Salmonella Typhimurium DT104, Italy

To the Editor: The recent article by Helms et al. described the distribution of *Salmonella enterica* serovar Typhimurium definitive page type 104 (DT104) infections in 29 countries from 1992 to 2001 (*1*). Results from Italy were not presented because routine phage typing was not performed before 2001. Since 2002, circulation of *S.* Typhimurium phage types has been monitored by the laboratory-based surveillance system Enter-net Italia, which was coordinated by Istituto Superiore di Sanità as part of the European network for the surveillance of foodborne infections (*2*). From 2000 to 2004, *S.* Typhimurium accounted for ≈40% of all human *Salmonella* isolates each year. Since 2002, ≈20% of the *S.* Typhimurium isolates were identified as DT104, and all had a pentavalent resistance pattern (resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline) (*3*). Although the results reported by Helms et al. (*1*) refer to a different period (1992–2001), the Italian data are similar to those from many other countries in northern and western Europe.

According to the Colindale scheme for phage typing ([*4*] and L.R. Ward, pers. comm.), numerous distinguishable DT104 subtypes can be identified as DT104 A, B, C, H, and L. Most (90%) *S.* Typhimurium DT104 strains isolated during the last 2 years belonged to subtype DT104L.

Emergence of phage subtype DT104A was identified in June 2004 during an outbreak of salmonellosis in Rome. This subtype had never been previously identified in Italy. All DT104A isolates were susceptible to the Enter-net panel of antimicrobial drugs (*2*), a feature unusual for *S.* Typhimurium (*5*). A total of 63 cases were confirmed; 61 were from Rome, and 2 were from a neighboring region. All isolates had similar pulsed-field gel electrophoretic profiles when analyzed with the Salm-gene protocol (*6*). Since the outbreak, 1 additional human isolate of DT104A was identified from a resident of the same neighboring region. This isolate was also susceptible to the panel of antimicrobial drugs. A fermented pork salami was epidemiologically implicated as the vehicle of infection. No microbiologic evidence was found because no food samples were available when the outbreak was recognized.

The incidence of DT104 in Italy has remained stable from 2002 through 2004. However, emergence of subtype DT104A during a recent outbreak highlights the need for subtyping in identifying communitywide outbreaks and in monitoring changing subtype patterns.

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Echovirus 13 Aseptic Meningitis, Brazil

To the Editor: Human enteroviruses (polioviruses, coxsackievirus A, coxsackievirus B, echoviruses, enterovirus 71, and newer recognized serotypes) belong to the *Picornaviridae* family, *Enterovirus* genus (*1*). They are common viral agents associated with a diversity of clinical manifestations, including respiratory illness; nonspecific rashes; hand, foot, and mouth disease; myocarditis; acute hemorrhagic conjunctivitis; and central nervous system (CNS) syndromes (*2*). Acute viral infections of the CNS are the source of a group of globally distributed diseases, which affect the population in a sporadic, endemic, or epidemic way. These infections cause a number of illnesses, particularly in children, and may result in serious sequelae; in severe cases, they can be fatal (*3*). Meningitis, encephalitis, acute flaccid paralysis (poliomyelitis), mononeuritis, polyneuritis, and Reye syndrome constitute most of the illnesses (*4*). Nonpolio enteroviruses are responsible for >80% of viral meningitis cases in which the etiologic agent

is identified (*2*). Several of the 28 currently recognized serotypes of echovirus are found in association with these infections (*3*).

We describe an outbreak of aseptic meningitis that occurred in southern Brazil in 2003 with echovirus 13 (E13) virus as the etiologic agent. This is the first meningitis outbreak due to E13 reported in the country.

From March to April 2003, 17 children and young adults from Horizontina City (population 16,800), Rio Grande do Sul State, southern Brazil, with symptoms of meningitis, sought medical attention at the local hospital. Seven of these case-patients were linked to each other either by school or domiciliary contact. Lumbar puncture showed clear cerebrospinal fluid (CSF), which suggests a viral cause. The following symptoms were associated with patients: fever (92%), headache (84%), vomiting (79%), diarrhea, stiff neck, and fatigue (7.69% each). Patients' ages ranged from 1 to 19 years of age, with the age peak incidence in children 5–9 years of age (46%). Fifty-eight percent of patients were male. All patients recovered, and no sequelae or deaths were identified. The pattern of meningitis associated with E13 in this outbreak was clinically similar to those observed in aseptic meningitis due to other enteroviruses in previous outbreaks.

