

The New England Journal of Medicine

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VOLUME 339

NOVEMBER 12, 1998

NUMBER 20



ABBREVIATED REGIMENS OF ZIDOVUDINE PROPHYLAXIS AND PERINATAL TRANSMISSION OF THE HUMAN IMMUNODEFICIENCY VIRUS

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ABSTRACT

Background The Pediatric AIDS Clinical Trials Group Protocol 076 reported a reduction in the rate of perinatal transmission of the human immunodeficiency virus (HIV) from 25.5 percent to 8.3 percent with a three-part regimen of zidovudine given ante partum, intra partum, and to the newborn. We examined the effects of abbreviated zidovudine regimens on perinatal HIV transmission using data from the HIV polymerase-chain-reaction (PCR) testing service of the New York State Department of Health. Pregnant women who received abbreviated regimens rather than the recommended regimens did so because of limited prenatal care or by choice.

Methods The requisition form used by the PCR testing service included information on the demographic characteristics of the infants and the timing of any perinatal treatment with zidovudine. We also analyzed data on the timing of zidovudine prophylaxis collected by chart review in a subgroup of 454 infants as a means of validating the results in the entire cohort.

Results From August 1, 1995, through January 31, 1997, specimens from 939 HIV-exposed infants who were 180 days of age or younger were submitted for PCR testing. The rates of perinatal HIV transmission varied depending on when zidovudine prophylaxis was begun. When treatment was begun in the prenatal period, the rate of HIV transmission was 6.1 percent (95 percent confidence interval, 4.1 to 8.9 percent); when begun intra partum, the rate was 10.0 percent (3.3 to 21.8 percent); when begun within the first 48 hours of life, the rate was 9.3 percent (4.1 to 17.5 percent); and when begun on day 3 of life or later, the rate was 18.4 percent (7.7 to 34.3 percent). In the absence of zidovudine prophylaxis, the rate of HIV transmission was 26.6 percent (21.1 to 32.7 percent).

Conclusions These results confirm the efficacy of zidovudine prophylaxis and suggest that there are reductions in the rates of perinatal transmission of HIV even with the use of abbreviated regimens that are begun intra partum or in the first 48 hours of life. (N Engl J Med 1998;339:1409-14.)

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IN 1994, the Pediatric AIDS Clinical Trials Group Protocol 076 demonstrated the efficacy of a three-part regimen of zidovudine prophylaxis in reducing perinatal transmission of the human immunodeficiency virus (HIV) from 25.5 percent to 8.3 percent.¹ On the basis of these results, prenatal HIV counseling and testing and zidovudine prophylaxis to reduce perinatal HIV transmission became the standard of care in the United States.²⁻⁶ Since 1990, the New York State Department of Health has initiated programs with the goal of ensuring that all pregnant women receive HIV counseling and undergo voluntary testing for the virus. In 1996 the New York State Department of Health promulgated regulations requiring that HIV counseling be provided and testing be recommended to all pregnant women as part of prenatal care in all regulated settings⁷ and recommended that zidovudine prophylaxis be offered to all HIV-infected pregnant women.

Despite these efforts, there are a number of reasons why the full Protocol 076 regimen might not be administered. Some women may not receive prenatal care, whereas others who do receive prenatal care may not be counseled or offered HIV testing. Some women may decline HIV testing after counseling. HIV-positive women who know their infection status may decline or be unable to take zidovudine, or the regimen may not have been offered by the health care provider during all periods.

Recent data from a trial in Thailand have shown

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that an abbreviated regimen of oral zidovudine beginning at 36 weeks of gestation and continuing until delivery, with no neonatal component, can reduce the risk of transmission by approximately 50 percent.⁸ Although this decrease is significant, it is somewhat lower than the relative reduction in the risk of transmission of 67.5 percent reported for Protocol 076. Whether even shorter regimens, such as ones involving only intrapartum treatment or neonatal treatment, which might be necessary if women do not receive prenatal care, reduce the risk of transmission is not known.

