

## SPECIAL ARTICLE

PROPHYLAXIS AGAINST *PNEUMOCYSTIS CARINII* PNEUMONIA AMONG CHILDREN WITH PERINATALLY ACQUIRED HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN THE UNITED STATES

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**Abstract** *Background.* *Pneumocystis carinii* pneumonia (PCP) remains a common and often fatal opportunistic infection among children infected with the human immunodeficiency virus (HIV). HIV-infected infants between three and six months of age are particularly vulnerable. Current guidelines recommend prophylaxis in children from birth to 11 months old who have CD4+ counts below 1500 cells per cubic millimeter.

*Methods.* We used national surveillance data to estimate the annual incidence of PCP among children less than one year old. We reviewed the medical records of 300 children given a diagnosis of PCP between January 1991 and June 1993 to determine why treatment according to the 1991 guidelines for prophylaxis against PCP either was not given or failed to prevent the disease.

*Results.* In our study the incidence of PCP in the first year of life among infants born to HIV-infected mothers changed little between 1989 and 1992. Among 7080 children born to HIV-infected mothers in 1992, PCP devel-

oped in 2.4 percent. Of 300 children with PCP diagnosed from January 1991 through June 1993, 199 (66 percent) had never received prophylaxis, and for 118 of those children (59 percent) exposure to HIV was first identified 30 days or less before the diagnosis of PCP. Among 129 children less than one year old, the CD4+ count declined by an estimated 967 cells per cubic millimeter (95 percent confidence interval, 724 to 1210 cells per cubic millimeter) during the three months before the diagnosis of PCP. Among infants in whom CD4+ counts were determined within one month of the diagnosis of PCP, 18 percent (20 of 113) had at least 1500 cells per cubic millimeter, a level higher than the currently recommended threshold for prophylaxis.

*Conclusions.* In the United States the incidence of PCP among HIV-infected infants has not declined. If this infection is to be prevented, infants exposed to HIV must be identified earlier, and prophylaxis must be offered to more children than the guidelines currently recommend. (N Engl J Med 1995;332:786-90.)

MOST cases of *Pneumocystis carinii* pneumonia (PCP) in children infected perinatally with the human immunodeficiency virus (HIV) occur in infants between three and six months of age.<sup>1</sup> Because PCP is the most common opportunistic infection classified as indicating the presence of the acquired immunodeficiency syndrome (AIDS) in children,<sup>1</sup> because it is often rapidly fatal,<sup>2</sup> and because it can be prevented by chemoprophylaxis,<sup>3</sup> clinicians and public health officials emphasize its prevention as part of the care of children exposed to HIV and in setting priorities for public health policy. In 1991, a panel of experts in pediatric HIV infection issued guidelines that recommended evaluating the risk of PCP in children born to HIV-infected mothers by measuring the CD4+ cell count and offering chemoprophylaxis if the count is lower than an established age-specific threshold.<sup>4</sup> The thresholds for prophylaxis were as follows: for children from birth through 11 months old, a CD4+ count below 1500 cells per cubic millimeter; 12 through 23 months old, below 750 cells per cubic millimeter; 2 through 5 years old, below 500 cells per cubic millimeter; and 6 through 12 years old, below 200 cells per cubic millimeter.<sup>4</sup>

Low CD4+ cell counts were thought to identify the HIV-exposed children who were at highest risk for PCP even early in life, when the available techniques were unable to establish a diagnosis of HIV infection.<sup>5,6</sup> Recognizing that PCP occurs most frequently in early infancy, the panel also stressed the need to identify exposure to HIV as soon as possible.

Concern has been aroused about whether the recommended practices can adequately prevent PCP in children born to HIV-infected mothers.<sup>7-9</sup> In one report HIV exposure was often not identified in time for prophylaxis to be given during the peak risk period for PCP in early infancy.<sup>7</sup> Other small studies have suggested that monitoring CD4+ cell counts as recommended in the current guidelines may not be adequate to determine the risk of PCP during the first year of life.<sup>8,9</sup>

To evaluate the 1991 guidelines for prophylaxis, we estimated trends in the incidence of PCP among infants born to HIV-infected mothers between 1989 and 1992. In addition, we conducted a retrospective study of more than half the U.S. children given a diagnosis of PCP in recent years in order to determine how often HIV exposure is identified before PCP is diagnosed, how often the risk of PCP in such children is evaluated by means of CD4+ cell counts, and whether prophylaxis is initiated as recommended in the 1991 guidelines. To determine whether the currently recommended thresholds for prophylaxis and schedules for monitoring are adequate to identify the children at greatest risk for PCP, we also analyzed data on CD4+

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cell counts at the time of the diagnosis of PCP and estimated the rate of decline in these counts.

