Correspondence

Prevention of Neural-Tube Defects

To the Editor: Palomaki et al. (April 1 issue)[1] reported recently that 96 women from Maine had pregnancies, with estimated or actual dates of delivery between 1991 and 1996, in which open spina bifida or anencephaly developed in the fetuses. In addition, they found no decrease in the prevalence of these preventable birth defects.

In 1991, the Medical Research Council Vitamin Study Research Group reported the results of a randomized, controlled trial that found that synthetic folic acid taken in the form of a pill prevents 72 percent of cases of spina bifida and anencephaly.[2] Had an effective program of folic acid supplementation been implemented in Maine immediately after the publication of the results of the Medical Research Council vitamin study, most of the women in the study by Palomaki et al. would not have had pregnancies affected by these birth defects. Had there been an effective national program, 20,000 pregnancies in the United States between 1992 and 1999 would not have been affected — more than the number of pregnancies affected by thalidomide-induced birth defects in Europe 40 years ago.

The failure to implement effective programs for protection against folic acid–preventable birth defects is causing a continuing public health emergency. Since 1991, approximately 64 children have lost their lives because of front-seat air bags. The 20,000 pregnancies unnecessarily affected by folic acid–preventable birth defects constitute an opportunity for prevention more than 300 times as great as the opportunity to control the number of deaths among children resulting from front-seat air bags.

It is not surprising that the emergency continues. The Food and Drug Administration waited four years before requiring inadequate levels of folic acid fortification that result in the average woman's consuming only 25 percent of the amount of folic acid recommended by the Public Health Service in 1992 and the Institute of Medicine in 1998 — a deficiency tantamount to marketing polio vaccine containing only the least common of the three vaccine strains. The current administration both permitted the inadequate fortification regulation to be formulated and failed to ask Congress to appropriate a single penny for the Centers for Disease Control and Prevention (CDC) to build an effective supplementation program. Congress appropriated only about $1 million for the effort, which, to be effective, would require about $100 million a year. Since the early 1990s, Congress has made approximately $100 million a year available for a CDC-sponsored program to prevent *Haemophilus influenzae* meningitis. We have nearly eliminated this killer and disabler of children — what a great public health success! It is time for the President to implement a fully protective folic acid fortification program and, until that program is in place, for Congress to provide the CDC with the resources to teach women to consume vitamin supplements containing folic acid.

GODFREY P. OAKLEY, JR., M.D., M.S.P.M.
Emory University
Atlanta, GA 30322

1. Palomaki GE, Williams JR, Haddow JE. Prenatal screening for open neural-tube defects in Maine. N Engl J Med 1999;340:1049-50.
2. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991; 338:131-7.

Fluoroquinolone Resistance in *Streptococcus pneumoniae*

To the Editor: Chen et al. (July 22 issue)[1] report an increasing prevalence of *Streptococcus pneumoniae* strains with reduced susceptibility to fluoroquinolones in Canada. We have found similar results in Barcelona, Spain.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 400 words (please include a word count). •It must have no more than five references and one figure or table. •It should not be signed by more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •You should inform us if you or any co-authors have any financial relationships with any company whose products are mentioned in the letter or a company making a competing product. •Please include your full address, telephone number, and fax number (if you have one). •You may send us your letter by post, fax, or electronic mail.

Our address: **Letters to the Editor • *New England Journal of Medicine* • 10 Shattuck St. • Boston, MA 02115**

Our fax numbers: **617-739-9864** and **617-734-4457**

Our e-mail address: **letters@nejm.org**

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. We are unable to provide prepublication proofs. Please enclose a stamped, self-addressed envelope if you want unpublished material returned to you. Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various editions (print, data base, and optical disk) and in anthologies, revisions, and any other form or medium.

The New England Journal of Medicine
Downloaded from nejm.org at UNIVERSITAT DE BARCELONA CRAI on July 2, 2014. For personal use only. No other uses without permission.
Copyright © 1999 Massachusetts Medical Society. All rights reserved.

Of 2822 pneumococcal isolates studied in our institution from 1991 through 1998, 57 (2.0 percent) were resistant to ciprofloxacin (minimal inhibitory concentration, ≥ 4 μg per milliliter). We have seen an increase of ciprofloxacin-resistant pneumococci, from 0.9 percent (6 of 675 strains) in 1991–1992 to 3.0 percent (22 of 727 strains) in 1997–1998 ($P=0.004$). The use of fluoroquinolones in Spain has also increased during the past 13 years, from 0.91 defined daily dose per 1000 inhabitants in 1985 to 2.22 in 1997.[2] At our institution, 88.7 percent of fluoroquinolone-resistant pneumococcal strains were isolated from sputum, most were from older patients, and about half the patients had received fluoroquinolones during the previous three months.

