

GROUP B STREPTOCOCCAL DISEASE IN THE ERA OF INTRAPARTUM ANTIBIOTIC PROPHYLAXIS

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ABSTRACT

Background Group B streptococcal infections are a leading cause of neonatal mortality, and they also affect pregnant women and the elderly. Many cases of the disease in newborns can be prevented by the administration of prophylactic intrapartum antibiotics. In the 1990s, prevention efforts increased. In 1996, consensus guidelines recommended use of either a risk-based or a screening-based approach to identify candidates for intrapartum antibiotics. To assess the effects of the preventive efforts, we analyzed trends in the incidence of group B streptococcal disease from 1993 to 1998.

Methods Active, population-based surveillance was conducted in selected counties of eight states. A case was defined by the isolation of group B streptococci from a normally sterile site. Census and live-birth data were used to calculate the race-specific incidence of disease; national projections were adjusted for race.

Results Disease in infants less than seven days old accounted for 20 percent of all 7867 group B streptococcal infections. The incidence of early-onset neonatal infections decreased by 65 percent, from 1.7 per 1000 live births in 1993 to 0.6 per 1000 in 1998. The excess incidence of early-onset disease in black infants, as compared with white infants, decreased by 75 percent. Projecting our findings to the entire United States, we estimate that 3900 early-onset infections and 200 neonatal deaths were prevented in 1998 by the use of intrapartum antibiotics. Among pregnant girls and women, the incidence of invasive group B streptococcal disease declined by 21 percent. The incidence among nonpregnant adults did not decline.

Conclusions Over a six-year period, there has been a substantial decline in the incidence of group B streptococcal disease in newborns, including a major reduction in the excess incidence of these infections in black infants. These improvements coincide with the efforts to prevent perinatal disease by the wider use of prophylactic intrapartum antibiotics. (N Engl J Med 2000;342:15-20.)

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INVASIVE group B streptococcal disease emerged in the 1970s as a leading cause of neonatal morbidity and mortality in the United States.¹⁻⁴ In the 1990s, 4 to 6 percent of affected newborns died from the infection.^{5,6} Surviving infants often have developmental disabilities, including mental retardation and hearing or vision loss. The incidence of group B streptococcal disease is also high among pregnant women and the elderly.⁷

Clinical trials in the mid-1980s demonstrated that antibiotic prophylaxis administered during labor to mothers colonized with group B streptococci was highly effective in preventing disease in newborns.⁸ However, the medical community was slow to incorporate intrapartum prophylaxis into routine practice. In 1989 the Centers for Disease Control (CDC) established active multistate surveillance for group B streptococcal disease. In the early 1990s, the cost effectiveness of alternative prevention strategies was evaluated,⁹⁻¹² and a national advocacy group was formed by parents of infants with group B streptococcal disease (Group B Strep Association, which can be contacted on the Internet at www.groupbstrep.org). In 1996 consensus guidelines for the prevention of perinatal group B streptococcal disease were issued by the American Academy of Pediatrics,¹³ the American College of Obstetricians and Gynecologists,¹⁴ and the CDC.¹⁵ These guidelines recommend the use of a risk-based or screening-based approach to identify candidates for intrapartum prophylaxis. According to the risk-based approach, women who present at the time of labor with risk factors for disease transmission (fever, prolonged rupture of the membranes, or imminent preterm delivery) are offered intrapartum chemoprophylaxis. According to the screening-based approach, all women are screened for carriage of group B streptococci between 35 and 37 weeks of gestation, and intrapartum chemoprophylaxis is offered to carriers.

We analyzed data from a program of active surveillance for invasive group B streptococcal disease in selected areas of the United States to determine how efforts at prevention affected the incidence of disease from 1993 to 1998. This surveillance system, which was designed to identify all cases of invasive disease in a population ranging from 12 million (in 1993) to more than 20 million (in 1998), provides data on national trends in the incidence of invasive group B

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The members of the surveillance team are listed in the Appendix.

streptococcal disease in the era of perinatal disease prevention.