For diagnostic purposes, 12 CSF and 8 fecal specimens were collected from the 17 patients with clinically suspected viral meningitis. For viral diagnosis, RD and HEp2 cells were injected with 0.2 mL of each clinical specimen (clarified fecal specimens and CSF) and examined daily for at least 7 days postinoculation. Enterovirus characteristic cytopathic effect was observed in 6 (50%) of 12 CSF samples and in 5 (62.5%) of 8 fecal samples. All isolates were typed as echovirus 13 by a reverse transcription–PCR and nucleotide sequencing of a portion of the VP1 gene (*5*).

Before 2000, echovirus 13 was considered a rare serotype of enterovirus (*6*) and had never been reported in association with outbreaks (*7*). In the United States, before 2001, this enterovirus accounted for only 65 of the 45,000 reported enteroviral isolates (*6*). However, the incidence of E13 is increasing; several meningitis outbreaks have been recently reported in England, Germany, Belgium, Spain, France, Israel, and Japan (*8*).

In spite of the temporal clustering and close contact of 7 patients, the causes of the outbreak were not completely defined and remain speculative. The sudden emergence of E13 as a prominent enterovirus associated with viral meningitis in many countries, including Brazil, demonstrates the potential of enteroviruses to circulate widely and to unpredictably cause diseases, which underscores the continued need for enterovirus surveillance.

Although this specific outbreak was restricted both geographically and in terms of magnitude (only 17 cases), E13 seemed to be widely distributed in Brazil and has been detected in fecal specimens obtained from patients with acute flaccid paralysis since 1998 (C. Blal, unpub. data). Epidemiologic surveillance plays a crucial role in understanding the changing patterns of enterovirus infection and disease associations. Such knowledge may help in the control of diseases (*9,10*). Although identifying the enterovirus serotype does not contribute substantially to patient management, establishing the dominant virus each year or in each outbreak is essential for epidemiologic purposes.

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Nonsteroidal Antiinflammatory Drugs and Group A Streptococcal Infection

To the Editor: Factor et al. recently reported the results of a population-based, case-control study regarding risk factors for pediatric invasive group A streptococcal (GAS) infection (*1*), noting that the "new" use of nonsteroidal antiinflammatory drugs (NSAIDs), defined as NSAID use <2 weeks before diagnosis, was associated with invasive GAS infection, whereas self-defined "regular" NSAID use was not. The control population consisted of nonhospitalized, age-matched children contacted by telephone (*1*). Although we endorse the authors' conclusion that, "…the measurements of new use and regular use [of NSAIDs] are too crude to clearly identify their role as a risk factor," a more detailed discussion of their findings and conclusions is warranted.

Because of their antiinflammatory effects, NSAIDs have been suspected of suppressing host immunity during infection, particularly GAS infection (*2*). However, determining a causal association between NSAID use and infectious diseases has been problematic, especially when using retrospective studies (*3*). The results of such observational studies often suffer from protopathic bias, in which drugs are applied to treat symptoms that are actually early manifestations of the outcome of interest (*4*). Consequently, rather than being a direct determinant (i.e., causative risk factor) for invasive GAS infection, NSAID use could mark the onset of disease symptoms (fever, localized pain, and inflammation). Therefore, because of protopathic bias, the study by Factor et al. had a substantial chance of identifying an association between NSAID use and invasive GAS infection a priori.

Neither the fact that patients in the study by Factor et al. received NSAIDs any time during the 2 weeks before the diagnosis of invasive GAS infection nor the finding that nonhospitalized children (controls) were unlikely to have received NSAIDs in the 2 weeks before their interview should be surprising. A more informative case-control study would have matched case-patients with similar-aged children who had febrile infections not caused by GAS infection; both groups of children would have been equally likely to have received analgesic and antipyretic medications. Furthermore, population-based data suggest that most patients with invasive GAS infection are hospitalized (*5*), so hospital-based controls, rather than population controls, might have provided a more appropriate comparison group.

Prospective studies have failed to define a causal link between NSAIDs and invasive GAS infections (*3*), though such studies were not specifically designed to investigate this relationship. To best test the hypothesis that NSAIDs increase the risk for invasive GAS infection, a randomized, prospective trial should be done. Such a trial is unlikely to take place, however, because of questionable ethics and because the sample necessary to detect a significant difference would be prohibitively large.

Although NSAIDs may neither alter the risk of developing an invasive GAS infection nor accelerate an established infection, these drugs can mollify the signs and symptoms of streptococcal infection, possibly delaying appropriate management and treatment (*3*). However, the potential adverse consequences of suppressing clinical indicators of disease severity (e.g., fever, pain, and inflammation) with NSAIDs apply to myriad infectious and inflammatory conditions, not just invasive streptococcal disease.

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