Reactive Arthritis after Enteric Infections in the United States: The Problem of Definition

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Bacterial enteric infections cause substantial morbidity in the United States both from acute illness and sequelae that follow. Reactive arthritis (ReA) is a poorly defined term that is used to describe a variety of rheumatologic phenomena that may occur after *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* infection, as well as other types of infections (eg, *Chlamydia*). This review focuses on clinical and epidemiologic investigations of ReA following bacterial enteric infection in the United States.

Only 2 population-based studies of ReA following enteric infection have been performed in the United States. ReA following outbreaks of *Campylobacter* and *Yersinia* infection has not been studied, and investigations following *Shigella* and *Salmonella* outbreaks have focused primarily on the more narrowly defined, but now outdated, concept of “Reiter’s syndrome” rather than ReA. Additional epidemiologic studies are needed to determine the burden of illness due to ReA following enteric infection, but a clearer definition of the term is a prerequisite.

“*What’s in a name? That which we call a rose
By any other name would smell as sweet.*
—William Shakespeare, Romeo and Juliet

“It depends upon what the meaning of the word ‘is’ is.”
—Bill Clinton, 1998

Acute infections due to enteric pathogens cause significant morbidity and mortality in the United States. In 1999, the Centers for Disease Control and Prevention (CDC) estimated that 76 million cases of foodborne disease occur in the United States each year, resulting in 325,000 hospitalizations and 5000 deaths [1]. Incidence of *Salmonella* infection has not decreased in the past decade, and incidence of *Campylobacter, Shigella,* and *Yersinia* species infections has remained virtually unchanged since 2004 [2]. FoodNet surveillance determined in 2007 that the incidence of culture-confirmed infection due to these 4 pathogens was 12.79, 14.92, 6.26, and 0.36 cases per 100,000 persons respectively [3]. These infections may be followed by a characteristic pattern of sterile arthritis sometimes accompanied by inflammation in other tissues, such as tendons (tendonitis), tendon insertion sites (enthesitis), eyes (conjunctivitis, uveitis), genitourinary tract (urethritis), and skin (erythema nodosum, keratoderma blenorrhagica). In 2003, $322.8 billion were spent in the United States on medical costs related to rheumatologic conditions [4], and it is likely that a significant proportion of these costs were related to antecedent infection [5].

**TERMINOLOGY**

The phenomenon of inflammation in joints and other tissues following enteric infection has had many names. The term “reactive arthritis” (ReA) is currently the most accepted label applied. It was first introduced in 1969 by Ahvonen and colleagues to describe arthritis that occurs during or after an infection at another body site, without evidence of microorganisms entering the joint [6]. Unfortunately, the name fails to reveal much about the characteristics of the illness to which it applies, except that it conveys that the arthritis is a reaction to something. The ambiguity of the name is emblematic of the continued imprecision of clinical and epidemiologic studies of the phenomenon. There are no universally accepted diagnostic or classification criteria for ReA, and case definitions vary widely from one study to another [7, 8].

ReA has been used synonymously with the eponym “Reiter’s” disease or syndrome, which came into common usage in the 1940s, especially in the United States. An American rheuma-
tology text in 1941 and a journal article by Bauer and Engelman in 1942 popularized the term, in misguided deference [9] to Hans Reiter, a German physician who reported a case of a soldier with arthritis, conjunctivitis, and urethritis beginning 8 days after onset of bloody diarrhea. Reiter attributed the syndrome to a sexually transmitted disease and referred to it as “Spirochaetosis arthritica” [10, 11].

In his classic review of 344 cases in 1948, Ilmari Paronen aptly pointed out that to use the eponym “Reiter’s” was “rather inappropriate,” because Reiter was not the first, or most important, observer of the syndrome. He suggested that “dysenteric arthritis” might be more descriptive but used “Reiter’s” anyway because it was a widely accepted term at the time, especially in American medicine. Paronen noted that the arthritis that followed dysentery was not always accompanied by conjunctivitis and urethritis but could occur with only one or none of these extra-articular findings [10]. Subsequent investigators also found that the complete so-called “classic triad” was not always present, but they held tight to the eponym anyway, referring to these cases as “Incomplete Reiter’s” [12–14]. In France, the eponym “Feissinger-LeRoy” syndrome was more common, named after 2 French investigators who reported on 4 cases of arthritis, urethritis, and conjunctivitis just days before Reiter reported his case [11]. They suggested the more descriptive term “syndrome conjonctivo-urétro-synovial” [10].

