resistant (1-3). Throughout Italy, the use of macrolides, particularly the newest ones (azithromycin and clarithromycin), has increased in the treatment of infections caused by Group A streptococci. This therapeutic approach is contrary to current guidelines, which recommend using betalactam antibiotics as first-choice therapy and reserving macrolides only for patients allergic to betalactams.

In 1997 in Finland, a decrease was observed in the use of macrolide antibiotics in ambulatory patients from 2.40 defined daily doses per 1,000 inhabitants in 1991 to 1.38 in 1992. Subsequently, the maintenance of doses at 1.28 to 1.74 defined daily doses resulted in a substantial decrease in the percentage of group A streptococcal resistance to erythromycin, reported as 16.5% in 1992, 19% in 1993, 15.6% in 1994, 10% in 1995, and 8.6% in 1996 (4). These data prompted us to evaluate such phenomena in our geographic area, the urban area of Genoa, Italy (approximately 120,000 inhabitants).

From January 1991 to June 1998, 311 (6.1%) of 5,117 strains of *S. pyogenes* throat swabs from patients with pharyngotonsillitis were isolated. We observed a higher number of group A streptococci isolates from throat swabs starting in 1996 than we had in 1991 to 1995 (chi-square = 35.653, $p < 0.0001$). All isolates were tested for susceptibility to penicillin and erythromycin by standard susceptibility tests (broth microdilution) as recommended by the National Committee for Clinical Laboratory Standards. All isolates were susceptible to penicillin. From 1991 to 1996, the percentage of *S. pyogenes* resistant or with intermediate resistance to erythromycin increased from 0% to 50% (1992, 6%; 1993, 13%; 1994, 14%; 1995, 24%; 1996, 50%). In 1997 and the first half of 1998, resistance to erythromycin decreased to 39% and 34%, respectively. The number of resistant strains before 1996 was significantly lower than from 1996 to 1998 (chi-square = 50.386, $p < 0.0001$). Analysis of antibiotic consumption in our district showed an increase in the use of macrolides (erythromycin and the new compounds clarithromycin and azithromycin) from 0.445 defined daily dose per 1,000 inhabitants in 1994 to 1.140 in 1996. In 1997 and in the first half of 1998, consumption decreased to 0.9 and 0.8, respectively; we observed a correlation between the number of resistant isolates and the defined daily dose increase (correlation $[R^2] = 0.795$, $p = 0.0153$).

S. pyogenes resistance to erythromycin rose from 6% to 50% in only 4 years and then rapidly decreased from 50% to 34% in an 18-month period, corresponding to a 57% decrease in defined daily dose (from 1.41 in 1996 to 0.8 in the first half of 1998). Our data suggest that *S. pyogenes* resistance to erythromycin is associated with frequency of macrolide use.

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Estimated Incidence of *Clostridium difficile* Infection

To the Editor: Since the publication of our article Increasing hospitalization and death, possibly due to *Clostridium difficile* diarrheal disease (1), we have received several requests to estimate the incidence of *C. difficile* infection. Our original study included only hospitalized patients treated at the Lovelace Medical Center from 1993 to 1996, and no information on the incidence of *C. difficile* infection. In response to these requests, we used inpatient and outpatient medical claims for the Lovelace managed care population to calculate incidence rates. We searched medical claims for the Lovelace Health Plan/Senior Plan (LHP) to identify patients who had a *C. difficile* diagnosis between January 1, 1993, and December 31, 1997. LHP members are residents of New Mexico, most residing in or near Albuquerque.

LHP had approximately 713,000 person-years of enrollment from 1993 to 1997. We identified 104 members with a *C. difficile* diagnosis on a claims record during this period. This group includes most of the patients in our original study. Most patients (62.5%) were identified exclusively from inpatient records; another 15.4% had both an inpatient and an outpatient record with a *C. difficile* diagnosis; and 22.1% had only an outpatient *C. difficile* diagnosis. We calculated an age-adjusted rate of infection (adjusted to the 1990 U.S. population), for each year and for the 5-year period. The incidence of *C. difficile* infection for all members during 1993 to 1997 was 14.8 cases per 100,000 person-years of enrollment. The patients rates for male and female were essentially the same (14.4 vs. 15.5, respectively). The rates increased dramatically with age. For persons ages 0-4, the age-adjusted rate per 100,000 person-years of enrollment (number of cases) was 5.3 (2); for 5-14, 2.7 (3), for 15-24, 2.2 (2); for 24-34, 6.4 (6); for 35-44, 9.2 (12); for 45-54, 15.7 (17); 55-64, 16.8 (10); 65-74, 38.5 (19); and 75+, 98.9 (33). The overall average rate of infection was 15.4; there were 104 cases.

The rate of infection may have declined since 1993 in this population. The 1993 rate was 24.5 per 100,000 person-years of enrollment, declining to 11.1 in 1997 (1993, 24.4; 1994, 19.1; 1995, 9.9; 1996, 12.3; and 1997, 11.1).

Our method for estimating rates has some limitations. We did not examine laboratory records to confirm the diagnosis. In addition, some laboratory-confirmed infections may not have resulted in a claims record with a *C. difficile* diagnosis. The Lovelace managed-care population is an insured, generally healthy population that may not have the characteristics of patients in other health care delivery settings or, because of its geographic restriction, the characteristics of the general U.S. population. Nevertheless, these estimates provide a basis for determining the magnitude of the public health problem of *C. difficile* infection. Additional surveillance studies are needed to better estimate the incidence of infection and to determine whether the incidence has declined during recent years.

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Diphtheria in Eastern Nepal

To the Editor: Diphtheria, caused by *Corynebacterium diphtheriae*, was a major childhood killer until the advent of the Expanded Program on Immunization when diphtheria, pertussis, and tetanus (DPT) vaccination was greatly increased; diphtheria gradually declined in many countries. We report two cases of diphtheria identified at the B.P. Koirala Institute of Health Sciences Hospital, Dharan, Nepal.

During April 1996, a 6-year-old patient had fever (for 5 days), difficulty in swallowing and breathing, and change of voice (for 4 days). Throat examination showed a grayish-white membrane over the right tonsil, uvula, and adjacent soft palate. The membrane could not be removed, and the larynx could not be examined. Swabs were taken from the membrane area and sent to the laboratory, where smears were made and stained by Gram and Albert stains. Gram-stained smears showed a large number of gram-positive bacilli with the appearance of Chinese letters, and Albert stain showed bacilli with numerous metachromatic granules. A diagnosis of faucial diphtheria, with a strong possibility of laryngeal diphtheria, was made. The patient was treated with parenteral penicillin and diphtheria antitoxin. His condition improved after 6 days of therapy.

In December 1996, a 9-year-old patient sought treatment for chronic pain and discharge in the left ear. On examination, he had mucopurulent discharge, antral perforation, and mastoid tenderness. Throat examination showed bilateral tonsilitis. A provisional diagnosis of acute mastoiditis associated with acute septic tonsillitis was made. Throat swabs were collected and sent to the laboratory; smear findings showed typical organisms morphologically resembling *C. diphtheriae*. Culture done on 10% defibrinated sheep blood agar and Loefflers serum slope grew colonies consistent with *C. diphtheriae*. In addition to local antibiotic to the ear, the patient was given parenteral penicillin, gentamicin, and metronidazole. Because the patient had no features of systemic