## METHODS

### Estimation of the Incidence of PCP and AIDS in the First Year of Life

We used U.S. surveillance data on AIDS and data from the anonymous U.S. HIV Serosurvey of Childbearing Women to calculate the incidence of PCP and AIDS in the first year of life among children with perinatally acquired HIV infection.

AIDS is a reportable disease throughout the United States. Local health departments collect standardized data on each person reported to have AIDS and transmit these data to the Centers for Disease Control and Prevention (CDC) without personal identifiers. Reporting of AIDS among adults and adolescents is estimated to be over 85 percent complete<sup>10</sup>; no comparable estimate is available for cases among children. For this analysis, we included data on all U.S. children in whom AIDS was diagnosed in the first year of life, whose HIV infection was acquired perinatally, and who were born between 1989 and 1992. We used data reported to the CDC through March 1994 and made adjustments in the number of cases to allow for delays in reporting.<sup>11</sup>

Since 1988, most state health departments have collaborated with the CDC on an anonymous program of testing for antibody to HIV type 1 among women who gave birth; this survey uses residual dried-blood specimens collected from newborns for routine metabolic screening.<sup>12</sup> For this analysis, we used the results of specimens collected from all participating states and the District of Columbia (35 jurisdictions in 1989 and 44 in 1992). To estimate the total number of children born each year to women with HIV infection in the United States (excluding Puerto Rico and the territories), we divided the number of children born to HIV-infected women in the survey by the proportion of all U.S. cases of AIDS acquired perinatally that were reported from the participating areas.<sup>12</sup>

We calculated the incidence of PCP in the first year of life by dividing the number of children born in each year and reported to have been given the diagnosis of PCP by one year of age (with adjustment for delays in reporting) by the estimated number of births to HIV-infected women that year. The incidence of AIDS in the first year of life was calculated similarly.

### Evaluation of Recent Cases of PCP

From July 1993 through October 1993, we retrospectively reviewed the medical records of children with perinatally acquired HIV infection in whom PCP was diagnosed for the first time between January 1, 1991, and June 30, 1993. We reviewed the records of 300 children with cases of PCP reported through July 1993 from three projects funded by the CDC: a program of population-based AIDS surveillance conducted by health departments in New York City, Florida, and New Jersey (areas with a high incidence of PCP among children); the Pediatric Spectrum of Disease (PSD) project; and the Perinatal AIDS Collaborative Transmission Studies (PACTS).

The PSD project conducts active surveillance for HIV infection in children at seven sites: throughout the state of Massachusetts, throughout Los Angeles County, California, and in selected medical centers in New York City, Washington, D.C., Puerto Rico, Texas, and the San Francisco Bay area.<sup>13</sup> Data are abstracted every six months from the medical records of all the children in each study area known to have been born to HIV-infected mothers.

PACTS is a group of five collaborative, prospective studies of perinatal HIV transmission and of the natural history of HIV infection in children in New York City; Newark, New Jersey; Baltimore; and Atlanta. These studies enroll children of HIV-infected mothers at birth and record laboratory and clinical data on these children prospectively.

For this study, we used a standardized form to collect data from existing data bases and medical records. For each child, we recorded the date of birth, the date of death if the child had died, the date and method of diagnosis of PCP, the date when HIV exposure was first recognized, whether the diagnosis of HIV infection in the child's mother was made before the child's birth, the dates and values for all available CD4+ cell counts, and the starting date and type of prophylaxis against PCP, if it was prescribed. No information was avail-

able on the extent of adherence to prescribed prophylactic regimens. We determined whether the child was first evaluated for HIV infection more than 30 days before PCP was diagnosed, because the 1-to-2-month incubation period for PCP<sup>14</sup> suggests that this is the minimal time needed for prophylaxis to be effective.

### Statistical Analysis

We used the chi-square statistic with continuity correction to test for differences in proportions between groups. A difference was considered statistically significant if the P value was below 0.05.