METHODS

Active, laboratory-based surveillance for invasive group B streptococcal infection from 1993 to 1998 was conducted by previously described methods.⁵ Project personnel communicated at least twice a month with contacts in all participating microbiology laboratories serving acute care hospitals in the following areas: Maryland, all counties from 1993; California, 3 counties (Alameda, Contra Costa, and San Francisco) from 1993; Georgia, 8 counties (Cobb, Clayton, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale) from 1993, and 12 additional counties in the Atlanta area from 1997; Tennessee, 4 counties (Davidson, Hamilton, Knox, and Shelby) from 1993, and Williamson County from 1995; Connecticut, all counties from 1995; Minnesota, 7 counties (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington) from 1995; Oregon, 3 counties (Clackamas, Multnomah, and Washington) from 1995; and New York, 7 counties (Genesee, Livingston, Monroe, Ontario, Orleans, Wayne, and Yates) from 1997.

A case was defined by the isolation of group B streptococci from a normally sterile site (e.g., blood or cerebrospinal fluid) in a resident within a surveillance area; cases identified on the basis of isolation of group B streptococci from amniotic fluid, placenta, or urine alone were not included. Periodic audits were conducted in each area. Any cases newly identified by audits were included in the surveillance data base.

We defined early-onset neonatal disease as that occurring in infants less than 7 days old, late-onset disease as that occurring in infants 7 to 89 days old, childhood disease as that occurring in children from 90 days to 14 years old, and adult disease as that occurring in persons 15 years of age or older.⁵ Pregnant girls and women, including those under 14 years of age, were analyzed as a separate category from nonpregnant adults and children. Because the samples were small after stratification according to race, we reduced this variable to three categories — black, white, and other — on the basis of previous observations that invasive group B streptococcal disease is more common among blacks than in other groups.⁵ The racial distribution in the population under surveillance ranged from 24 percent black and 69 percent white in 1993 to 19 percent black and 75 percent white in 1997. Data on ethnic background were available for 61 percent of the patients with group B streptococcal disease. Of these, 367 (8 percent) were Hispanic, 56 percent of whom identified themselves as white Hispanics.

To describe epidemiologic characteristics of persons with invasive disease, we analyzed data from all participating surveillance areas between 1993 and 1998. However, we limited our analysis of changes in the incidence of disease over time to sites where surveillance data were available for the entire period (1993 through 1998 in Georgia, California, Maryland, and Tennessee). To place the trends from 1993 to 1998 in a broader context, in Figure 1 we show data from 1990 to 1998 for the three surveillance areas (California, Georgia, and Tennessee) where continuous data were available. Estimates of age- and race-specific incidence for these surveillance areas were calculated by using population data from the U.S. Bureau of the Census and data on live births from the National Center for Health Statistics. For 1998, live-birth figures for the year 1997, obtained directly from the state health departments and Census data, were used as denominators.

National estimates of the incidence of group B streptococcal disease were calculated by multiplying age- and race-specific incidence in the aggregate surveillance areas by the appropriate live-birth and population figures for the United States. When calculating the incidence of disease and projecting it to the total U.S. population, we assigned patients of unknown race to one of the three categories (white, black, and other) on the basis of the proportion of known cases occurring in each racial group. Changes in incidence over time were analyzed by Poisson regression with the PROC GENMOD procedure (SAS, version 6.12, SAS, Cary, N.C.). Ninety-five percent confidence intervals are reported throughout.

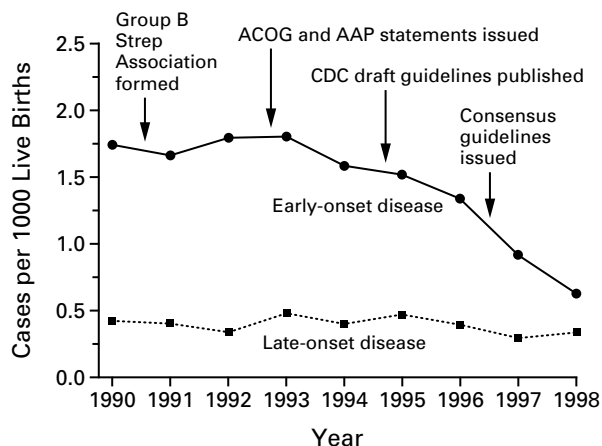


Figure 1. Incidence of Early- and Late-Onset Invasive Group B Streptococcal Disease in Three Active Surveillance Areas (California, Georgia, and Tennessee), 1990 through 1998, and Activities for the Prevention of Group B Streptococcal Disease.

