Impact of Maternal Influenza Vaccination During Pregnancy on the Incidence of Acute Respiratory Illness Visits Among Infants

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Objective: To determine whether influenza vaccination of pregnant women prevents visits for respiratory illness in their infants born during the influenza season.

Design: Retrospective matched cohort study.

Setting: Four managed care organizations in the United States.

Patients: A total of 41,129 infants (31,60 and 37,969 born to vaccinated and unvaccinated mothers, respectively) born between 1995 and 2001.

Main Exposure: Maternal influenza vaccination. Infants were considered exposed if their gestational age at birth was at least 30 weeks, if the time from maternal vaccination to birth was at least 28 days, and if they were exposed to at least 14 days of the influenza season.

Main Outcome Measures: Incidence of acute respiratory illnesses (outpatient, emergency department, and inpatient settings combined) and incident rate ratios (IRRs) for infants exposed and unexposed to maternal vaccination during the following 4 periods: peak influenza, respiratory syncytial virus predominant, perinatal, and summer weeks. The time to the first acute respiratory illness during peak influenza weeks was also assessed.

Results: During the peak influenza weeks, infant visit rates were 15.4 and 17.1 per 100 person-months for exposed and unexposed infants, respectively (IRR, 0.90; 95% confidence interval, 0.80-1.02). Adjusted IRRs for the 4 periods found a protective effect of infant female sex, whereas Medicaid status and maternal high-risk status increased infant visit rates. Maternal influenza vaccination did not reduce visit rates during any of the 4 time periods (IRR for peak influenza season, 0.96; 95% confidence interval, 0.86-1.07) and did not delay the onset of first respiratory illness.

Conclusion: We were unable to demonstrate that maternal influenza vaccination reduces respiratory illness visit rates among their infants.

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Beginning in 2004, the Advisory Committee on Immunization Practices has recommended universal influenza vaccination of children aged 6 to 23 months. This recommendation was based primarily on studies that found high hospitalization rates for infants attributable to influenza illness, particularly for infants younger than 6 months. Influenza vaccination of infants younger than 6 months has not succeeded owing to the poor immunogenic response elicited by vaccination in this age group, also, the immature immune system of neonates has posed a challenge to the efforts of vaccinating newborns. Tetanus immunization of women during pregnancy has been very successful in reducing the incidence of neonatal tetanus worldwide. Experts have proposed that influenza vaccination of the mother during pregnancy could protect infants during the first few months of life through transplacentally acquired antibodies or by reducing exposure to a mother with influenza infection.

To date, 2 small studies have explored the effect of maternally acquired antibodies on influenza illness in infants. Puck et al found a direct correlation between the level of cord blood antibody to influenza A and the time of culture-documented influenza A infection in 26 infants younger than 4 months: infants with high levels of antibody to influenza A had a delay in influenza illness.
enza A infection. Reuman et al\textsuperscript{12} followed up 39 families in Houston, Tex, and found no difference in the rate of influenza virus infection between infants based on levels of cord blood antibodies to influenza A (H1N1). The onset of illness from the beginning of the influenza season was significantly later for infants with high antibody levels in cord blood (27.0 vs 8.2 days), and the duration of respiratory symptoms (cough and rapid breathing) was shorter. In both of these studies, cord blood antibodies to influenza A were from naturally acquired infections in the mothers rather than from influenza vaccination during pregnancy. A third study by Englund et al\textsuperscript{13} assessed the effect of maternal influenza vaccination on infant cord blood antibodies to influenza virus and found significantly increased levels of IgG specific to influenza virus in the cord blood of infants born to vaccinated mothers compared with those born to unvaccinated mothers.

We undertook this study to determine whether infants born to mothers who received influenza vaccination during their pregnancy had lower incidence rates of medically attended acute respiratory illnesses (MAARIs) (combined outpatient, inpatient, and emergency department settings) during peak influenza weeks compared with infants born to unvaccinated mothers. A study performed in 2003 at Northern California Kaiser Permanente that assessed the effectiveness and safety of the influenza vaccine among pregnant women and their infants found no impact of the mother's vaccination on the rates of infant health care visits during the influenza season.\textsuperscript{14} Our current study expands on this work by using viral surveillance data to define peak influenza weeks, by requiring 4 weeks from vaccination to birth to ensure maternal antibody transfer, and by measuring incidence of acute respiratory illness across 4 periods (peak influenza, respiratory syncytial virus [RSV]–predominant, periseasonal, and summer weeks). We hypothesized that the incidence rate ratio (IRR) would be less than 1 (ie, protective) during peak influenza weeks, whereas the IRRs during the RSV-predominant and summer weeks would equal 1 (ie, no protective effect). Our secondary objectives were to determine whether infants born during the peak influenza weeks to vaccinated mothers had a delay in their first acute respiratory illness compared with infants born to unvaccinated mothers and to determine whether the proportion of infants with severe MAARIs (eg, pneumonia and hospitalization) differed between these 2 groups.