To estimate the decline in CD4+ cell counts before the diagnosis of PCP, we used a robust, locally weighted, smoothed regression ("lowess").<sup>15</sup> To assess the variability of this estimated decline during the three months before the diagnosis of PCP, we used a bootstrap technique for regression methods.<sup>16</sup> Two hundred replicates were obtained by sampling with replacement from the residuals of the locally weighted, smoothed regression (the difference between the observed and smoothed values for the CD4+ cell count) and adding the sampled residuals to the smoothed values obtained from the observed data. The regression procedure was repeated for each bootstrap sample. The mean and standard deviation for the decline in CD4+ cell counts during the three months before PCP was diagnosed were computed from these 200 smoothed estimates.

## RESULTS

The incidence of PCP in the first year of life among children born to mothers with HIV infection changed little between 1989 and 1992 (Table 1). Assuming a mother-to-child HIV-transmission rate of approximately 20 percent, we estimated the incidence of PCP in the first year of life among HIV-infected children born in 1992 to be approximately 12 percent; this was calculated as 0.024 (the incidence of PCP among children born to HIV-infected mothers) ÷ 0.2 (mother-to-child transmission rate) = 0.12 (the incidence of PCP among HIV-infected children). The overall incidence of AIDS in the first year of life also remained essentially unchanged between 1989 and 1992 (Table 1).

We collected retrospective data on 300 (64 percent) of the 472 U.S. children with perinatally acquired HIV infection who were given a diagnosis of PCP between January 1991 and June 1993 (Fig. 1). This population was made up of 197 (95 percent) of the 207 children with perinatally acquired HIV infection and PCP who were reported through the AIDS-surveillance programs in New York City, Florida, and New Jersey; all 85 children with PCP enrolled in the PSD project (excluding those reported through the AIDS-surveillance program in New York City); and all 18 children with

Table 1. Children Born to HIV-Infected Mothers, Those with PCP Diagnosed in the First Year of Life, and Those with AIDS Diagnosed in the First Year of Life, According to Year of Birth.

YEAR OF BIRTH	BORN TO HIV-INFECTED MOTHERS*	PCP DIAGNOSED IN FIRST YEAR OF LIFE†	AIDS DIAGNOSED IN FIRST YEAR OF LIFE†
	no.	number (percent)	
1989	6400	165 (2.6)	281 (4.4)
1990	6770	193 (2.9)	307 (4.5)
1991	7030	157 (2.2)	329 (4.7)
1992	7080	167 (2.4)	301 (4.3)

\*Estimates for the entire United States (excluding Puerto Rico and the territories), based on survey data from 35 states in 1989, 43 in 1990, and 44 in 1991 and 1992.

†Based on AIDS case reports, with adjustment for reporting delays.<sup>11</sup>

PCP who were enrolled in PACTS studies or cared for in medical centers participating in PACTS (excluding those reported through AIDS-surveillance programs in New Jersey and New York City).

The median age of the 300 children at the time of diagnosis of PCP was 5 months (5th and 95th percentiles, 2 and 80 months); 222 children (74 percent) were less than 1 year old. PCP was diagnosed in 130 children in 1991, 124 children in 1992, and 46 children in January through June 1993. PCP was definitively diagnosed (on the basis of examination of histologic or cytologic specimens) in 219 children (73 percent), of whom 174 (79 percent) were less than one year old. A total of 123 (52 percent) of the 236 children for whom such information was available had mothers known to have HIV infection before or at the time of delivery. Of the 300 children, 133 (44 percent) were reported to have died by the time of the study, and 94 (31 percent) died within two months of the diagnosis of PCP. Death was thought to be related to PCP in 89 of the 116 children for whom this information was available (77 percent).

Of the 300 children, 89 (30 percent) had begun prophylaxis against PCP before PCP was diagnosed, and 199 (66 percent) had not; for 12 children (4 percent) this information was not known (Fig. 1). Children whose mothers were known to be infected with HIV at or before delivery were more likely than other children to receive prophylaxis before PCP was diagnosed (41 percent vs. 21 percent,  $P < 0.01$ ). Of the 89 children who had begun prophylaxis before PCP developed, 70 (79 percent) were apparently still receiving prophylaxis against PCP when the disease was diagnosed; however, 14 of those children (20 percent) had been receiving prophylaxis for no more than 30 days before PCP was diagnosed. Prophylaxis at the time of diagnosis consisted of trimethoprim-sulfamethoxazole for 51 children (73 percent), dapsone for 10 (14 percent), aerosolized pentamidine for 6 (9 percent), and intravenous pentamidine for 3 (4 percent).