In the past decade, Hans Reiter has been exposed as a Nazi war criminal who oversaw and approved medical atrocities, such as conducting lethal experiments with typhus on prisoners at Buchenwald [15, 16]. This fact, in addition to his relatively minor role in the clinical description of the syndrome, has led to a trend away from the use of the Reiter eponym, although it unfortunately continues to be widely used, especially in the United States [17].

**DEFINITION**

There is general agreement among rheumatologists that ReA shares some clinical characteristics with other members of the spondyloarthropathy (SpA) group of disorders, such as ankylosing spondylitis and psoriatic arthritis [18, 19]. Experts also agree that, as with other SpA disorders, ReA is associated with human leukocyte antigen (HLA)-B27, and patients typically present with findings such as a predominantly lower-limb arthritis, enthesitis, dactylitis, or inflammatory back pain [6, 20]. The European Spondyloarthropathy Study Group (ESSG) has published preliminary criteria for classification of SpA [21] that includes ReA following diarrhea. However, there is significant difference of opinion as to which of these findings are required for the diagnosis of ReA. Experts at the Fourth International Workshop on Reactive Arthritis in 1999 disagreed on whether even arthritis must be present for the diagnosis of ReA; some thought that other features of SpA, such as enthesopathy and inflammatory back pain, could be sufficient [20]. Other areas of ambiguity included criteria for the minimum and maximal time interval between the onset of arthritis or other symptoms and the occurrence of the primary infection and the minimum duration of any symptom. Most agreed that ReA should be applied only to infection caused by *Campylobacter, Salmonella, Shigella, Yersinia*, or *Chlamydia* species and that sterile arthritis that followed other infection should be labeled “postinfectious arthritis.” Nevertheless, many authors have applied the term ReA for arthritis following infection due to a variety of organisms, including *Clostridium difficile* [22–28], *Cryptosporidium* [29], *Giardia* [30–33], and *Strongyloides* species [34, 35].

**ATTACK RATES IN UNITED STATES (US) OUTBREAK INVESTIGATIONS**

Estimates of the incidence of ReA and frequency with which it occurs following an episode of infection depend in large part on how ReA is defined and the epidemiologic investigation methods used. Most of the investigations of ReA associated with disease outbreaks in the United States have focused on identifying patients with use of a narrow case definition that includes the triad of symptoms attributed to Reiter (Table 1).

**Shigellosis outbreaks.** There have been no published investigations of shigellosis outbreaks in US populations that have used the broader ReA concept; all have used the term “Reiter’s syndrome.” In 1966, Noer [36] described an outbreak involving 9 cases of Reiter’s syndrome diagnosed after 602 sailors on a US navy ship of 1276 men developed dysentery caused by *Shigella*. The case definition is not explicitly stated, but no patient with only 1 element of the triad received a diagnosis of Reiter’s syndrome. Cases were ascertained as they presented to the ship’s sick bay. Those with pre-existing joint disease were not excluded; one-half of the patients who received a diagnosis of Reiter’s syndrome had previous joint or tendon disorders. Use of a standard questionnaire and active case finding for additional cases was not performed during this investigation, and the number of sailors with mild or moderate symptoms or those who once may have been called “incomplete Reiter’s syndrome” was not stated. The author concluded that ~3 (1.5%) of every 200 cases of shigellosis will result in Reiter’s syndrome. A more inclusive case definition and active case finding might have resulted in a higher proportion of cases that would today be diagnosed as ReA.