**METHODS**

**STUDY POPULATION**

Infants who were born before or during the influenza season at 4 managed care organizations (MCOs) (Kaiser Permanente Colorado, Denver; Kaiser Permanente Northern California, Oakland; Kaiser Permanente Northwest, Portland, Ore; and Group Health Cooperative, Seattle, Wash) between October 1, 1995, and September 30, 2001, were eligible for study inclusion. Mother-infant pairs were included in the final study population if (1) the mothers were aged 18 to 45 years and enrolled in the MCO for longer than 1 year; (2) the infants’ gestational age was at least 30 weeks at birth; (3) the infants were continuous MCO members for at least 14 days during the influenza season; and (4) the infants had at least 1 outpatient visit during the first 3 months of life. To ensure adequate maternal transfer of IgG, an infant was considered exposed if the mother was vaccinated against influenza during the pregnancy and there were at least 28 days from the vaccination date of the mother to the birth date of the infant.\textsuperscript{15} Infants of mothers vaccinated within 27 days of birth were excluded from the primary analysis. Infants born during the influenza season began contributing person-time on the day after their birth hospitalization discharge; if the date of discharge from the birth hospitalization was unavailable, person-time began after the first outpatient visit.

In comparing acute respiratory illness rates between exposed and unexposed infants, important potential confounders include age, MCO site, and season. Unexposed infants were therefore matched by birth week and MCO to exposed infants, and thus also matched for influenza season.

**HEALTH SERVICES DATA**

We used data sets created for the Vaccine Safety Datalink (VSD) Study to perform all analyses. The VSD is a large, linked database project that is funded by the Centers for Disease Control and Prevention (CDC).\textsuperscript{16} Member enrollment dates, vaccination histories, and inpatient, outpatient, and emergency department visits are included in these data sets. During the study period (1995-2001), a specific MCO site would contribute data only for those years in which reliable data were available. For example, outpatient data were available from Kaiser Permanente Northwest from 1997 through 2001. The study was approved by the institutional review boards at each of the 4 MCOs and the CDC.

Comorbid conditions in the mother were defined by the codes from the International Classification of Diseases, Ninth Revision (ICD-9) assigned to medical encounters in the year before delivery. Mothers were considered at high risk for complications of influenza if, in the year before delivery, they had an ICD-9 diagnosis code for a high-risk condition (cardiac, pulmonary, renal, or hematologic disease; diabetes or metabolic disorders; neoplasm or immunodeficiencies; or hepatic or neurological disorders). A total of 1617 ICD-9 codes across the 10 conditions were used; this list was developed for a CDC-sponsored study of the impact of influenza on adult health care services utilization (available from the authors on request). In addition to high-risk status, other maternal variables used in the analyses include influenza vaccination status (current and preceding season), age, high-risk status, and Medicaid insurance coverage. Other variables used include infant gestational age at birth, MCO site, and influenza season.

Influenza illness in young children is not often coded as influenza, per se, but as a number of illnesses that can be caused by the influenza virus (eg, upper respiratory infection, febrile illness, sepsis, and pneumonia). A visit was defined as a MAARI if any of the following ICD-9 codes were used: 460, 462, 463, 464.0, 464.10, 464.11, 464.20, 464.21, 464.4, 465.0, 465.8, 465.9, 478.9, 487.1, 487.8, 490, 078.89, 079.99, or 786.2 for viral or upper respiratory infection; 466, 480.8, 480.9, 481.0, 482.2, 482.3, 482.4, 482.41, 482.49, 484.0, 484.1, 485, 486, 487.0, or 511.9 for lower respiratory infection or pneumonia; 038 for sepsis; 780.31 or 779.0 for febrile seizure; or 780.6 for fever. To maximize power, we combined outpatient, emergency department, and inpatient visits for acute respiratory illnesses in the primary analysis.

