-infection IBD, novel disease biomarkers such as IL-6, IL-23, ASCA and pANCA have expanded our understanding of disease patho-etiology (*Yau* et al., 2013). While omics-based studies of samples obtained from the DoD serum repository are not readily available in the peer-reviewed literature, the accessibility of these serum samples combined with new technologies and platforms with which to conduct novel assays has the opportunity to enhance our understanding of the inter-relational association between the human genome, proteome and metabolome and further our understanding of the pathophysiology of the sequelae of acute enteric infection.

Importantly, these samples are not without limitations which have been highlighted previously and include storage temperature (-30°C), available aliquot volume (50 cc), number of freeze/thaw cycles and potential gaps in the cold chain from specimen collection to storage (*Moore* et al., 2010). Furthermore, from a research perspective, the temporality of specimen collection around an event(s) of interest may be sub-optimal. For example, we recently conducted a sero-epidemiologic study which required the last serum sample prior to initiating basic training during which an exposure of interest (norovirus outbreak) had occurred. The mean time from sample collection until the exposure of interest was approximately 6 months. Despite this (and other) limitation, one of the most unique attributes of the DODSR is its longitudinal nature which enables measurements of seroconversion and/or the development of novel biomarkers not present in previous (or subsequent) samples.

OTHER LARGE EPIDEMIOLOGIC DATABASES

As alluded to previously, the US military is not the sole source of medical encounter data. Country-wide systems exists globally as do those that are specific to given managed care organizations or those established to enable long-term cohort studies. For example, Norway has a universal healthcare system in which all citizens have unrestricted access to healthcare and in which medical encounters at hospital-based clinics are documented (*Lofthus* et al., 2005). In 2012, a total of 1.7 million patients received care on at least one occasion at one of the public hospitals, approximately 500K of which were associated with an in-patient stay (https://www.ssb.no/en/pasient). A subset of these data are querable online (https://www.ssb.no/en/helse).

This registry is inherently encrypted with no link to personal identification information. However, encrypted data can be linked to other sources of data utilizing identifiable information (*Bakken* et al., 2012). While an invaluable resource to researchers, these data are not without limitations. Specifically, linking data for single individuals across multiple years is difficult as identifiable information is often replaced with a unique identifier specific to the year in which care was sought (*Lofthus* et al., 2005). Additionally, for specific years, available diagnoses may be limited; furthermore, it is unclear if procedure codes are incorporated into the available data (*Lofthus* et al., 2005). Similar systems exists in other Nordic countries including Den-

mark (*Andersen* et al., 1999), Finland (*Sund*, 2012) and Sweden (*Ludvigsson* et al., 2011) with recent efforts to combine registries across countries to further expand the available study population (*Furu* et al., 2010; *Olsen* et al., 2010).

In addition to country-wide registries, other population-based cohort studies have been prospectively designed to allow research among a cross-section of populations. One specific study to note is the National Health and Nutrition Examination Study (NHANES). This study, initiated in the early 1960s, is designed as a survey-based cohort study on specific populations and health-related topics. Since 1999, approximately 5,000 persons are surveyed annually for demographic, socioeconomic, dietary and other health-related information as well as medical examinations to include dental, psychological assessments and laboratory tests. Data obtained from NHANES have been utilized in a multitude of research studies involving infectious and non-infectious diseases (*Tuteja* et al., 2008). In addition to epidemiologic data, NHANES also maintains a biorepository with plasma, serum and purified DNA that can be linked to health-related data. However, these samples are not collected on a longitudinal basis as are the DODSR samples. Furthermore, these data are inherently different than those described in the US military system and the Nordic countries in that they are obtained for the sole purpose of research while the medical encounter data are collected as part of routine medical care. Complete understanding of these differences, some of which are outlined in Table 3, is key to ensuring appropriate data interpretation and extrapolation to other populations.