New York State has the highest HIV seroprevalence rate among childbearing women in the United States (0.41 percent), with 995 HIV-positive women giving birth in 1997 (unpublished data). To aid in the early diagnosis of HIV infection in infants who have been exposed to the virus, the New York State Department of Health established a pediatric diagnostic testing service in 1995 that offers DNA polymerase-chain-reaction (PCR) testing for HIV.⁹ Approximately 70 percent of HIV-seropositive infants in the state were tested by this service during the study period. Using the resulting data, we examined whether the use of abbreviated zidovudine regimens could reduce perinatal HIV transmission. Abbreviated regimens were not recommended therapy but were used as a result of the lack of or limited prenatal care or maternal choice.

METHODS

The Pediatric HIV PCR Testing Service

The Pediatric HIV PCR Testing Service was instituted by the New York State Department of Health in April 1995. Physicians were made aware of the service through the distribution of written materials and through clinical conferences. From April 1995 through December 1997, more than 2000 HIV-exposed infants were tested.

The PCR requisition form requests demographic information, including the infant's date of birth, age, sex, race or ethnic group, birth weight, and county of residence as well as information on whether antiretroviral prophylaxis was administered during the prenatal or intrapartum periods, within 48 hours after birth, or from 3 to 42 days of life. All information is supplied by the pediatric care provider.

The qualitative PCR procedure has been described previously.⁹ All blood specimens from the infants were collected in EDTA-treated tubes and shipped at room temperature by overnight mail to the laboratory.

Study Cohort

Data were examined from the Pediatric HIV PCR Testing Service for infants who were 180 days of age or younger at the time of the initial collection of blood for PCR testing and whose specimens were received from August 1, 1995, to January 31, 1997. For this study, infants were classified as infected with HIV if they had had at least one positive PCR test at any age, and as not infected with HIV if they had had no positive PCR tests and at least one negative PCR test after the age of one month.

Validation Study

To ensure that the data were reliable and complete, we analyzed a sample of the full study cohort (the validation sample). Infants

in our study cohort were eligible to be included in this validation sample if the request for the initial HIV PCR test was submitted from the same health care facility where they were born, in order to facilitate access to the maternal, neonatal, and pediatric medical records. We telephoned the director of the pediatric HIV clinic at each hospital or the physician who ordered the PCR tests (if he or she was not part of a pediatric HIV clinic) to describe the project and to provide guidance on the completion of the medical-record-abstraction forms. A list of patient-identification numbers from the Pediatric HIV PCR Testing Service was then sent to the physicians, and they completed the medical-record-abstraction form, which provided data on the timing of perinatal zidovudine prophylaxis and other information of interest. The 40 hospitals that supplied data for the study are listed in the Appendix.

Statistical Analysis

Bivariate analyses were conducted with data from both the full study cohort and the validation sample to examine the rates of HIV transmission according to the time of initiation of zidovudine therapy. The relative risks (with 95 percent confidence intervals) of a positive PCR test according to the timing of zidovudine therapy were examined with the Mantel-Haenszel procedure.¹⁰ Multivariate logistic-regression analysis was used to determine the predictors of a positive PCR test.^{11,12} All variables were entered into the model. All statistical analyses were conducted with SAS software.¹³

RESULTS

Characteristics of the Infants

Data on 939 HIV-exposed infants whose age was 180 days or younger at the time of their initial PCR test and whose PCR specimens were submitted between August 1, 1995, and January 31, 1997, were included in the study. Of the initial 939 infants, 504 (53.7 percent) born at 40 hospitals had their PCR specimens submitted from the hospital of birth and were included in the validation sample. The survey forms for 489 of these infants (97 percent) were completed and returned. Thirty-two infants who had a negative PCR test before the age of one month but did not have a negative test after the age of one month were excluded from further study; three pairs of twins were counted as one infant each (discordant pairs were considered infected). Thus, 454 infants were included in the final validation sample.