Of the 199 children who did not receive prophylaxis against PCP before the disease was diagnosed, 60 (30 percent) were first evaluated for HIV infection at the time of diagnosis of PCP, 58 (29 percent) were evaluated 1 to 30 days before the diagnosis of PCP, and 81 (41 percent) more than 30 days before diagnosis (Fig. 1). The proportion of children who were first evaluated for HIV infection no more than 30 days before the diagnosis of PCP was higher among children whose mothers were not known to have HIV infection at or before delivery than among those with mothers who

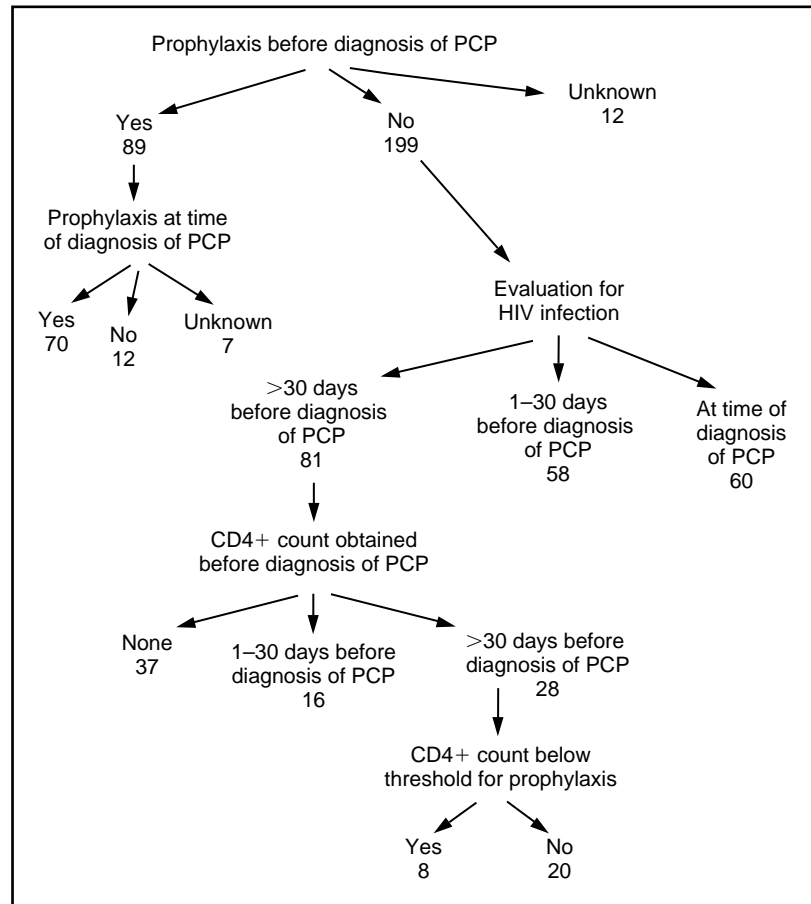


Figure 1. Timing of Prophylaxis among 300 Children with Perinatally Acquired HIV Infection in Whom PCP Was Diagnosed between January 1991 and June 1993.

had recognized HIV infection (84 percent vs. 21 percent; relative risk, 4.9; 95 percent confidence interval, 3.0 to 8.0;  $P < 0.001$ ); these percentages did not change significantly from 1991 through 1993.

Of the 81 children who did not receive prophylaxis and who were first evaluated for HIV infection more than 30 days before PCP was diagnosed, 53 (65 percent) apparently had no CD4+ cell counts performed at all or none more than 30 days before the diagnosis of PCP. Of the 28 children for whom CD4+ cell counts were available more than 30 days before PCP was diagnosed, 20 (71 percent) had no counts below the recommended threshold for prophylaxis against PCP. Fifteen of these 20 children (75 percent) were less than one year old, and PCP was diagnosed definitively in 15 (75 percent).