CONCLUSION

The US DOD medical encounter databases and serum repository are invaluable assets with the ability to modify our understanding of many disease processes. Historically, well-designed epidemiologic studies have been at the fore of linking exposures with outcomes and have enabled estimates of outcome risk, identifying host- and pathogen-specific risk factors and understanding the timing from exposure to outcome. Studies of the post-infectious sequelae of enteric diseases are no different as highlighted by several systematic reviews on the epidemiologic evidence (*Halvorson* et al., 2006; *Thabane* et al., 2007; *Poropatich* et al., 2010; *Deising* et al., 2013; *Pike* et al., 2013; *Porter* et al., 2013b). While these studies are have enhanced our appreciation of the acute/chronic disease link, additional research is needed. The OMICs revolution has paved the way for the utilization of the DOD SR linked with relevant medical encounter data to further enhance our understanding of disease patho-etiology. Importantly, these studies must be accompanied by improved mechanistic preclinical studies, which to date suggest multifactorial biological processes leading to PI-FGD. Together these studies have the potential to begin unravelling the complexity of post-IGE sequelae and revolutionize our understanding of the long-term impacts of acute infection.

LITERATURE

Andersen, T.F., Madsen, M., Jørgensen, J., Mellemkjoer, L., and Olsen, J.H.: The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan. Med. Bull. 46, 263-268 (1999).

Arbuckle, M.R., McClain, M.T., Rubertone, M.V., Scofield, R.H., Dennis, G.J., James, J.A., and Harley, J.B.: Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N. Engl. J. Med. 349, 1526-1533 (2003).

Bakken, I.J., Gystad, S.O., Christensen, Ø.O., Huse, U.E., Larønningen, S., Nygård, J., Holmstrøm, L., Johannesen, T.B., Møller, B., and Larsen, K.: Comparison of data from the Norwegian Patient Register and the Cancer Registry of Norway. Tidsskr. Nor. Laegeforen, 132, 1336-40 (2012).

Curry, J.A., Riddle, M.S., Gormley, R.P., Tribble, D.R., and Porter, C.K.: The epidemiology of infectious gastroenteritis related reactive arthritis in U.S. military personnel: a case-control study. BMC Infect. Dis. 10, 266 (2010).

Dawber, T.R., Meadors, G.F., and Moore, F.E. Jr.: Epidemiological approaches to heart disease: the Framingham Study. Am. J. Public Health Nations Health 41, 279-281 (1951).

Deising, A., Gutierrez, R.L., Porter, C.K., and Riddle, M.S.: Postinfectious functional gastrointestinal disorders: a focus on epidemiology and research agendas. Gastroenterol. Hepatol. (NY) 9, 145-157 (2013).

Doll, R. and Hill, A.B.: The mortality of doctors in relation to their smoking habits; a preliminary report. Br. Med. J. 1 1451-1455 (1954).

Doll, R. and Pike, M.C.: Trends in mortality among British doctors in relation to their smoking habits. J. R. Coll. Physicians Lond. 6, 216-222 (1972).

Drossman, D.A.: Abuse, trauma, and GI illness: is there a link? Am. J. Gastroenterol. 106, 14-25 (2011).

Furu, K., Wettermark, B., Andersen, M., Martikainen, J.E., Almarsdottir, A.B., and Sørensen, H.T.: The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin. Pharmacol. Toxicol. 106, 86-94 (2010).

Green, P.H. and Cellier, C.: Celiac disease. N. Engl. J. Med. 357, 1731-1743 (2007).

Halvorson, H.A., Schlett, C.D., and Riddle, M.S.: Postinfectious irritable bowel syndrome--a meta-analysis. Am. J. Gastroenterol. 101, 1894-1899; quiz 1942 (2006).

Hong, Y.S., Hong, K.S., Park, M.H., Ahn, Y.T., Lee, J.H., Huh, C.S., Lee, J., Kim, I.K., Hwang, G.S., and Kim, J.S.: Metabonomic understanding of probiotic effects in humans with irritable bowel syndrome. J. Clin. Gastroenterol. 45, 415-425 (2011).

Karlinger, K., Györke, T., Makö, E., Mester, A., and Tarján, Z.: The epidemiology and the pathogenesis of inflammatory bowel disease. Eur. J. Radiol. 35, 154-167 (2000).

Koebnick, C., Smith, N., Huang, K., Martinez, M.P., Clancy, H.A., Williams, A.E., and Kushi, L.H.: OBAYA (obesity and adverse health outcomes in young adults): feasibility of a population-based multiethnic cohort study using electronic medical records. Popul. Health Metr. 10, 15 (2012).