Live births for 1998 were approximated on the basis of 1997 data. Arrows designate the dates when prevention activities occurred. ACOG denotes the American College of Obstetricians and Gynecologists, and AAP the American Academy of Pediatrics.

RESULTS

From 1993 through 1998, the active surveillance system identified 7867 cases of invasive group B streptococcal disease in the surveillance areas. Eighty-four percent of isolates were obtained from blood, 4 percent from cerebrospinal fluid, 4 percent from synovial fluid, and the remainder from the following normally sterile sites: bone (2 percent), peritoneal fluid (2 percent), surgical specimens (2 percent), pleural fluid (1 percent), and other sites (1 percent).

Of the cases that were identified, 2196 (28 percent) occurred in infants less than three months old. The majority of neonatal cases (1584 of 2196, or 72 percent) presented as early-onset neonatal disease and were identified on the day of birth (1140 of 1584, or 72 percent of early-onset cases). The percentage of early-onset cases identified on the day of birth declined from 76 percent in 1993 to 71 percent in 1998, but this decline was not statistically significant (χ^2 for linear trend = 1.7, $P = 0.19$). Early-onset neonatal disease presented primarily as bacteremia (80 percent), meningitis (6 percent), or pneumonia (7 percent). The case fatality rate associated with each of these presentations was 4 percent. Preterm infants (those with a gestational age of less than 37 weeks) who had early-onset disease had a higher risk of dying than did term infants with similar disease (relative risk, 6.7; 95 percent confidence interval, 4.5 to 10.0) (Table 1).

Late-onset disease presented primarily as bacteremia (63 percent), meningitis (24 percent), or pneumonia (2 percent). Late-onset disease was more likely than early-onset disease to present as meningitis (rel-

TABLE 1. NUMBER OF CASES OF EARLY-ONSET NEONATAL INVASIVE GROUP B STREPTOCOCCAL DISEASE AND CASE FATALITY RATES ACCORDING TO GESTATIONAL AGE IN SELECTED COUNTIES IN THE UNITED STATES, 1993 TO 1998.

GESTATIONAL AGE	NO. (% OF EARLY-ONSET CASES)	CASE FATALITY RATE (%)*
≤33 wk	137 (9)	30
34–36 wk	116 (7)	10
≥37 wk	1247 (83)	2

*Data on both gestational age and outcome were available for 1500 of 1584 of infants with early-onset disease (95 percent).

TABLE 2. NUMBER OF CASES OF INVASIVE GROUP B STREPTOCOCCAL DISEASE AND CASE FATALITY RATES ACCORDING TO AGE AT DISEASE ONSET IN SELECTED COUNTIES IN THE UNITED STATES, 1993 THROUGH 1998.

AGE AT ONSET	NO. (% OF TOTAL CASES)	CASE FATALITY RATE (%)*
Neonatal disease		
0–6 days	1584 (20)	4.7
7–89 days	612 (8)	2.8
Childhood disease		
90 days–14 yr and not pregnant	175 (2)	9.0
Adult disease		
15–64 yr and not pregnant	2559 (33)	8.0
≥65 yr	2559 (33)	15.0
Pregnant girls and women	345 (4)	0.003

*Information on disease outcome was available for 7636 of 7834 cases (97 percent) for which data on age were also available.

ative risk, 4.3; 95 percent confidence interval, 3.4 to 5.5; $P < 0.001$). The overall case fatality rate for late-onset disease was 2.8 percent (Table 2), which was only marginally lower than that for early-onset disease (χ^2 with Yates' correction = 3.51, $P = 0.06$).