Including both children who had been given prophylaxis against PCP and those who had not, 180 children had a total of 378 CD4+ cell counts performed before or at the time of the diagnosis of PCP. The estimated decline in the CD4+ cell count during the three months before the diagnosis of PCP was 967 cells per cubic millimeter (95 percent confidence interval, 724 to 1210 cells) among 129 children less than one year old (Fig. 2) and 15 cells per cubic millimeter (95 percent confidence interval, 0 to 62 cells) among 51 children at least one year old.

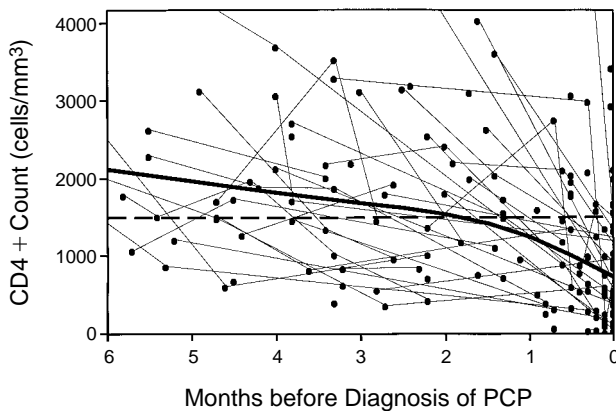


Figure 2. CD4+ Cell Counts during the Six Months before the Diagnosis of PCP in 129 Children  $\leq 11$  Months Old at the Time of Diagnosis.

Points indicate CD4+ cell counts; the thin lines connect measurements in the same child; the thick line represents the locally weighted, smoothed regression curve; and the dashed line represents the current threshold for prophylaxis against PCP in this age group ( $< 1500$  cells per cubic millimeter).

For 141 children (47 percent), the CD4+ cell count was measured within one month of the diagnosis of PCP (Table 2). Among the 113 of these children who were less than one year old at the time of diagnosis, the median CD4+ count was 552 cells per cubic millimeter (25th and 75th percentiles, 249 and 1250 cells). Among the 28 children who were at least one year old at diagnosis, the median CD4+ count was 29 cells per cubic millimeter (25th and 75th percentiles, 7 and 461 cells). Twenty of the 113 children less than one year old at the time of diagnosis (18 percent) had CD4+ counts of 1500 or more cells per cubic millimeter. For 160 children, either the number or the percentage of CD4+ cells was measured within one month of the diagnosis of PCP; 24 of 129 children less than one year old (19 percent) and 7 of 31 children one year old or older (23 percent) did not fall below the recommended threshold for initiating prophylaxis in terms of either CD4+ cell counts or percentage of CD4+ cells (20 percent of total lymphocytes for children of any age).<sup>4</sup>

## DISCUSSION

Despite the publication in 1991 of guidelines for prophylaxis against PCP<sup>4</sup> and even with continuing increases in the use of prophylaxis,<sup>17,18</sup> the estimated incidence of PCP in the first year of life among children with perinatally acquired HIV infection in the United States (12 percent) has changed little in recent years and is virtually identical to the rate of 11.8 percent reported among children prospectively followed in the European Collaborative Study, very few of whom had received prophylaxis.<sup>9</sup>

Although limited by our reliance on data collected retrospectively, our evaluation of a large sample of U.S. children with perinatally acquired HIV infection in whom PCP was diagnosed between January 1991 and June 1993 highlights several important factors contributing to the continued substantial incidence of PCP. Most of the children we studied (66 percent) did not re-

ceive prophylaxis before PCP was diagnosed. Because many of these cases might have been prevented by prophylaxis, they represent a failure of current strategies for identifying exposure to HIV, evaluating the risk of PCP, and initiating prophylaxis in the children with the highest risk.

The most prominent gap in efforts to prevent PCP in HIV-infected children remains the failure to recognize HIV exposure soon enough to begin prophylaxis before PCP develops. Over half the children in this study who were not given prophylaxis before PCP developed were not recognized as having exposure to HIV in time for prophylaxis to prevent the disease. Moreover, this proportion did not decrease over the 2½ years of the study. Not surprisingly, lack of knowledge of the mother's HIV infection before birth was associated with late recognition of exposure to HIV among the children in this study.

Some young children may not be protected by prophylaxis because the length of time required to obtain a CD4+ cell count in some communities may delay the initiation of therapy until after the period of highest risk for PCP (three to six months of age). In this study, nearly two thirds of children whose exposure to HIV was identified but who were not given prophylaxis had no record of CD4+ cell counts until 30 days or less before the diagnosis of PCP was made. Although some of these children may have had measurements that were not entered in the available medical records, it is likely that for others PCP developed before the CD4+ cell count was determined.