Levin, L.I., Chang, E.T., Ambinder, R.F., Lennette, E.T., Rubertone, M.V., Mann, R.B., Borowitz, M., Weir, E.G., Abbondanzo, S.L., and Mueller, N.E.: Atypical prediagnosis Epstein-Barr virus serology restricted to EBV-positive Hodgkin lymphoma. Blood, 120, 3750-3755 (2012).

Li, X., Kan, E.M., Lu, J., Cao, Y., Wong, R.K., Keshavarzian, A., and Wilder-Smith, C.H.: Combat-training increases intestinal permeability, immune activation and gastrointestinal symptoms in soldiers. Aliment. Pharmacol. Ther. 37, 799-809 (2013).

Lofthus, C.M., Cappelen, I., Osnes, E.K., Falch, J.A., Kristiansen, I.S., Medhus, A.W., Nordsletten, L., and Meyer, H.E.: Local and national electronic databases in

Norway demonstrate a varying degree of validity. J. Clin. Epidemiol. 58, 280-285 (2005).

Ludvigsson, J.F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.L., Reuterwall, C., Heurgren, M., and Olausson, P.O.: External review and validation of the Swedish national inpatient register. BMC Public Health 11, 450 (2011).

Marshall, J.K., Thabane, M., Garg, A.X., Clark, W.F., Salvadori, M., Collins, S.M.; Walkerton Health Study Investigators: Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. Gastroenterology 131, 445-450; quiz 660 (2006).

Mearin, F.: Postinfectious functional gastrointestinal disorders. J. Clin. Gastroenterol. 45 Suppl, S102-S105 (2011).

Moore, M., Eiseman, E., Fisher, G., Olmsted, S.S., Sama, P.R., and Zambrano, J.A.: Harnessing full value from the DoD Serum Repository and the Defense Medical Surveillance System. The RAND Corporation, Santa Monica, CA, USA (2010).

Munger, K.L., Levin, L.I., Massa, J., Horst, R., Orban, T., and Ascherio, A.: Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. Am. J. Epidemiol. 177, 411-419 (2013).

Neal, K.R., Hebden, J., and Spiller, R.: Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. BMJ 314, 779-782 (1997).

Olsen, J., Brønnum-Hansen, H., Gissler, M., Hakama, M., Hjern, A., Kampeer-Jørgensen, F., Rafnsson, V., Tell, G.S., Thaulow, I., and Thygesen, L.C.: High-throughput epidemiology: combining existing data from the Nordic countries in health-related collaborative research. Scand. J. Public Health 38, 777-779 (2010).

Payne, D.C., Rose, C.E. Jr., Aranas, A., Zhang, Y., Tolentino, H., Weston, E., McNeil< M.M., and Ruscio, B.: Assessment of anthrax vaccination data in the Defense Medical Surveillance System, 1998-2004. Pharmacoepidemiol. Drug Saf. 16, 605-611 (2007).

Pike, B.L., Porter, C.KJ., Sorell, T.J., and Riddle, M.S.: Acute gastroenteritis and the risk of functional dyspepsia: a systematic review and meta-analysis. Am. J. Gastroenterol. 108, 1558-1563 (2013).

Poropatich, K.O., Walker, C.L., and Black, R.E.: Quantifying the association between Campylobacter infection and Guillain-Barre syndrome: a systematic review. J. Health Popul. Nutr. 28, 545-552 (2010).

Porter, C.K., Tribble, D.R., Aliaga, P.A., Halvorson, H.A., and Riddle, M.S.: Infectious gastroenteritis and risk of developing inflammatory bowel disease. Gastroenterology 135, 781-786 (2008).

Porter, C.K., Gormley, R., Tribble, D.R., Cash, B.D., and Riddle, M.S.: The incidence and gastrointestinal infectious risk of functional gastrointestinal disorders in a healthy US adult population. Am. J. Gastroenterol. 106, 130-138 (2011a).

Porter, C.K., Gloor, K., Cash, B.D., and Riddle, M.S.: Risk of functional gastrointestinal disorders in U.S. military following self-reported diarrhea and vomiting during deployment. Dig. Dis. Sci. 56, 3262-3269 (2011b).

Porter, C.K., Cash, B.D., Pimentel, M., Akinseye, A., and Riddle, M.S.: Risk of inflammatory bowel disease following a diagnosis of irritable bowel syndrome. BMC Gastroenterol. 12, 55 (2012a).