Changes in the Incidence of Disease in Young Infants

The incidence of early-onset neonatal disease remained fairly stable between 1990 and 1993 and then declined from 1993 to 1998 (Fig. 1). A steep decline coincided with the release of the consensus guidelines in 1996 (Fig. 1). In the four areas with continuous active surveillance, the incidence of early-onset disease declined by 65 percent, from 1.7 per 1000 live births in 1993 to 0.6 per 1000 live births in 1998 (slope = -0.19, $\chi^2 = 121.0$, $P < 0.001$). In California and Maryland, the largest decline in incidence (28 percent and 34 percent, respectively) in a one-year period occurred between 1993 and 1994, whereas in

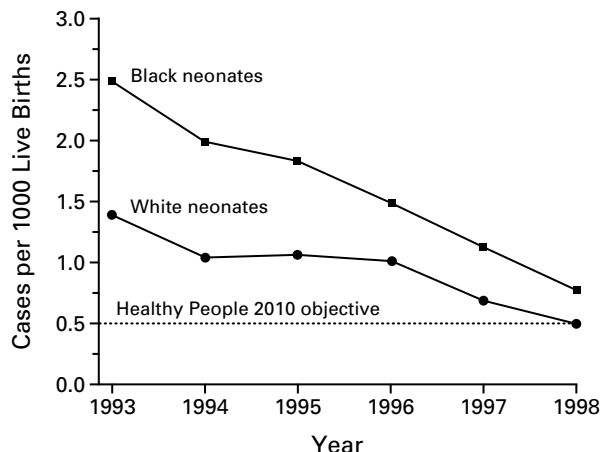


Figure 2. Incidence of Early-Onset Invasive Group B Streptococcal Disease in Black Neonates and White Neonates in Four Active Surveillance Areas (California, Georgia, Tennessee, and Maryland), 1993 through 1998.

The Healthy People 2010 objectives, released by the U.S. Department of Health and Human Services, constitute a national prevention strategy for substantially improving the health of people in the United States.¹⁶ Live births for 1998 were approximated on the basis of 1997 data.

Tennessee the largest decline (45 percent) occurred between 1997 and 1998.

The incidence of early-onset disease declined more steeply among black neonates than among white neonates during this period, and the difference between blacks and whites in the incidence of early-onset disease was reduced by 75 percent (Fig. 2). In 1998 the rate of early-onset disease in both black neonates (0.8 per 1000 live births) and white neonates (0.5 per 1000 live births) already approached the Healthy People 2010 objective¹⁶ of a reduction in the incidence of early-onset disease to 0.5 case per 1000 live births for all races (Fig. 2).

The overall rate of late-onset disease, in contrast, changed little between 1990 and 1998 (Fig. 1). Between 1993 and 1998, there was a downward trend in the incidence of late-onset disease that was marginally significant by Poisson regression (slope = -0.05, $\chi^2 = 3.3$, $P = 0.07$). In Georgia the rate of late-onset disease increased from 0.34 per 1000 live births in 1997 to 0.52 per 1000 live births in 1998, whereas in other sites there were declines in the rate of late-onset disease between 1997 and 1998.

Childhood and Adult Disease

We identified 175 culture-confirmed cases among children 90 days to 14 years old. Although childhood disease represented a much smaller percentage of the disease burden than did neonatal disease (Table 2), patients from 90 days to 14 years of age were roughly twice as likely to die from group B streptococcal disease as newborns with early-onset disease (relative risk,

1.9; 95 percent confidence interval, 1.1 to 3.2; $P=0.02$). Two thirds (116 of 175, or 66 percent) of the cases among children 90 days to 14 years old occurred in those less than 1 year of age, with 54 percent (94 of 175) in children less than 6 months of age.

Of the 5118 cases among nonpregnant adults, the majority (53 percent) presented with bacteremia, although adults presented with a wider variety of syndromes than did neonates. Rare manifestations (fewer than 30 cases during the surveillance period) included abscess (28 cases), necrotizing fasciitis (14 cases), pericarditis (9 cases), and epiglottitis (2 cases). Only 2 percent of adults with disease presented with meningitis.

The incidence of invasive disease in pregnant girls and women declined significantly, from 0.29 per 1000 live births in 1993 to 0.23 per 1000 live births in 1998 (slope = -0.08 , $\chi^2=4.86$, $P<0.03$). The data from these patients were not sufficiently detailed to determine the proportion of cases occurring during labor or after delivery. Among pregnant girls and women (345 cases), bacteremia was again the primary manifestation, accounting for 64 percent of cases. Bacteremic chorioamnionitis and endometritis each occurred in 10 percent of cases (35 of 345), and septic abortion accounted for 7 percent of cases (23 of 345). From 1993 to 1998, group B streptococcal disease among pregnant girls and women represented 6.3 percent of all adult cases of invasive disease (345 of 5463). Among those for whom the outcome of pregnancy was known (281 of 345, or 81 percent of pregnant girls and women with disease), 54 percent had infants who did not have clinical illness, 17 percent had infants who had clinical illness but survived, and 29 percent had spontaneous abortions, stillborn infants, or infants who died of the infection.