Simon et al [38] compared the frequency of Reiter’s syndrome occurring after dysentery outbreaks in 1978. The outbreaks involved *Shigella flexneri* 1b infection in 204 of 709 passengers of a cruise ship, *S. flexneri* 2a infection in 206 of 636 persons attending conventions, and *Shigella sonnei* infections in 85 of 184 children and young adults with who attended a summer camp. Subjects with and without diarrhea were
screened for possible Reiter's syndrome with a mailed questionnaire sent 4–9 weeks after each outbreak; for definite cases, a diagnosis was made by additional interviews with patients and their physicians. At least 2 of 3 Reiter’s syndrome symptoms were required to meet the case definition, unless HLA-B27 antigen was present, in which case, only joint pain or swelling had to be present for at least 7 days and have onset at least 4 days after onset of diarrhea. The investigations found 3 cases in each of the Shigella flexneri outbreaks (1.5%), all of whom involved female patients. No cases were found among S. sonnei outbreaks (1.5%), all of whom involved female patients. Whether based studies has been significantly lower among children than adults [44, 45], age-specific incidence determined in population-based studies has been significantly lower among children than adults [44, 45]. Whether S. sonnei causes ReA in US populations is important in any determination of the burden of illness due to Shigella, because nearly 75% of shigellosis cases in the United States are caused by S. sonnei (http://www.cdc.gov/ncidod/dbmd/phlisdata/shigella.htm#2005).

Finch et al [39] used a more elaborate definition of Reiter's syndrome in a 1986 investigation of a cruise-ship outbreak of S. flexneri 2a infection that affected 205 of 344 passengers. Subjects reporting new symptoms were divided into categories of "probable Reiter’s syndrome," "possible Reiter’s syndrome," and "doubtful Reiter’s syndrome." The onset of symptoms had to occur “within 6 weeks after the diarrheal illness”. Although this definition may seem very specific at first, it does not indicate whether the onset of joint symptoms should be within 6 weeks of onset of the diarrheal illness or after the resolution of it. It does not allow clear conclusions to be drawn, because the duration of the diarrhea for each patient is not reported. Fifty (28.5%) of 175 passengers with diarrhea who were interviewed reported symptoms compatible with Reiter’s syndrome.

**Table 1. Enteric Disease Outbreak Investigations in United States Populations Studying Reiter’s Syndrome (RS) or Reactive Arthritis (ReA), 1966 to Present**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Organism</th>
<th>Terminology</th>
<th>Case definition</th>
<th>Proportion with HLA-B27</th>
<th>Attack rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noer, 1966 [36, 37]</td>
<td>Shigella</td>
<td>RS</td>
<td>Not explicitly stated. Diagnosis required arthritis, conjunctivitis, and urethritis</td>
<td>4/5</td>
<td>1.5</td>
</tr>
<tr>
<td>Simon, 1981 [38]</td>
<td>Shigella flexneri 2a</td>
<td>RS</td>
<td>&gt;=2 symptoms (joint pain or swelling for 7 days; dysuria, eye pain, redness, or discharge) or new joint pain or swelling plus HLA-B27; onset &gt;=4 days after diarrhea</td>
<td>2/3</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>S. flexneri 1b</td>
<td>RS</td>
<td>&gt;=2 symptoms (joint pain or swelling for 7 days; dysuria, eye pain, redness, or discharge) or new joint pain or swelling plus HLA-B27; onset &gt;=4 days after diarrhea</td>
<td>3/3</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Shigella sonnei</td>
<td>RS</td>
<td>&gt;=2 symptoms (joint pain or swelling for 7 days; dysuria, eye pain, redness, or discharge) or new joint pain or swelling plus HLA-B27; onset &gt;=4 days after diarrhea</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>Finch, 1986 [39]</td>
<td>S. flexneri 2a</td>
<td>Probable RS</td>
<td>Inflammation in weight-bearing joints or acute polyarthritis any joint diagnosed by physician</td>
<td>4/5</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>S. flexneri 2a</td>
<td>Possible RS</td>
<td>Inflammation in non–weight-bearing joint without physician documentation or &gt;=2 extra-articular symptoms</td>
<td>0/12</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>S. flexneri 2a</td>
<td>Doubtful RS</td>
<td>New symptoms only and/or signs of eye inflammation Onset within 6 weeks of diarrheal illness (all categories)</td>
<td>0/20</td>
<td>2.3</td>
</tr>
<tr>
<td>Samuel, 1995 [40]</td>
<td>Salmonella Typhimurium</td>
<td>ReA</td>
<td>Subjective joint symptoms on QUEST 2 questionnaire</td>
<td>Not tested</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td>Salmonella Typhimurium</td>
<td>ReA</td>
<td>Objective joint disease on examination</td>
<td>3/5</td>
<td>1.2</td>
</tr>
<tr>
<td>Dworkin, 2001 [41]</td>
<td>Salmonella Enteritidis</td>
<td>RS</td>
<td>Self reported symptoms of arthritis, conjunctivitis, and urethritis or cervicitis, onset &lt;= 1 month of onset of gastroenteritis</td>
<td>Not tested</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Salmonella Enteritidis</td>
<td>ReA</td>
<td>Self report of new joint pain, swelling, or redness, onset &lt;= 1 month onset of gastroenteritis</td>
<td>...</td>
<td>29.0</td>
</tr>
</tbody>
</table>