As shown in Table 1, the validation sample did not differ significantly from the cohort as a whole with respect to sex, race or ethnic group, region of residence, and birth weight.

Timing of Antiretroviral Prophylaxis and HIV Transmission

The relative risk of HIV transmission according to the timing of the prophylactic zidovudine regimen is shown both for the entire study cohort (Table 2) and for the validation sample (Table 3). The rate of transmission was lowest when zidovudine was initiated during the prenatal period (entire cohort, 6.1 percent; 95 percent confidence interval, 4.1 to 8.9 percent; and validation sample, 5.0 percent; 95 percent confidence interval, 2.8 to 8.2 percent) and highest when zidovudine was not administered (entire cohort, 26.6 percent; 95 percent confidence interval, 21.1 to 32.7 percent; and validation sample, 31.6 percent;

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE ENTIRE STUDY COHORT AND THE VALIDATION SAMPLE.*

CHARACTERISTIC	ENTIRE COHORT (N=939)	VALIDATION SAMPLE (N=454)
	no. (%)	
Sex		
Male	487 (51.9)	236 (52.0)
Female	452 (48.1)	218 (48.0)
Race or ethnic group†		
White	98 (10.5)	43 (9.6)
Black	546 (58.3)	254 (56.8)
Hispanic	254 (27.1)	136 (30.4)
Other	39 (4.2)	14 (3.1)
Region of residence‡		
New York City	646 (74.9)	341 (75.1)
Rest of state	216 (25.1)	113 (24.9)
Birth weight§		
≥2500 g	576 (70.2)	324 (73.8)
<2500 g	245 (29.8)	115 (26.2)

*Because of rounding not all percentages total 100.

†Data were missing for two infants in the entire cohort and seven infants in the validation sample.

‡Data were missing for 77 infants in the entire cohort.

§Data were missing for 118 infants in the entire cohort and 15 infants in the validation sample.

95 percent confidence interval, 22.4 to 41.9 percent). Intermediate levels of transmission were observed when zidovudine prophylaxis was initiated either in the intrapartum period (entire cohort, 10.0 percent; 95 percent confidence interval, 3.3 to 21.8 percent; and validation sample, 5.3 percent; 95 percent confidence interval, 0.1 to 26.0 percent) or within the first 48 hours after birth (entire cohort, 9.3 percent;

95 percent confidence interval, 4.1 to 17.5 percent; and validation sample, 9.5 percent; 95 percent confidence interval, 1.2 to 30.4 percent). Among the infants who were exposed to zidovudine, the rate of transmission was highest when zidovudine was delayed until the infants were three days of age or older (entire cohort, 18.4 percent; 95 percent confidence interval, 7.7 to 34.3 percent; and validation sample, 25.0 percent; 95 percent confidence interval, 7.3 to 52.4 percent).

Initiating zidovudine prophylaxis in the intrapartum period was associated with a lower relative risk of transmission than was the use of no zidovudine therapy (entire cohort, 0.38; 95 percent confidence interval, 0.18 to 0.81; and validation sample, 0.17; 95 percent confidence interval, 0.04 to 0.75). The initiation of zidovudine prophylaxis within the first 48 hours of life was also associated with a lower risk of transmission than was the use of no zidovudine prophylaxis (entire cohort, 0.35; 95 percent confidence interval, 0.19 to 0.65; and validation sample, 0.30; 95 percent confidence interval, 0.10 to 0.96). A similar reduction in risk was seen with the initiation of zidovudine prophylaxis in the prenatal period (entire cohort, 0.23; 95 percent confidence interval, 0.16 to 0.34; and validation sample, 0.16; 95 percent confidence interval, 0.09 to 0.27).