The case fatality rate associated with adult disease was significantly higher than that associated with neonatal disease (12 percent vs. 4 percent; relative risk, 2.5; 95 percent confidence interval, 2.0 to 3.1; $P<0.001$). Moreover, adults 65 years of age or older were at higher risk of dying from group B streptococcal disease than adolescents and adults 15 to 64 years of age (15 percent vs. 8 percent; relative risk, 1.9; 95 percent confidence interval, 1.7 to 2.4; $P<0.001$) (Table 2). Adults with meningitis were also more likely to die than adults with other clinical syndromes (28 percent vs. 12 percent; relative risk, 2.1; 95 percent confidence interval, 1.4 to 3.2; $P=0.003$). During the six-year study period, one pregnant woman died of invasive group B streptococcal disease.

For the surveillance areas in which underlying conditions associated with invasive disease were recorded (California starting in 1994 and Connecticut, New York, and Oregon starting in 1997), information on the presence of underlying conditions was available for 63 percent of adults with invasive disease (1164 of 1854). The majority (70 percent) of these adults had

TABLE 3. PROJECTED CASES OF INVASIVE GROUP B STREPTOCOCCAL DISEASE IN THE UNITED STATES AS A WHOLE, 1998.

AGE GROUP	INCIDENCE*	PROJECTED NO. OF CASES (% OF TOTAL CASES)†	PROJECTED NO. OF DEATHS‡
0–6 days	0.6/1000	2,200 (13)	100
7–89 days	0.4/1000	1,400 (8)	40
1–14 yr	0.2/100,000	80 (0.5)	10
15–64 yr	3.6/100,000	6,300 (37)	500
≥65 yr	20.1/100,000	6,900 (41)	1000
Total		16,880	1650

*The projected incidence among neonates is reported per 1000 live births; the projected incidence among children and adults is reported per 100,000 population.

†Projections were adjusted for age and race on the basis of surveillance data from selected counties in eight states.

‡The projected number of deaths is based on the case fatality rates in Table 2.

at least one of the following underlying conditions: diabetes mellitus (37 percent), cardiovascular disease (23 percent), nonhematologic cancer (19 percent), congestive heart failure (15 percent), alcoholism (11 percent), and cirrhosis (8 percent).

The rates of adult disease fluctuated during the six-year period but showed no evidence of a decline. Moreover, in contrast to early-onset disease, the rate of adult disease in blacks did not decline from 1993 to 1998 (slope = -0.004 , $\chi^2=0.06$, $P=0.80$); in 1998 the risk of invasive disease among black adults at least 15 years of age remained twice that among white adults (relative risk, 2.0; 95 percent confidence interval, 1.7 to 2.3; $P<0.001$).

Projections to the U.S. Population in 1998

On the basis of data from all surveillance areas in 1998, the projected number of cases of invasive group B streptococcal disease in the United States according to the age at disease onset is shown in Table 3. For those 15 years of age or over, the gap in incidence between blacks and whites remains large (data not shown).

Using surveillance data from 1993 to project incidence to the United States as a whole, we estimated a base-line number of 6100 cases of early-onset disease annually before active prevention efforts began. We thus estimate that in 1998, 3900 early-onset neonatal cases and 200 neonatal deaths were prevented in the United States by the intrapartum use of antibiotic prophylaxis.

DISCUSSION

The incidence of early-onset neonatal group B streptococcal disease declined by a striking 65 percent from 1993 to 1998 within our surveillance areas. Ev-

idence of a decline in some surveillance areas was first apparent in 1994 and 1995⁶ and can be documented in all four areas of continuous surveillance by 1997. This decline was due in part to a large decrease in the incidence of early-onset disease in black neonates from 1993 to 1998. The gap between black and white infants in the incidence of early-onset disease was reduced by 75 percent during this period. If one assumes that the rate of early-onset disease in 1998 would have remained unchanged from 1993 in the absence of active prevention measures, then nearly 4000 cases of early-onset disease were prevented in the United States in 1998.