Porter, C.K., Faix, D.J., Shiau, D., Espiritu, J., Espinosa, B.J., and Riddle, M.S.: Postinfectious gastrointestinal disorders following norovirus outbreaks. Clin. Infect. Dis. 55, 915-922 (2012b).

Porter, C.K., Choi, D., and Riddle, M.S.: Pathogen-specific risk of reactive arthritis from bacterial causes of foodborne illness. J. Rheumatol. 40, 712-714 (2013a).

Porter, C.K., Thura, N., and Riddle, M.S.: Quantifying the incidence and burden of postinfectious enteric sequelae. Mil. Med. 178, 452-469 (2013b).

Porter, C.K., Choi, D., Cash, B., Pimentel, M.,

Murray, J., May, L., and Riddle, M.S.: Pathogen-specific risk of chronic gastrointestinal disorders following bacterial causes of foodborne illness. BMC Gastroenterol. 13, 46 (2013c).

Riddle, M.S., Murray, J.A., and Porter, C.K.: The incidence and risk of celiac disease in a healthy US adult population. Am. J. Gastroenterol. 107, 1248-1255 (2012).

Riddle, M.S., Murray, J.A., Cash, B.D., Pimentel, M., and Porter, C.K.: Pathogen-specific risk of celiac disease following bacterial causes of foodborne illness: a retrospective cohort study. Dig. Dis Sci. 58, 3242-3245 (2013).

Rubertone, M.V. and Brundage, J.F.: The Defense Medical Surveillance System and the Department of Defense serum repository: glimpses of the future of public health surveillance. Am. J. Public Health 92, 1900-1904 (2002).

Scallan, E., Griffin, P.M., Angulo, F.J., Tauxe, R.V., and Hoekstra, R.M.: Foodborne illness acquired in the United States --unspecified agents. Emerg. Infect. Dis. 17, 16-22 (2011a).

Scallan, E., Hoekstra, R.M., Angulo, F.J., Tauxe, R.V., Widdowson, M.A., Roy, S.L., Jones, J.L., and Griffin, P.M.: Foodborne illness acquired in the United States--major pathogens. Emerg. Infect. Dis. 17, 7-15 (2011b).

Scher, A.I., Wu, H., Tsao, J.W., Blom, H.J., Feit, P., Nevin, R.L., and Schwab, K.A.: MTHFR C677T genotype as a risk factor for epilepsy including post-traumatic epilepsy in a representative military cohort. J. Neurotrauma 28, 1739-1745 (2011).

Schneeweiss, S. and Avorn, J.: A review of uses of health care utilization databases for epidemiologic research on therapeutics. J. Clin. Epidemiol. 58, 323-337 (2005).

Stephenson, J.J., Barghout, V., Kahler, K.H., Fernandes, J., Beaulieu, J.F., Joo, S., and Boccuzzi, S.J.: Effectiveness of tegaserod therapy on GI-related resource utilization in a managed care population. Am. J. Manag. Care 11 (1 Suppl), S35-S42 (2005).

Sund, R.: Quality of the Finnish Hospital Discharge Register: a systematic review. Scand. J. Public Health 40, 505-515 (2012).

Thabane, M., Kottachchi, D.T., and Marshall, J.K.: Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Aliment. Pharmacol. Ther. 26, 535-544 (2007).

Tuteja, A.K., Talley, N.J., Gelman, S.S., Alder, S.C., Thompson, C., Tolman, K., and Hale, D.C.: Development of functional diarrhea, constipation, irritable bowel syndrome, and dyspepsia during and after traveling outside the USA. Dig. Dis. Sci. 53, 271-276 (2008).

Vaiopoulou, A., Gazouli, M., Theodoropoulos, G., and Zografos, G.: Current advantages in the application of proteomics in inflammatory bowel disease. Dig. Dis. Sci. 57, 2755-2764 (2012).

Villani, A.C., Lemire, M., Thabane, M., Belisle, A., Geneau, G., Garg, A.X., Clark, W.F., Moayyedi, P., Collins, S.M., Franchimont, D., and Marshall, J.L.: Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. Gastroenterology 138, 1502-1513 (2010).

Yau, Y., Leong, R.W., Zeng, M., and Wasinger, V.C.: Proteomics and metabolomics in inflammatory bowel disease. J. Gastroenterol. Hepatol. 28, 1076-1086 (2013).