Multivariate Analysis

We used multivariate logistic-regression analysis (Table 4) to determine the risk of HIV transmission in the validation sample according to the zidovudine regimen used, after adjustment for five variables: the infant's sex, race or ethnic group, age at the time of the first PCR test, and birth weight and the timing of the initiation of zidovudine prophylaxis. The initiation of zidovudine prophylaxis during the prenatal

TABLE 2. TIMING OF ZIDOVUDINE PROPHYLAXIS AND THE RISK OF A POSITIVE PCR TEST IN THE ENTIRE STUDY COHORT.*

TIME OF INITIATION OF ZIDOVUDINE PROPHYLAXIS	NO. OF INFANTS (%)	POSITIVE PCR TEST		RELATIVE RISK (95% CI)
		NO. (%)	95% CI	
Prenatal	423 (45.1)	26 (6.1)	4.1–8.9	0.23 (0.16–0.34)†
Intra partum	50 (5.3)	5 (10.0)	3.3–21.8	0.38 (0.18–0.81)†
Within 48 hr after birth	86 (9.2)	8 (9.3)	4.1–17.5	0.35 (0.19–0.65)†
≥3 Days after birth (up to 42 days)	38 (4.0)	7 (18.4)	7.7–34.3	0.69 (0.35–1.36)
No zidovudine prophylaxis	237 (25.2)	63 (26.6)	21.1–32.7	1.00‡
Unknown	105 (11.2)	12 (11.4)	6.0–19.1	NA
Total	939 (100)	121 (12.9)	10.8–15.2	

*CI denotes confidence interval, and NA not applicable.

†P<0.05 for the comparison with the reference group (no zidovudine prophylaxis).

‡The group with no zidovudine prophylaxis served as the reference group.

TABLE 3. TIMING OF ZIDOVUDINE PROPHYLAXIS AND THE RISK OF A POSITIVE PCR TEST IN THE VALIDATION SAMPLE.*

TIME OF INITIATION OF ZIDOVUDINE PROPHYLAXIS	NO. OF INFANTS (%)	POSITIVE PCR TEST		RELATIVE RISK (95% CI)
		NO. (%)	95% CI	
Prenatal†	280 (61.7)	14 (5.0)	2.8–8.2	0.16 (0.09–0.27)‡
Intra partum§	19 (4.2)	1 (5.3)	0.1–26.0	0.17 (0.04–0.75)‡
Within 48 hr after birth	21 (4.6)	2 (9.5)	1.2–30.4	0.30 (0.10–0.96)‡
≥3 Days after birth (up to 42 days)	16 (3.5)	4 (25.0)	7.3–52.4	0.79 (0.33–1.89)
No zidovudine prophylaxis	95 (20.9)	30 (31.6)	22.4–41.9	1.00¶
Unknown	23 (5.1)	3 (13.0)	2.8–33.6	NA
Total	454 (100)	54 (11.9)	9.1–15.2	

*During the prenatal period, 276 of 280 infants (98.6 percent) received zidovudine. Nine infants (3.2 percent) received a second antiretroviral drug. In the case of four infants (1.4 percent), the name of the antiretroviral drug was unknown. During the intrapartum period, 274 of 280 infants (97.9 percent) received zidovudine. All 19 infants in the intrapartum group, who had received no antiretroviral drug prenatally, received zidovudine. Three infants (1.1 percent) received a second antiretroviral drug, and one received a third antiretroviral drug. In the case of six infants (2.1 percent), the name of the antiretroviral drug was unknown. During the newborn period, 340 of 343 infants (99.1 percent) received zidovudine. One infant (0.3 percent) received a second antiretroviral drug. In the case of two infants (0.6 percent), the name of the antiretroviral drug was unknown. CI denotes confidence interval, and NA not applicable.

†A total of 253 of the 280 infants (90.4 percent) received prophylaxis during all three periods, 3 infants (1.1 percent) received zidovudine during the prenatal and intrapartum periods only, 12 infants (4.3 percent) received zidovudine during the prenatal and newborn periods only, and 12 infants (4.3 percent) had missing information on the intrapartum or newborn period. Removal of these 27 infants from the analysis did not significantly change the results.