**NOTE.** Case reports and single family clusters are not included in the table. HLA, human leukocyte antigen; QUEST, Questionnaire Utilizing Epidemic Spondyloarthropathy traits.
Interestingly, 2 of 89 well passengers interviewed also had possible Reiter’s syndrome.

**Salmonellosis outbreaks.** Although there are many published outbreak investigations documenting the association between salmonellosis and ReA, only 2 of these were conducted in US populations [40, 41] (Table 1). Both investigations were performed in US states bordering Canada with predominantly Caucasian populations [46]. The case definitions and frequencies of ReA in various *Salmonella* outbreak investigations conducted outside the United States are shown in Table 2 for comparison.

In 1993, Samuel et al used a reportedly validated questionnaire (Questionnaire Utilizing Epidemic Spondyloarthropathy traits or “QUEST 2”) to screen 919 ill restaurant patrons in Syracuse, New York, for symptoms of ReA [40]. *Salmonella typhimurium* was cultured from 54% of those who reported illness. The authors do not explicitly state their case definition for ReA but divide the respondents into those with subjective joint symptoms and objective joint symptoms. No well restaurant patrons (controls) were interviewed. Because the survey response rate was only 33% and only 18% of those with new symptoms agreed to physical examinations, a precise determination of the frequency of ReA in this outbreak is not possible. Nevertheless, of 321 persons who returned the questionnaire, a striking 170 (53%) reported new joint symptoms; 130 (40%) reported new joint symptoms when subsequently interviewed by phone, giving the authors an estimated “minimum frequency” of subjective joint symptoms of 14% (130 of 911). Outbreaks of salmonellosis investigated in Canada that have used the same QUEST 2 or modifications thereof have reported similar high frequencies of subjective joint symptoms [52, 57, 58]. Among 23 subjects who agreed to be examined; 6 (1.2%) of 545 culture-confirmed cases involved objective joint disease.

Dworkin et al [41] investigated the frequency of ReA and Reiter’s syndrome following an outbreak in Tacoma, Washington, in 2001 that involved 2110 persons exposed to *Salmonella Enteritidis*. Both case and control patients were sent a detailed questionnaire 2–3 months after the outbreak. ReA was reported in 29% of those with diarrhea and in 8% of controls. Three percent received a diagnosis of Reiter’s syndrome. No limitation was placed on the duration of joint pain, distribution of involved joints, or time from diarrhea onset to onset of joint

