As international travel to developing countries increases, more people seek medical advice concerning food and water-borne diseases, including typhoid fever.\textsuperscript{1,2,3} Prevention of typhoid fever in high-risk groups (travelers to endemic areas, laboratory workers and household contacts of typhoid carriers) should rely primarily on prevention of exposure. However, immunization is an important adjunct. The decision to immunize against typhoid fever should be individualized, taking into account the benefits versus the risk of possible adverse reactions.\textsuperscript{2}

Cases of reactive arthritis have been associated with the heat-phenol inactivated ‘whole cell’ parenteral vaccine,\textsuperscript{4,5} but to our knowledge reactive arthritis has not been previously reported with the oral form (Ty21a). This is a report of HLA-B27 negative reactive arthritis occurring in two travelers after the administration of oral Ty21a typhoid vaccine.

**Case 1**

A 27-year-old previously healthy white female physician developed asymmetric, additive polyarthritis 8 weeks after receiving oral Ty21a typhoid vaccine. No other vaccines or medications were taken. Initially she reported mild nausea and abdominal cramping on days two through four of taking the vaccine. After her trip she remained asymptomatic for 8 weeks. She then developed swelling and tenderness of her knees, ankles and hands. She also reported numbness in the ulnar distribution of the right hand and recalled having a transitory enthesopathy of the right elbow and scapula which was slightly relieved by ibuprofen. There was no history of fever, rash, dysuria, gastroenteritis, conjunctivitis or mucosal ulcers. Physical examination was only remarkable for swelling, warmth and tenderness over the joints listed above.

Laboratory examination revealed normal complete blood cell count, chemistry and electrolyte profiles, and urinalysis. The sedimentation rate was slightly elevated at 25 (Normal: 0–10) and the rheumatoid factor was positive but not at high titer. The ANA and HbsAg were negative. (Her HbsAb turned positive 1-year earlier following vaccination with HBV vaccine). The patient was HLA B27 negative. In the absence of gastrointestinal symptoms, no stool culture was obtained.

All symptoms resolved promptly with nonsteroidal anti-inflammatory drug therapy. Physical activity was limited for 1 month due to knee soreness.

**Case 2**

A 66-year-old Chinese American woman developed bilateral sacroiliitis 1 day after completing the series of four Ty21a capsules. Initially, she recalled having crampy abdominal pain and loose stools while taking the vaccine. The sacroiliac pain on the left side resolved spontaneously, but persisted on the right. Three weeks later the patient developed urinary urgency, frequency and dysuria, and also reported purulent conjunctivitis. She denied any history of fever, rash or peripheral joint involvement. Her past medical history was remarkable for transient and self-limited spondyloarthropathy that involved several PIP and sacroiliac joints 17 years prior to this episode.

On physical examination purulent conjunctivitis and tenderness over the left sacroiliac joint was confirmed.

Laboratory examination revealed normal complete blood cell count, chemistry and electrolyte profiles, and urinalysis. The sedimentation rate was normal. The rheumatoid factor, ANA and HbsAg were negative. The patient was HLA B27 negative. Her lumbar sacral spine and SI joints radiographs were normal.

A rheumatologist evaluated both patients and in both cases felt strongly that the diagnosis was reactive arthritis, most likely vaccine-related.

**Discussion**

Three typhoid vaccines (two parenteral and one oral) are currently available for use.\textsuperscript{6} The parenteral heat-
phenol inactivated ‘whole cell’ vaccine is reported to be the most effective one. With a high prevalence of adverse reactions this vaccine is now infrequently used.1 Adverse reactions can be local or systemic and range from moderate local pain to an anaphylactoid reaction and death.2 Other reported adverse effects include severe headache, erythema nodosum,6 IgA nephropathy,9 neurological problems, and reactive arthropathy.2,4,5 The parenteral Vi capsular polysaccharide antigen vaccine has the advantage of minimal, more transient and less severe side effects, such as local tenderness, malaise, fever and headache.2,6 The oral typhoid vaccine (live-attenuated Sal-

monella typhi Ty21a strains in enteric coated capsules) is frequently prescribed in the USA, because of its oral administration and minimal side effects, such as nausea, vomiting, abdominal pain, diarrhea, fever and rash.2,6 Reactive arthritis has not been reported, as assessed by a Medline search and personal communication with the manufacturer.

Reactive arthritis is defined as a nonpurulent joint inflammation following documented or presumed infection in a remote part of the body and usually occurs 1 to 4 weeks after an inciting event. This syndrome includes rheumatic fever, post-dysentery or urethritis arthritis, arthritis associated with human immunodeficiency virus (HIV) and hepatitis B infections and inflammatory bowel disease, and many idiopathic arthritides with no evidence of a triggering infection. The most prominent symptom is the abrupt onset of a nonpurulent, asymmetrical, transitory oligoarticular arthritis involving large and small joints, which usually occurs in association with one or more of the following: tendonitis at insertion sites (enthesitis), conjunctivitis, uveitis, urethritis, balanitis, keratoderma blenorrhagica, and erythema nodosum. The disease is associated with a genetic susceptibility. In most series 75% of affected individuals are HLA-B27 positive, while the gene is present in only 9% of most ethnic groups.10 Reactive arthritis is most prevalent in developing countries that have higher rates of enteric infections.5,10

Classically, the recognized infectious agents related to reactive arthritis are predominately gram-negative, intracellular organisms including many strains of Salmonella spp., Verminia enteroxolitica, Campylobacter jejuni, Shigella flexneri and Chlamydia trachomatis. The list of organisms has expanded to include Clostridium difficile, Parvovirus, Ross River Virus, hepatitis B virus, mumps, Giardia lamblia, leptospirosa, Brucella, Chlamydia pneumoniae, Ureaplasma urealyticum, Streptococcus epidermidis and Streptococcus pyogenes.6

Although there are several studies of vaccine-induced reactive arthritis, to date it has been usually associated with the heat-phenol inactivated parenteral form of typhoid vaccination and with hepatitis B vaccine.5,6,11 Our patients indicate that reactive arthritis following oral Ty21a vac-
cine may occur. Because of the usual prolonged period of time between the inciting event and the onset of symptoms of reactive arthritis (as evidenced in the first case), the true incidence of this adverse reaction might be underreported due to failure to associate these symptoms with previous vaccination. The rapid onset of symptoms (as noted in the second patient) has been reported once before following vaccination with parenteral heat-phenol inactivated typhoid vaccine. How-
ever, the previous episode of arthropathy in this patient might also have contributed to the unusually rapid onset of symptoms. Prospective surveillance will be necessary to determine the true incidence of reactive arthritis following oral Ty21a typhoid vaccine.

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