‡ $P < 0.05$ for the comparison with the reference group (no zidovudine prophylaxis).

§Seventeen of the 19 infants (89.5 percent) received zidovudine prophylaxis during both the intrapartum and newborn periods, 1 infant (5.3 percent) received zidovudine during the intrapartum period only, and 1 infant (5.3 percent) had missing information on the newborn period. Removal of these two infants from the analysis did not significantly change the results.

¶The group with no zidovudine prophylaxis served as the reference group.

period, the intrapartum period, and the first 48 hours of life (as compared with the use of no zidovudine prophylaxis) remained significantly associated with a reduction in the risk of HIV transmission after adjustment for these factors. The risk of transmission when zidovudine prophylaxis was initiated when the infant was three days of age or older was not significantly different from that when no zidovudine prophylaxis was given.

DISCUSSION

The Protocol 076 study reported a 67.5 percent reduction in the relative risk of perinatal HIV transmission (from 25.5 percent to 8.3 percent) among newborns who were treated with zidovudine before, during, and after birth.¹ Our study yielded similar results, with transmission rates of 6.1 percent in the entire cohort and 5.0 percent in the validation sample when zidovudine prophylaxis was initiated during the prenatal period, as compared with rates of 26.6 percent and 31.6 percent, respectively, in the absence of zidovudine prophylaxis. Other studies have reported similar declines in the rates of perinatal HIV transmission since the widespread use of the three-part prophylactic zidovudine regimen has become a standard of care. The rate of perinatal transmission of HIV in a cohort of infants in North Carolina de-

clined from 21 percent in 1993 to 6.2 percent in the first half of 1996.¹⁴ A multicenter study of the natural history of HIV infection in the United States reported that the transmission rate was 19 percent before March 1, 1994, and thereafter decreased to 8 percent, coinciding with an increase in the use of zidovudine.¹⁵

We also found that the partial use of the Protocol 076 regimen was associated with reduced rates of perinatal HIV transmission. The rates were only 10.0 percent in the entire cohort and 5.3 percent in the validation sample when zidovudine was initiated in the intrapartum period, and 9.3 percent and 9.5 percent, respectively, when zidovudine was initiated within the first 48 hours of life. When the initiation of zidovudine prophylaxis was delayed until the infant was three days of age or older, the transmission rate was not significantly different from that associated with the absence of zidovudine prophylaxis.

A reduction in the rate of perinatal transmission could result from the use of only part of the Protocol 076 regimen for a number of reasons. Initiating zidovudine prophylaxis in the intrapartum or neonatal period may amount to the use of postexposure prophylaxis for newborns who are not infected with HIV in utero. The potential efficacy of postexposure prophylaxis has been demonstrated in several studies in animals. Oral administration of zidovudine at the time

TABLE 4. MULTIVARIATE LOGISTIC-REGRESSION ANALYSIS OF THE PREDICTORS OF A POSITIVE PCR TEST IN THE VALIDATION SAMPLE.*

CATEGORY	ADJUSTED ODDS RATIO (95% CI)†
Sex	
Male	1.0‡
Female	1.5 (0.8–3.1)
Race or ethnic group	
White	1.0‡
Black	1.0 (0.3–4.9)
Hispanic	1.5 (0.4–7.5)
Other	1.8 (0.3–13.4)
Age at time of initial PCR test	
0–31 days	1.0‡
32–60 days	0.9 (0.4–2.1)
61–120 days	1.1 (0.4–3.0)
121–180 days	5.5 (1.6–17.9)
Birth weight	
≥2500 g	1.0‡
<2500 g	2.3 (1.2–4.6)
Time of initiation of zidovudine prophylaxis	
Prenatal	0.1 (0.1–0.3)
Intra partum	0.2 (0.0–0.9)
Within 48 hr after birth	0.2 (0.0–0.7)
≥3 Days after birth (up to 42 days)	0.9 (0.2–2.9)
No zidovudine prophylaxis	1.0‡

*Forty infants with missing data on one or more variables were excluded from the analysis.