### Table 2. Reactive Arthritis and Selected *Salmonella* Outbreaks Outside of the United States

<table>
<thead>
<tr>
<th>Citation</th>
<th>Serotype</th>
<th>Population</th>
<th>Case definition</th>
<th>Proportion with HLA-B27</th>
<th>ReA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, 2005</td>
<td>Typhimurium</td>
<td>N = 461; 79% children; Australia</td>
<td>History or examination findings consistent with inflammatory arthritis; onset ≤3 months after onset of gastroenteritis</td>
<td>5/30</td>
<td>14.6</td>
</tr>
<tr>
<td>Hannu, 2002</td>
<td>Typhimurium</td>
<td>N = 78; 79% adults; Finland</td>
<td>Synovitis (joint swelling and pain) in previously asymptomatic joint, within first weeks after gastrointestinal infection</td>
<td>2/4</td>
<td>7.9</td>
</tr>
<tr>
<td>McColl, 2000</td>
<td>Typhimurium</td>
<td>N = 424; 88% Asian; Australia</td>
<td>New joint swelling, inflammatory back pain, or extra-articular inflammation typical of Reiter’s, ≤3 months after onset of gastroenteritis symptoms</td>
<td>2/19</td>
<td>4.2</td>
</tr>
<tr>
<td>Locht, 2002</td>
<td>Enteritidis</td>
<td>N = 94; doctors and spouses; Denmark</td>
<td>Pain in a previously asymptomatic joint or onset of cervical or lumbar back pain, onset ≤4 weeks after onset of gastroenteritis</td>
<td>Not tested</td>
<td>18.7</td>
</tr>
<tr>
<td>Rudwaleit, 2001</td>
<td>Enteritidis</td>
<td>N = 286; children; Germany</td>
<td>Not stated</td>
<td>...</td>
<td>0.0</td>
</tr>
<tr>
<td>Thomson, 1994</td>
<td>Enteritidis</td>
<td>N = 88; wedding reception; Canada</td>
<td>“Inflammatory arthritis or enthesitis” by history or examination; onset ≤2 months after onset of dysentery</td>
<td>5/11</td>
<td>12.5</td>
</tr>
<tr>
<td>Locht, 1993</td>
<td>Enteritidis</td>
<td>N = 108; radiologists; Sweden</td>
<td>Pain in a previously healthy joint at a well defined anatomical location; onset ≤4 weeks after exposure to Salmonella</td>
<td>Not studied</td>
<td>15.0</td>
</tr>
<tr>
<td>Mattila, 1998</td>
<td>Bovismorbidans</td>
<td>N = 191; 85% adults; Finland</td>
<td>New onset synovitis (swelling and tenderness) within “first weeks” after exposure in a patient without previous or current rheumatologic diagnosis</td>
<td>10/22</td>
<td>11.5</td>
</tr>
<tr>
<td>Mattila, 1994</td>
<td>Serovar 4,5,12-b-</td>
<td>N = 246; median age, 14 years; Finland</td>
<td>New onset synovitis (swelling and tenderness) within “first weeks” after exposure in a patient without previous or current rheumatologic diagnosis</td>
<td>4/13</td>
<td>6.5</td>
</tr>
<tr>
<td>Thomson, 1992</td>
<td>Heidelberg</td>
<td>N = 83; 95% women; Canada</td>
<td>Arthritis (joint swelling or erythema, morning stiffness &gt;1 h) in previously asymptomatic joint, in a patient without other rheumatologic diagnosis; onset ≤4 weeks after onset of gastroenteritis</td>
<td>0</td>
<td>7.2</td>
</tr>
</tbody>
</table>
pain, and no confirmation of the findings was made by personal interviews, physician review, or physical examinations.

**Campylobacter and Yersinia.** No outbreak investigation of Campylobacter or Yersinia infection in the United States has focused on either ReA or Reiter’s syndrome, although numerous studies have been performed in Scandinavian countries [59–63].

**POPULATION-BASED STUDIES**

Although much of the variation in estimates of the frequency of ReA stems from inconsistencies in case definitions and study methods, another source of variation may be differences in virulence factors among various outbreak strains, the inoculum size involved in a given outbreak, and in the demographic characteristics of the small, highly selected outbreak populations. Population-based studies allow for a determination of incidence with use of an unselected group of patients and bacterial strain types. Only 2 population-based studies of arthritis following enteric infection in the United States have been performed [45, 64] (Table 3).