Even among children whose CD4+ cell counts were evaluated as recommended, the established thresholds for prophylaxis may have caused many children at high risk for PCP to be categorized as needing no prophylaxis; this was especially true of those in the first year of life, when the risk of PCP is greatest,<sup>1</sup> for whom the criterion for prophylaxis is a CD4+ count of less than 1500 cells per cubic millimeter. Moreover, because CD4+ cell counts in infants may decline rapidly, the monitoring of counts every three months, as recommended in the 1991 guidelines, may not permit detection of the drop early enough for prophylaxis to be useful. The estimated rate of decline of more than 300 cells per cubic millimeter per month before the diagnosis of PCP in infants less than one year old is much greater than the declines of fewer than 100 cells per cubic millimeter per month reported among HIV-infected

Table 2. CD4+ Cell Counts within One Month of the Diagnosis of PCP, According to Age at Diagnosis.

CD4+ COUNT (CELLS/MM <sup>3</sup> )	AGE (MO)			
	0-11	12-23	24-71	$\geq 72$
$\geq 1500$	20	1	0	0
750-1499	29	1	2	0
500-749	14	1	1	1
200-499	27	0	2	1
$< 200$	23	1	10	7
Total	113	4	15	9

and uninfected infants and older children in other studies<sup>19-22</sup> and among older children in this study.

In some children, PCP may have occurred despite prophylaxis; as many as 23 percent of the children with PCP in this study may have been receiving prophylaxis at the time the disease was diagnosed. However, this figure may overestimate the number of children for whom prophylaxis truly failed, because we do not know whether the children actually received the medication. In addition, without a control group of HIV-infected children in whom PCP did not develop, we cannot assess the efficacy of different regimens for prophylaxis against PCP. Clinical trials have demonstrated the efficacy of prophylaxis against PCP among children with cancer<sup>3</sup> and adults with HIV infection,<sup>23</sup> but none have been conducted among HIV-infected children.

Effective prevention of PCP in children with HIV infection requires that their exposure to HIV be identified and prophylaxis begun before two months of age. The recent demonstration that zidovudine can substantially reduce perinatal transmission of HIV offers a compelling reason for prenatal identification of infection.<sup>24</sup> The diagnosis of HIV infection in a woman during or even before pregnancy allows her to receive medical and other services to preserve her own health, permits interventions such as zidovudine therapy to be prescribed to reduce the risk of HIV infection in her child, and makes possible the early initiation of prophylaxis against PCP for the child. Offering counseling and voluntary testing for HIV to all pregnant women may be the single most important step toward preventing PCP in children. The Public Health Service is currently revising its guidelines for the counseling and voluntary HIV testing of pregnant women.

Data from this study also suggest that the current strategies for prophylaxis may not be effective in preventing PCP in the infants who are at highest risk for the disease. A working group convened by the National Pediatric HIV Resource Center and the CDC has recently developed revised guidelines for prophylaxis against PCP in children that recommend starting prophylaxis for all infants born to HIV-infected mothers, beginning at four to six weeks of life. The guidelines recommend discontinuing prophylaxis in children who are determined not to have HIV infection but continuing it throughout the first year of life for all HIV-infected children.

#### APPENDIX

In addition to the authors, the *Pneumocystis carinii* Pneumonia Prophylaxis Evaluation Working Group includes the following: the PSD project (H.-W. Hsu, Massachusetts Department of Health, Boston; L. Mascola, Los Angeles County Department of Health, Los Angeles; K. Shaner, Texas Department of Health, Austin; Y. Maldonado, Stanford University, Palo Alto, Calif.; I. Ortiz, Puerto Rico Department of Health, San Juan; R. Parrott, Washington Children's National Medical Center, Washington, D.C.; and P. Thomas, New York City Department of Health, New York); the CDC PACTS (D. Thea, Medical and Health Research Association, New York; E. Schoenbaum, Montefiore Medical Center, New York; P. Palumbo, University of Medicine and Dentistry of New Jersey, Newark; J. Farley, University of Maryland, Baltimore; and S. Nesheim, Emory University, Atlanta); G. Connolly, Florida Department of Health and Rehabilitative Serv-

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