Declining rates of early-onset neonatal disease coincide with the active public health and clinical efforts to increase the administration of prophylactic intrapartum antibiotics to mothers at risk of transmitting the disease to their newborns. Between 1994 and 1997, the proportion of hospitals with a policy for the prevention of neonatal group B streptococcal disease increased from 39 percent to 58 percent.¹⁷

It remains unclear why the rates of invasive group B streptococcal infection are higher among blacks than in other racial groups. However, implementation of prevention in this group at higher risk has effectively reduced the rate of early-onset disease among black newborns.

The potential effect of intrapartum antibiotic prophylaxis on late-onset disease has not been evaluated. In some infants, late-onset infections develop after passage through a heavily colonized birth canal, and reduction in the degree of colonization might result from the use of parenteral antibiotics during labor. However, late-onset disease has a maternal origin in only 50 percent of cases.¹⁸ We did not find evidence of a significant decline in the incidence of late-onset disease as a result of perinatal preventive efforts (Fig. 1), although there is evidence to suggest a small downward trend. It is possible that the size of the population under study in our surveillance areas was insufficient for an adequate assessment of the effect of preventive efforts on the incidence of late-onset disease.

Because pregnant women who have been colonized by group B streptococci are at increased risk for amnionitis,^{19,20} perinatal disease-prevention strategies may also reduce the incidence of disease among pregnant women. A recent study found that rates of chorioamnionitis and endometritis decreased significantly after the adoption of aggressive strategies for the prevention of group B streptococcal disease.²¹ In the areas with continuous surveillance from 1993 to 1998, the incidence of invasive disease in pregnant girls and women declined significantly.

In contrast to the decline in early-onset neonatal disease, the rate of adult disease did not decline from 1993 to 1998. The gap in the incidence of disease between black adults and white adults also remained unchanged.⁵

The epidemiologic features of adult disease during this period are similar to those described before active efforts for the prevention of neonatal disease. As observed in 1990, adults over the age of 65 remained at the highest risk of dying from invasive group B streptococcal disease.⁵ Similarly, the case fatality rate for adults with meningitis was higher than that for adults with other clinical presentations. Adults also had underlying conditions that have been previously identified as independent risk factors for invasive disease in adults.⁷

The surveillance data that we analyzed have certain limitations. Foremost is the low representation of Hispanics and members of races other than blacks and whites in our surveillance population, factors that may bias our projections of the incidence of disease in the United States as a whole. Furthermore, clinicians in surveillance areas were exposed to preventive education and surveys and thus may have had a heightened awareness of group B streptococcal disease, as compared with practitioners in other regions. In addition, the areas participating in the active-surveillance program changed during the period from 1993 to 1998, thus limiting our analyses of trends over time to four areas with continuous surveillance.

Despite these limitations, our surveillance system was able to capture laboratory-confirmed cases of invasive disease from a large, multistate population base; the resulting data provided the opportunity to characterize key clinical and epidemiologic characteristics of group B streptococcal disease in the era of perinatal disease prevention. The trends we observed suggest that preventive strategies have led to substantial declines in the incidence of early-onset disease. However, we estimate that there were still over 2000 cases of early-onset group B streptococcal disease in neonates in the United States in 1998. Assessing how many of these cases represent failures of prevention will be important in setting objectives for prevention in the future. Moreover, as the use of intrapartum antibiotic prophylaxis increases, closer surveillance for antibiotic resistance among all bacteria causing neonatal sepsis is important.²² To date, penicillin remains the first-line antibiotic for intrapartum prophylaxis, and penicillin-resistant group B streptococci have not yet been detected. However, erythromycin resistance has been found in 7.4 to 15 percent of isolates, and clindamycin resistance in 3.4 to 13 percent of isolates.^{23,24}

Development of vaccines against group B streptococci may decrease the need for antibiotic prophylaxis in the future.^{25,26} Such vaccines may also offer protection for pregnant women and for the elderly,²⁵ for whom the incidence of disease and case fatality rates remain high.²⁷

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APPENDIX

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