The 2 US studies differed significantly in the determined frequency of arthritis after infection. Variations in case definitions and study methods likely play a role in this difference, although genetic factors in the disparate populations could also have contributed. The California study was performed using a mailed screening questionnaire that addressed arthritis and other symptoms. The questionnaire was mailed to 1276 persons with laboratory-confirmed enteric infection, mostly due to Campylobacter, Salmonella, and Shigella species. Joint symptoms were elicited with the following question: “Since your infection, have you had a problem with arthritis? (Arthritis is pain, swelling, and/or reduced movement in one or more joints.)” Less than one-half of the surveys were returned, 60% of respondents were white, and 12 reported new arthritis. In Minnesota and Oregon, an attempt was made to conduct telephone interviews of all persons with culture-confirmed Campylobacter, Salmonella, Shigella, Yersinia, or Escherichia coli O157 infection within 8 weeks of their positive culture. A total of 4468 (70%) persons were interviewed; 89% were white, and a majority of the cases were due to Campylobacter and Salmonella species. In this study, the frequency of these symptoms was roughly 5–8 times the estimates in the California study. It has been estimated that for every culture-confirmed case of Salmonella or Campylobacter infection, ~38 actually occur [1, 69]. If one assumes that the proportion of Salmonella and Campylobacter cases that are not culture-confirmed are equally likely to result in ReA as those that are culture-confirmed, the actual incidence of ReA could be substantially higher than estimated. However, severe and prolonged acute illness has been associated with increased risk of ReA by many investigators [40, 41, 56, 66, 70], so the validity of such an assumption could be challenged.

Population-based studies performed in Scandinavia are shown in Table 3 for comparison. Hannu et al studied ReA after Campylobacter [65] and Shigella infections [44] with identical study designs. An advantage of these 2 studies is the inclusion of matched control subjects selected from the Finnish population registry and examination of symptomatic subjects by rheumatologists. A high proportion of subjects with infection reported recent musculoskeletal symptoms. The use of control subjects provides some reference as to the background rate of these symptoms in the general population, but the examining rheumatologists were not blinded to each subject’s history of enteric infection. Thus, the diagnoses of the control subjects are potentially biased away from ReA, because a recent infection was part of the criteria for that diagnosis. Söderlin et al [67, 68] studied patients referred to rheumatology clinics with new onset arthritis rather than subjects with confirmed infection, so whether these results reflect true incidence or ReA associated with enteric infection is debatable. Of note, these authors labeled arthritis associated with a diverse group of infections (respiratory tract infection, mastitis, soft-tissue infection) as ReA. A study by Locht et al [66] studied ReA following Campylobacter infection in Denmark with use of patients with enterotoxigenic E. coli infection as controls. The study found an increased risk of developing reactive joint symptoms following Campylobacter (16%) infection, compared with enterotoxigenic E. coli infection (6%), similar to the findings in Minnesota and Oregon [45]. The question then arises, is 6%–8% simply a background rate for musculoskeletal symptoms in these populations, or should enterotoxigenic E. coli and E. coli O157 be included among pathogens that could potentially cause ReA?