There was a relation between resistance to penicillin and resistance to ciprofloxacin: 20 of 1525 pneumococcal isolates that were susceptible to penicillin (1.3 percent), 18 of 715 with intermediate resistance to penicillin (2.5 percent), and 19 of 582 that were highly resistant to penicillin (3.3 percent) showed resistance to ciprofloxacin ($P=0.009$). In contrast to the findings of Chen et al., we found that macrolide-resistant pneumococci were also more resistant to ciprofloxacin: 36 of 2225 pneumococcal isolates that were susceptible to erythromycin (1.6 percent) and 21 of 597 that were resistant to erythromycin (3.5 percent) showed resistance to ciprofloxacin ($P=0.003$). These findings could be due to the higher prevalence of erythromycin resistance in Spain than in Canada.

We agree with Chen et al. that most of the current strains of ciprofloxacin-resistant pneumococci are not clonally related (17 of 18 of our ciprofloxacin-resistant strains were clonally distinct on pulsed-field gel electrophoresis).

Resistance to fluoroquinolones in pneumococci is an emerging problem, and it is associated with resistance to other antibiotics. Our experience,[3] as well as that of other investigators, suggests that, according to the current levels of resistance to beta-lactam antibiotics, most patients with nonmeningeal pneumococcal infections can still be treated with an appropriate beta-lactam agent. The newer fluoroquinolones, with higher levels of activity than ciprofloxacin against pneumococci, must be used prudently, and their use must be restricted to indications for which they offer a clear therapeutic advantage.[4]

JOSEFINA LIÑARES, M.D.
Hospital de Bellvitge
Hospitalet de Llobregat 08907, Spain

ADELA G. DE LA CAMPA, PH.D.
Centro Nacional de Biología Fundamental
Majadahonda 28220, Spain

ROMAN PALLARES, M.D.
Hospital de Bellvitge
Hospitalet de Llobregat 08907, Spain

1. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N Engl J Med 1999;341:233-9.
2. Ruiz-Tovar M, Ruiz-Bremon A. Consumo de quinolonas en el medio extrahospitalario en España. Bol Epidemiol Sem 1998;6:265-67.
3. Pallares R, Liñares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med 1995;333:474-80. [Erratum, N Engl J Med 1995;333:1655.]
4. Hooper DC. Expanding uses of fluoroquinolones: opportunities and challenges. Ann Intern Med 1998;129:908-10.

To the Editor: In the report by Chen et al., the data in Tables 2 and 3 implicate an age of 65 years or older as an independent risk factor for resistance, but Figure 1 appears to tell a different story. Although in 1994 the rate of resistance was notably higher among patients who were 65 years of age or older than among those who were 15 to 64 years old, this difference had virtually disappeared by 1998. In fact, if the trends shown in the figure — a steady yearly increase in resistance rates among persons 15 to 64 years old and no clear trend among older persons — have continued, the resistance rate in 1999 should be higher in the younger group. This does not appear to be consistent with the contention that because elderly patients have the highest rate of fluoroquinolone use, they also have the highest prevalence of resistance.

The authors also report that Ontario has the highest rate of fluoroquinolone use in Canada and the highest rate of resistance to fluoroquinolones. Ontario has higher prescription rates than the rest of Canada (e.g., 24 percent higher in 1997, although this figure would increase somewhat if one adjusted for Ontario's contribution to the overall figure for Canada). Yet according to Tables 2 and 3, resistance rates in Ontario are 3 to 4.6 times the rates elsewhere in Canada. That moderate increases in prescription rates can generate substantial changes in the prevalence of resistance is very important, if true. A careful examination of the correlation between each community's use of fluoroquinolones and the local institution's experience with respect to fluoroquinolone resistance, especially if done over time, could shed more light on this intriguing finding.

Although the study by Chen et al. is an important attempt to monitor the relation between the use of fluoroquinolones and resistance to them, the relation may not be as direct as their report implies.

DAN E. PETERSON, M.D., M.P.H.
MedEpi
Oakton, VA 22124

DANIEL F. SAHM, PH.D.
MRL
Herndon, VA 20171

The authors reply:

To the Editor: The findings of Liñares et al. parallel ours in all respects and suggest that *S. pneumoniae* strains with decreased susceptibility to fluoroquinolones may be more prevalent and widespread than previously thought.[1] In addition, their observation that resistant strains were primarily isolated from sputum samples obtained from older patients treated with fluoroquinolones suggests a source of such strains.

Fluoroquinolones have been approved for the treatment of acute exacerbations of chronic bronchitis since the introduction of ciprofloxacin in the mid-1980s. Chronic bronchitis affects up to 20 percent of adults in the United States and is most common in those over 65 years of age.[2] Approximately 15 percent of patients with acute exacerba-

The New England Journal of Medicine
Downloaded from nejm.org at UNIVERSITAT DE BARCELONA CRAI on July 2, 2014. For personal use only. No other uses without permission.
Copyright © 1999 Massachusetts Medical Society. All rights reserved.

tions of chronic bronchitis are colonized or infected with *S. pneumoniae*.[3] Treatment with a fluoroquinolone that does not achieve adequate bactericidal concentrations at the site of colonization or infection may create an environment that favors bacterial variants with reduced susceptibility. Although treatment with ciprofloxacin results in overall rates of bacteriologic eradication that range from 91 percent to 96 percent, the specific eradication rates for *S. pneumoniae* are lower, ranging from 63 percent to 90 percent.[4] Clinical trials of the treatment of acute exacerbations of chronic bronchitis have identified strains of *S. pneumoniae* that were resistant before fluoroquinolone therapy or that developed resistance during or after therapy.[4]