**VIRAL SURVEILLANCE DATA AND STUDY PERIODS**

For each influenza season, peak influenza and RSV-predominant weeks were defined using viral surveillance data.
from each of the MCO sites. Influenza surveillance data for each MCO’s area were provided by the CDC and were collected as part of the World Health Organization Influenza Surveillance system. Annual RSV data were collected by the National Respiratory and Enteric Virus Surveillance System at the Respiratory Enteric Viruses Branch of the CDC. Laboratories participating in these 2 national surveillance systems are in state or local health departments, universities, and hospitals. Because the surveillance data for the Portland area were unreliable for the 1999-2001 influenza seasons, we used the Northern California Kaiser Permanente laboratory viral surveillance data to define the peak influenza and RSV-predominant seasons in the Portland area. The 1997-1999 influenza surveillance data for Northern California Kaiser Permanente have a sensitivity of 69% and a specificity of 97% in matching peak influenza weeks to the 1997-1999 influenza surveillance data for Kaiser Permanente Northwest.

For this study, we defined 4 seasonal study periods:

1. **Peak influenza weeks** as any week from October 1 to April 30 in which influenza accounted for at least 5% of the season's total number of influenza virus isolates. Other viruses such as RSV could have been circulating during these weeks.

2. **RSV-predominant weeks** as any week from October 1 to April 30 in which RSV accounted for at least 5% of the season's total number of RSV virus isolates and influenza accounted for less than 5% of the season's total influenza virus isolates.

3. **Periseasonal weeks** as any week from October 1 to April 30 in which each week accounted for less than 3% of total RSV isolates and less than 3% of influenza virus isolates.

4. **Summer weeks** as the period each year from July 1 to September 30.

**STATISTICAL ANALYSIS OF THE STUDY HYPOTHESES**

The primary hypothesis of this study was that the incidence of MAARI visits during peak influenza weeks would be lower for infants born to mothers vaccinated against influenza compared with infants born to unvaccinated mothers and that the MAARI incidence rates during the RSV-predominant and summer weeks would be equal between the exposed and unexposed groups. We estimated a priori that there would be 4500 exposed and 40 000 unexposed infants in the VSD cohort based on an observed 2% annual maternal influenza vaccination rate at Kaiser Permanente Colorado and on the pregnancy rate across the MCOs. We assessed the power of this sample size by 2 methods. First, we determined our ability to see a reduction of a rare event, pneumonia, among exposed infants. Given a background incidence of 2.4 per 100 person-months, we would have 80% power to see a 20% reduction in the incidence of visits for pneumonia. Second, we determined that 1900 exposed infants during the peak influenza weeks would be needed to detect a 20% reduction in febrile illness, a common event, based on an assumed risk of 0.11 for developing this diagnosis during an 8-week period (estimate based on Kaiser Permanente Colorado data). Planned secondary analyses included the time to first illness, limited to infants born during the peak influenza weeks, and the severity of MAARI, assessed by comparing the proportion of MAARI coded as upper respiratory infection, pneumonia, and hospitalization.

Bivariate comparisons between exposed and unexposed infants were evaluated with the 2-tailed, unpaired t (or if not normally distributed, Wilcoxon signed rank) test for continuous and discrete variables, respectively. We calculated crude IRRs of exposed to unexposed infants during the 4 study periods for MAARI outcomes in all settings while ignoring match-

Before matching, a total of 54 385 women meeting all other inclusion criteria gave birth at the 4 MCOs between October 1 and April 30 of the included study years (1995-2001). The proportion of mothers vaccinated against influenza during a given season ranged from 0.7% to 20.8% across the 4 MCOs. Diagnoses for a condition that increased maternal risk for a complication from influenza infection were present in 11.5% of mothers (range across MCOs, 9.2%–12%); almost two thirds of these were for a pulmonary condition (primarily asthma). Combined data were available from 21 site-specific influenza seasons (6 seasons from 2 sites; 5 seasons from the third site, and 4 seasons from the fourth site). There were 124 peak influenza weeks, 97 RSV-predominant weeks, 310 periseasonal weeks, and 336 summer weeks among the 4 MCOs. Only 1 of the influenza seasons (1997-1998) had a notable mismatch between circulating influenza strains and the strains used in the seasonal vaccine.

