Author's response to reviews

Title: The Epidemiology of Infectious Gastroenteritis Related Reactive Arthritis in U.S. Military Personnel: A Case-Control Study

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To the referees:

Thank you for your review of our manuscript submission. As recommended, the overall length of the manuscript was shortened by 10%, mostly from the results and discussion sections.

The following comments address the concerns expressed by Dr. Anders Ternhag:

1. The opening text questioned “if outcome really measures reactive arthritis”

We agree the case definition for non-specific arthritis/arthalgia group is likely overly sensitive, and there is potential for misclassification when utilizing ICD-9 codes. The requirement for two separate visits with one of the non-specific ICD codes was an attempt to minimize the number of spurious diagnoses included in the non-specific arthritis/arthalgia group.

However, we do feel the description of the non-specific group is important to completely illustrate the potential burden of disease. Prior studies reporting reactive arthritis incidence have commonly utilized restrictive case definitions frequently requiring culture-confirmation of preceding gastroenteritis. Use of the ‘specific’ reactive arthritis ICD-9 categories in our study was an attempt to mimic those restrictive case definitions. In cases where a preceding infection is not recognized or is minimally symptomatic, the reactive nature of the arthritis is missed and would not be included in specific reactive arthritis incidence estimates. Despite the limitations of our ‘non-specific’ group, we did find a significant association with antecedent infectious gastroenteritis, and large number of persons affected suggests a potential target for preventative interventions. Our discussion was edited to further emphasize the limitations of our non-specific group.

Question 4 addressed subsequent specific diagnoses for the non-specific group.
Our data unfortunately did not allow us to exclude patients who were eventually given a more specific diagnosis such as gout, Lupus, or Rheumatoid arthritis. However, the median duration of care associated with these non-specific diagnoses was greater than 6 months, decreasing the likelihood of a more specific diagnosis.

2. From the opening text: “Culture confirmed gastroenteritis varies between 0.7-3.5% within 6 month prior to the joint problems. For the remaining patients (96.5%) are exposure defined as a doctor’s visit based on symptoms, or may not, be consistent with bacterial (or more likely viral) gastroenteritis” and Q7: “Does ‘documented infectious gastroenteritis’ mean culture confirmed (table 3)?”

To clarify, throughout our study we refer to documented (ie, ICD-9 coded) gastroenteritis, not culture confirmed gastroenteritis. Table 3 has been edited to clarify the distinction. Therefore, less than 4% of all patients – even those with a diagnosis of postdysenteric arthritis - had a preceding doctor’s visit (with a subsequent ICD-9 code) for gastroenteritis. The remaining 96.5% of patients had no preceding ICD-9 code for gastroenteritis. The small numbers with documented IGE are not unexpected. Less than 25% of patients with gastroenteritis present for care, and an even smaller percentage have appropriate microbiology performed.

3. From the opening text: “I have no problems with the categories Reiter’s disease and postdysenteric arthritis. In these cases have clinicians, based on their best judgment, decided that the joint problems are causally related to an IGE episode. But the far bigger category non-specific arthropathy are not related to the exposure, or than by record linkage………..and the incidence rate is exceptionally high compared to previous findings.”

We recognize the limitations of utilizing the non-specific diagnosis. The use of this category was an attempt to identify potential cases of reactive arthritis in which clinicians may have not recognized an antecedent IGE episode. We contend that relying on physician recognition of a prior IGE episode may reduce the reported cases of IGE-related reactive arthritis. Supporting that notion is the observation that studies requiring the full diagnostic criteria for reactive arthritis and culture confirmation of IGE estimated incidence rates of approximately 5 per 100,000. Studies relaxing the reactive arthritis diagnostic criteria but still requiring culture confirmation have estimated incidence rates up to 40 per 100,000.

The effect of including episodes of arthralgia/arthropathy that were not associated with an antecedent IGE episode would bias of our effect estimates to the null (i.e., an odds ratio of 1). This likely explains the variability in the effect estimates between the ‘specific’ and ‘non-specific’ categories. Nonetheless, we did identify a statistically significant association between the ‘non-specific’ outcome and antecedent IGE indicating that at least a portion of these cases followed a prior IGE medical event. Because of the concerns raised, these data were consistently presented separately so as to not over-state the results.

4. Question 3: duration of disease
The duration of disease we report is partially an artifact of U.S. military medical system (see the second to last discussion paragraph). Active duty personnel may have a longer medical care before clearance to return to full duty. This may result in a longer documented duration of disease.

It should be noted that Michet et al (Ref 47) described an extensive series of patients in Michigan, of whom 63% had symptoms beyond 6 months. We believe our reported duration of symptoms supports growing clinical recognition that reactive arthritis is not a benign, self-limited disease.

5.
Q1 and Q2: why the increasing incidence with age?
Q5: why the marked increased in the incidence of N.A.A between 1999 and 2007?
Q6: OR for high risk deployment: why the qualitative difference between specific ReA, and N.A.A?

We agree these are all key questions raised by our findings. The association with age, especially, bears further investigation as this is potentially applicable to a non-military population. However, given the limitations of our current data set, we are unable to provide more than conjecture as to the potential answers. Where possible, these were included in original submission (See discussion paragraphs 3 and 6).

Respectfully,

LCDR Jennifer Curry, MC USNR