†CI denotes confidence interval.

‡This is the reference group.

of inoculation with simian immunodeficiency virus (SIV) prevented infection in a newborn macaque.¹⁶ Administration of the antiviral agent (R)-9-(2-phosphonylmethoxypropyl)adenine 48 hours before, 4 hours after, or 24 hours after inoculation with SIV prevented infection in macaques, whereas all control monkeys were infected.¹⁷ In another study, treatment with the antiviral agent 2,3,-dideoxy-3'-hydroxymethylcytidine for as few as three days after inoculation with SIV or HIV type 2 was protective in macaques.¹⁸ Similarly, postexposure prophylaxis for health care workers after occupational exposure to HIV through needle-stick injuries is associated with a 79 percent reduction (95 percent confidence interval, 43 to 94 percent) in the risk of seroconversion.¹⁹ The significant reduction in the risk of HIV transmission in our study when zidovudine was initiated in the intrapartum period or within 48 hours after birth is consistent with these findings.

A decrease in the risk of transmission with abbreviated zidovudine prophylaxis was found in a retrospective epidemiologic study in North Carolina.¹⁴ In this study, 6 of 188 HIV-exposed newborns (3 percent) were found to be infected after zidovudine pro-

phylaxis was administered in the antenatal, intrapartum, and neonatal periods. When only intrapartum and neonatal prophylaxis was used, 1 of 16 infants (6 percent) became infected, a rate that is similar to the transmission rates of 5.0 percent and 5.3 percent in our study when zidovudine was initiated in the prenatal and intrapartum periods, respectively. In the North Carolina study, in contrast to our study, however, the transmission rate was 22.9 percent when no zidovudine was administered to the mother during pregnancy, whether or not the infant received zidovudine after birth. However, the study did not differentiate between treatments that were begun within 48 hours after birth and those that were begun later, as we did.

Finally, our results are consistent with the findings of a placebo-controlled trial in Thailand in which HIV-infected pregnant women received oral zidovudine beginning at 36 weeks of gestation and continuing through labor.⁸ This regimen resulted in a 51 percent decrease in the risk of transmission (9.2 percent in the treatment group, as compared with 18.6 percent in the placebo group).

Our study has a number of limitations. First, it is limited by its observational nature and by the small number of infants in the validation sample in whom zidovudine prophylaxis was initiated in the intrapartum period (19 patients) or the neonatal period (21 patients). This small number accounts for the wide confidence intervals around the transmission rates and relative risks in the two groups. These findings should be confirmed in studies of larger cohorts of infants. In addition, information on the precise dates on which zidovudine prophylaxis was initiated during pregnancy and on compliance with the zidovudine regimen was not available. For logistical ease, the validation sample was limited to infants whose PCR specimens were submitted for testing from the hospital in which they were born, although this selection criteria would not be expected to bias the results. Despite these shortcomings, the strikingly similar findings evident in both groups support our overall conclusions.

The Public Health Service issued guidelines in 1994 recommending a three-part regimen of zidovudine monotherapy to reduce the risk of perinatal transmission of HIV.² Additional information on the pathogenesis and treatment of HIV infection resulted in the publication of new guidelines in 1998.³ The new guidelines acknowledge that zidovudine monotherapy is not the optimal therapy for the HIV-infected pregnant woman and recommend that the initiation of combination therapy (including zidovudine) during pregnancy, both to treat the woman's disease and to prevent perinatal HIV transmission, should be carefully considered.