In all, 3815 infants were born to vaccinated mothers during the study period. The mean number of days between maternal influenza vaccination and birth of the infant was 68 (range, 1-172), and the mean gestational age of the infant at the time of maternal vaccination was 29.4 (range, 9.8-41.6) weeks. Six hundred fifty-five infants were exposed less than 28 days in utero and were excluded. A total of 37 969 infants born to unvaccinated mothers were matched by birth week and MCO to the 3160 infants exposed at least 28 days in utero, yielding 41 129 infants in the matched cohort (Figure).

**Table 1** compares exposed and unexposed mothers and infants across study variables. Vaccinated mothers were more likely to have a high-risk condition than were unvaccinated mothers ($P<.001$). The mean age of the exposed infants at the end of the influenza season was 65 (range, 14-177) days; of unexposed infants, 75 (range, 14-180) days. There were no meaningful differences in gestational age or birth weight between the groups. Hospital discharge dates were present in 98.4% of infants.

**Table 2** lists the crude incidence rates for acute respiratory illnesses across the 4 study periods in exposed and unexposed populations matched by infant age, MCO site, and influenza season. The IRRs across the 4 study periods were all similar: 0.90 (95% confidence interval [CI], 0.80-1.02) for the peak influenza weeks; 0.93 (93% CI, 0.84-1.02) for the RSV-predominant weeks; 1.12 (93%
CI, 0.94-1.34) for the perisessional weeks; and 1.04 (95% CI, 0.99-1.10) for the summer weeks. The MAARI incidence during the summer weeks, when the mean age of the exposed infants was 210 days, was similar to the MAARI incidence during the peak influenza weeks, when the mean age of the infants was 65 days.

Models using generalized estimating equations included the following independent variables: maternal vaccination status, infant gestational age at birth, infant sex, maternal age, Medicaid coverage, maternal history of prior influenza vaccination, and maternal high-risk status. Exposed infants were matched to unexposed infants by MCO site and birth week. Female sex was significantly associated with reduced infant MAARI incidence, whereas maternal high-risk status and infant Medicaid coverage were significantly associated with increased MAARI incidence (Table 3). Maternal influenza vaccination did not reduce MAARI incidence: the adjusted IRRs (95% CIs) for the peak influenza, RSV-predominant, perisessional, and seasonal periods were

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Among Exposed Infants</th>
<th>Among Unexposed Infants</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak influenza weeks†</td>
<td>15.4</td>
<td>17.1</td>
<td>0.90 (0.80-1.02)</td>
</tr>
<tr>
<td>RSV-predominant weeks‡</td>
<td>19.0</td>
<td>20.5</td>
<td>0.93 (0.84-1.02)</td>
</tr>
<tr>
<td>Perisessional weeks§</td>
<td>15.5</td>
<td>13.8</td>
<td>1.12 (0.94-1.34)</td>
</tr>
<tr>
<td>Summer weeks</td>
<td></td>
<td>17.6</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incident rate ratio; MAARI, medically attended acute respiratory illness; RSV, respiratory syncytial virus.

*Calculated as number of visits per 100 person-months, with outpatient, emergency department, and inpatient visits combined.
†Indicates any week during influenza season (October 1 to April 30) in which influenza accounted for 5% or more of the season’s total number of influenza virus isolates.
‡Indicates any week during influenza season in which each week accounted for less than 5% of total RSV virus isolates and less than 5% of the season’s total number of RSV virus isolates.
§Indicates any week during influenza season in which each week accounted for less than 3% of total RSV isolates and less than 3% of influenza virus isolates.
||Indicates any week from July 1 to September 30.