**ROLE OF HLA-B27**

Lack of a clearly defined definition of the term ReA also contributes to uncertainty about the precise role of genetics in determining risk of disease. It is often stated that susceptibility to ReA is strongly associated with HLA-B27 [18, 71]. Most of the investigations done in the United States have included small numbers of patients and selected for subjects with the most severe disease and/or extra-articular features of the so-called Reiter’s triad. In the investigation by Finch [39], HLA-B27 was even part of the case definition. In the population-based study in Minnesota and Oregon that included mostly cases of milder disease, the risk of developing ReA was not associated with HLA B27 [45]. Lack of association with HLA-B27 has also been demonstrated in a population-based study of Campylobacter infection in Finland [65]. In a Salmonella outbreak in Toronto, Canada, none of the patients with ReA had HLA-B27 [56], and a Salmonella outbreak investigation in Australia found...
<table>
<thead>
<tr>
<th>Citation</th>
<th>Population</th>
<th>Case definition</th>
<th>Percentage with ReA (questionnaire)</th>
<th>Percentage with ReA (examination)</th>
<th>Annual incidence, cases per 100,000 persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannu, 2002 [65]</td>
<td>Finland; 870 subjects with Campylobacter infection; 1440 matched controls</td>
<td>Synovitis, previously asymptomatic joint, or inflammatory low back pain =2 months after onset of GI infection</td>
<td>Cases, 38; controls, 24</td>
<td>Cases, 7; controls, 0</td>
<td>4.3</td>
</tr>
<tr>
<td>Locht, 2002 [66]</td>
<td>Denmark; 210 patients with Campylobacter; 177 patients with ETEC</td>
<td>No prior rheumatologic condition, joint symptoms ≤4 weeks of diarrhea onset</td>
<td>Campylobacter, 16; ETEC, 6.0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Söderlin, 2002 [67]</td>
<td>Sweden; 151 patients with new onset arthritis referred from health care centers; age &gt;16 years</td>
<td>Inflammatory joint disease preceded by infection, positive cultures or serology</td>
<td>…</td>
<td>Any infection, 24; enteric infection, 15.8</td>
<td>Any infection, 28; enteric infection, 18</td>
</tr>
<tr>
<td>Rees, 2004 [64]</td>
<td>United States; 1454 subjects with culture confirmed enteric infection; California FoodNet</td>
<td>Pain, swelling, and/or reduced movement in ≥1 joints since infection</td>
<td>Campylobacter, 2.8; Salmonella, 2.0; Shigella, 1.2</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Hannu, 2005 [44]</td>
<td>Finland; 270 subjects with Shigella; 597 matched controls</td>
<td>Synovitis, previously asymptomatic joint, or inflammatory low back pain =2 months after onset GI infection</td>
<td>Cases, 39; controls, 25</td>
<td>Cases, 7; controls, 0.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Townes, 2008 [45]</td>
<td>United States; 4488 persons aged &gt;1 year with culture confirmed infection; Oregon and Minnesota FoodNet</td>
<td>≥3 days of new onset joint pain, swelling or redness, heel pain, morning stiffness, or back pain within 8 weeks of culture</td>
<td>Campylobacter, 12.7; E. coli O157, 8.9; Salmonella, 15.0; Shigella, 9.7; Yersinia, 14.3</td>
<td>1.9–9.5</td>
<td>0.6–3.1</td>
</tr>
</tbody>
</table>

**NOTE.** ETEC, enterotoxigenic E. coli; GI, gastrointestinal.

* Synovitis is defined as either swelling or limitation of movement and pain

**a** Synovitis is defined as either swelling or limitation of movement and pain.

**b** Enteric infections were predominantly caused by *Campylobacter jejuni*. Other infections included “genitourinary” (1), tooth root infection (1), staphylococcal soft-tissue infection (2), *E. coli* septicemia (1), urosepsis (1), mastitis (1), and upper respiratory tract infection (6). A later study of a subset of this same cohort reported that 17 (63%) of 27 subjects with ReA had evidence of *C. jejuni* infection [67].
HLA-B27 in only 2 of 19 subjects with ReA [49]. Others have shown that HLA-B27 is associated with increased severity and duration of joint symptoms following Salmonella infection [72]. Thus, a case definition that is narrow, including only subjects with severe objective arthritis, would tend to overestimate the contribution of HLA-B27 to risk of ReA, compared with a definition that includes those patients with milder or subclinical findings [54, 55].

CONCLUSION

ReA is a concept, not a well-defined disease. Clearly, there are inflammatory changes that can occur in joints and other tissues following infection with enteric pathogens, causing a substantial burden of disease in the United States. It is difficult to determine the full extent of that burden, however, without agreement on more precise diagnostic and classification criteria. Additional follow-up studies of patients with enteric infection in ethnically diverse populations would help to clarify the clinical spectrum of illness and inform the development of objective classification criteria. Such studies should be population-based, use standardized, validated, and published questionnaires to elicit symptoms, and include physical examinations of both of ill subjects and carefully selected control subjects, some without infection and others with infection due to a variety of pathogens. Ideally, examiners would be blinded to the infection history of study subjects, and they should use objective measures to record inflammation and disability.

Acknowledgments

Potential conflicts of interest. J.M.T.: no conflicts.

References

70. Inman RD, Johnston ME, Hodge M, Falk J, Helewa A. Postdysenteric arthritis, psoriasiform lesions and protein loosing enteropathy second-