Our findings have several potentially important public health implications. If perinatal HIV transmission can be reduced, even if zidovudine prophylaxis

is begun in the intrapartum period or immediately after birth, there would be greater impetus to initiate zidovudine therapy in newborns whose mothers did not take zidovudine during pregnancy. Our data reinforce current recommendations of the Public Health Service that zidovudine prophylaxis should be offered intra partum to infected women who are pregnant even if they have not received zidovudine during pregnancy or before the onset of labor.⁴ Our findings also suggest that even if the identification of seropositivity for HIV is delayed in pregnant women, including women who did not receive prenatal care, some benefit may be gained by the late initiation of zidovudine prophylaxis. With the use of rapid HIV testing,²⁰ such women could be identified during delivery or within 48 hours post partum, and treatment with zidovudine could be initiated for the women and their infants. However, our findings do not diminish the importance of the administration of all three parts of the prophylactic regimen of zidovudine, an approach that has the greatest potential to reduce perinatal transmission.

To reduce perinatal HIV transmission to the greatest extent possible, a combination of efforts is needed to ensure that all pregnant women receive HIV counseling and are tested for HIV and, if positive, receive prophylaxis with zidovudine, alone or in combination with other antiretroviral agents. These efforts should be supplemented to ensure that women who do not receive zidovudine during pregnancy are identified so that they can receive antiretroviral prophylaxis during delivery and their infants can begin receiving zidovudine soon after birth.

Presented in preliminary form at the Fifth Conference on Retroviruses and Opportunistic Infections, Chicago, February 2–6, 1998.

We are indebted to Dale L. Morse, M.D., M.S., and Lynne M. Mofenson, M.D., for reviewing the manuscript; to Mary Ellen Mancinelli for assistance with the preparation of the manuscript; and to the staff members of the 40 hospitals listed in the Appendix who provided data for this study.

APPENDIX

The following persons and facilities in New York participated in the study: Beth Israel Medical Center (D. Ranieri), Bronx Lebanon Hospital Center (M. Crane), Brookdale Hospital Medical Center (S. Naqvi), Brooklyn Hospital Center (B. Doraiswamy), Catholic Medical Center of Brooklyn and Queens (M. Srivastava), Children's Hospital of Buffalo (B. Sullivan), Children's Medical Center—State University of New York Health Science Center at Brooklyn (N. Desai), Children's Hospital at Albany Medical Center (M. Lepow), Children's Hospital at University of Rochester (B. Murante), Coney Island Hospital (J. Watman), Cornell University Medical Center (J. Cervia), Elmhurst Hospital Center (R. Moran), Good Samaritan Hospital Medical Center (P. Mehta), Harlem Hospital Center (E. Abrams), Interfaith Medical Center (S. Choudhury), Jacobi Medical Center (M. Lugovoy), Jones Memorial Hospital (F. Miller), Lincoln Medical and Mental Health Center (S. Rao), Long Island College Hospital (B. Jackson), Lutheran Medical Center (L. Thompson), Maimonides Medical Center (A. Hakim), Mount Sinai Medical Center (D. Hodes), Mount Vernon Hospital (L. Se-

mel), Nassau County Medical Center (H. Balbi), New York Medical College—Metropolitan Hospital Center (M. Bamji), New York Medical College—Westchester County Medical Center (K. Li), North Central Bronx Hospital, North Shore University Hospital (G. Levine), Nyack Hospital (N. Neu), Queens Hospital Center (M. Schwartz), Saint Luke's—Roosevelt Hospital Center (S. Arpadi), Saint Peter's Family Health Center (K. Manjunath), Saint Vincent's Hospital and Medical Center of New York (S. Grubman), Saint Vincent's Medical Center of Richmond (D. Di John), Schneider Children's Hospital (S. Schuval), State University of New York Health Science Center at Stony Brook (S. Nachman), State University of New York Health Science Center at Syracuse (C. Cunningham), Staten Island University Hospital (R. Davison), Union Hospital of the Bronx (L. Lezcano), and Woodhull Medical and Mental Health Center (S. Ledlie).

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