We believe that our data and those of Liñares et al. provide convincing evidence that the main force behind the emergence of resistance to fluoroquinolones in pneumococci is the volume of fluoroquinolone use. We agree with Drs. Peterson and Sahm that this relation is neither simple nor linear; however, our sample was too small to permit an analysis of the goodness of fit for complex models.[5] A better understanding of the relation between antibiotic use and selection for resistance is clearly necessary if we are to stem the tide of fluoroquinolone resistance in pneumococci. Currently, the approval of new antibiotic agents requires only the demonstration of their efficacy and safety. Perhaps it is time to modify the approval process so that the selection of antimicrobial resistance will be considered when recommended doses, frequency of administration, and duration of therapy are determined.

DANNY K. CHEN, M.D.
ALLISON MCGEER, M.D.
DONALD E. LOW, M.D.
University of Toronto
Toronto, ON M5G 1X5, Canada

1. Barry AL. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in North America. Am J Med 1999;107:28S-33S.
2. Woolcock AJ. Epidemiology of chronic airways disease. Chest 1989;96: Suppl 3:302S-306S.
3. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. Chest 1995;108:Suppl:43S-52S.
4. Chodosh S, Schreurs A, Siami G, et al. Efficacy of oral ciprofloxacin vs. clarithromycin for treatment of acute bacterial exacerbations of chronic bronchitis. Clin Infect Dis 1998;27:730-8.
5. Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Proc Natl Acad Sci U S A 1999;96:1152-6.

Mother-to-Infant Transmission of the Human Immunodeficiency Virus during Primary Infection

To the Editor: The efficacy of antiretroviral-drug therapy in preventing mother-to-infant transmission of the human immunodeficiency virus (HIV) has led to the recommendation of universal testing of pregnant women as early as possible after conception.[1] However, this strategy precludes the identification of women who acquire HIV infection later in pregnancy, including women who are infected during the peripartum period. Either scenario can result in erroneous exclusion of infant HIV infection, as has been documented for congenital syphilis.[2] Early identification of infants with HIV infection is important for the initiation of prophylaxis against *Pneumocystis carinii* pneumonia and antiretroviral-drug therapy. We report a case of perinatal HIV infection that occurred during the period in which the mother was seronegative and that was further distinguished by the infant's rapid progression to AIDS and death without the development of detectable HIV antibodies.

A two-month-old girl was admitted to the hospital for failure to thrive. She had been born at term after a pregnancy complicated by syphilis during the first trimester. At that time, the mother and three of her partners had a negative result on an enzyme-linked immunosorbent assay for HIV antibodies. At admission, the infant was 10 g above birth weight; otherwise, the findings on physical examination were normal. The workup for failure to thrive was negative. Tests for HIV antibodies were negative in stored umbilical-cord serum as well as during hospitalization and seven weeks later. Eight weeks after admission, the infant had fever and respiratory failure. Severe lymphopenia was found, with an absolute CD4 count of 135 cells per cubic millimeter. HIV antibody tests remained negative, but tests for HIV DNA (by the polymerase chain reaction) and p24 antigen in plasma were positive, and the level of plasma HIV type 1 RNA was 32 million copies per milliliter. Despite maximal supportive care, the infant died. Autopsy revealed *P. carinii* pneumonia and disseminated cytomegalovirus infection. HIV antibodies were detected in the mother's serum at the time of the infant's death. The mother admitted to having had multiple sexual partners throughout pregnancy but said that she had not had symptoms of primary HIV infection before delivery.

The negative serologic tests early in pregnancy and in cord serum and the positive test in the mother post partum suggest maternal infection near the time of delivery. Seronegative HIV infection has been reported in rare cases in both adults and children and is usually associated with rapid progression of disease. This case highlights the need for repeated testing of pregnant women who are at high risk and the need for the use of direct virologic methods in infants with seronegative tests but clinical presentations suggestive of HIV infection.

BRIAN A. VAN TINE
GEORGE M. SHAW, M.D., PH.D.
GRACE ALDROVANDI, M.D.
University of Alabama at Birmingham
Birmingham, AL 35294

1. Stoto MA, Almario DA, McCormick MC, eds. Reducing the odds: preventing perinatal transmission of HIV in the United States. Washington, D.C.: National Academy Press, 1999.
2. Dorfman DH, Glaser JH. Congenital syphilis presenting in infants after the newborn period. N Engl J Med 1990;323:1299-302.

An Increase in the Number of Deaths in the United States in the First Week of the Month

To the Editor: Phillips et al. (July 8 issue)[1] report an increase in the number of deaths in the United States in the first week of the month, as compared with the last week of the preceding month, with a 14 percent increase in deaths attributable to substance abuse early in the month. However, the authors' suggestion that this increase is related to

The New England Journal of Medicine
Downloaded from nejm.org at UNIVERSITAT DE BARCELONA CRAI on July 2, 2014. For personal use only. No other uses without permission.
Copyright © 1999 Massachusetts Medical Society. All rights reserved.