For infants born during the peak influenza weeks, the mean time in days from birth to the first MAARI did not vary by exposure status: exposed and unexposed infants’ mean times to first acute respiratory illness were 49 and 53 days, respectively (P=.84). A Cox proportional hazards model comparing the time to the first
Our study found no reduction in the incidence rate of MAARIs during peak influenza weeks among infants born to mothers vaccinated against influenza during their pregnancy. This finding is consistent with the work by Black et al. performed at Kaiser Permanente Northern California. The presence of other circulating respiratory viruses during the peak influenza weeks could mask any potential reduction in MAARI visits associated with maternal influenza vaccination. Similarly, we did not see any evidence that maternal influenza vaccination delayed the onset or reduced the severity of MAARI illness among infants born during the peak influenza weeks. This study was designed to maximize the possibility of seeing an effect on infant MAARI visits of maternal influenza vaccination, and therefore the analysis was limited to infants who had at least 28 days in utero for development and transfer of maternal antibodies, focused on peak influenza weeks, required infants to contribute person-time during the influenza season, and used data from a large linked database to maximize the number of study subjects. Although our study confirmed known predictors of acute respiratory illness visits in infants (sex and Medicaid coverage), we did not see an effect of maternal vaccination on rates of infant MAARI health care visits. Although it may be that maternal influenza vaccination reduces the risk of serious influenza illness among infants during their first months of life, this does not translate to a decrease in the number of visits to the physician’s office or hospitals for acute respiratory illnesses.

We overestimated the maternal vaccination rate across our MCOs, which ranged from 0.7% to 20.8% during the 6 seasons, and thus had a smaller-than-expected number of infants exposed to maternal influenza vaccination. Because of the smaller sample size, our study is limited in its power to detect a reduced visit rate among exposed infants. Although we did not have the power to look at the effect of maternal vaccination on rare events such as infant pneumonia, our power to assess our primary outcome, MAARI incidence during peak influenza weeks, was good: We had the power to detect a 15% or greater reduction in MAARI visits (IRR, 0.85) during the peak influenza weeks (β = .80; α = .05; unexposed background incidence, 17 per 100 person-months).

Although we had information on important variables that predict infant health care services utilization (eg, sex, gestational age, and Medicaid coverage), some variables predicting the incidence of acute respiratory illness in infants are not available in the VSD data. These include the number of siblings in the home, parental smoking status, breastfeeding, and attendance at day care. Glezen et al. studied influenza illness during the first year of life and found that having at least 3 siblings constituted a significant risk for infant influenza infection. More data from another database are available on the 5530 Colorado infants in this study, which suggest that there may not be great differences between families of exposed and unexposed infants, because the numbers of first-time mothers (45% exposed vs 43% unexposed), mothers intending to breastfeed (83% exposed vs 78% unexposed), and mothers who smoked (8.4% exposed vs 10% unexposed) are all similar.

Influenza illness in the first 6 months of life is more likely to present as an afebrile upper respiratory infec-

### Table 3. Adjusted IRRs for Acute Respiratory Illnesses Among Matched Infants

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Peak Influenza Weeks</th>
<th>RSV-Predominant Weeks</th>
<th>Periseasonal Weeks</th>
<th>Summer Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed infants</td>
<td>0.96 (0.86-1.07)</td>
<td>0.95 (0.84-1.06)</td>
<td>1.12 (0.91-1.37)</td>
<td>1.04 (0.98-1.10)</td>
</tr>
<tr>
<td>Gestation age</td>
<td>0.96 (0.94-0.98)</td>
<td>0.98 (0.96-1.00)</td>
<td>0.96 (0.93-0.98)</td>
<td>0.99 (0.98-1.00)</td>
</tr>
<tr>
<td>Maternal high-risk status†</td>
<td>1.14 (1.01-1.27)</td>
<td>1.14 (1.03-1.27)</td>
<td>1.26 (1.10-1.44)</td>
<td>1.22 (1.15-1.29)</td>
</tr>
<tr>
<td>Infant female sex</td>
<td>0.88 (0.82-0.94)</td>
<td>0.85 (0.80-0.91)</td>
<td>0.95 (0.89-1.02)</td>
<td>0.89 (0.86-0.92)</td>
</tr>
<tr>
<td>Medicaid coverage</td>
<td>1.03 (0.85-1.25)</td>
<td>1.29 (1.05-1.58)</td>
<td>1.41 (1.08-1.85)</td>
<td>1.21 (1.11-1.33)</td>
</tr>
<tr>
<td>Maternal age at birth</td>
<td>0.98 (0.97-0.98)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.99 (0.99-0.99)</td>
</tr>
<tr>
<td>Maternal influenza vaccination in the preceding season</td>
<td>1.06 (0.90-1.23)</td>
<td>1.06 (0.94-1.20)</td>
<td>0.87 (0.68-1.10)</td>
<td>1.08 (1.01-1.16)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incident rate ratio; RSV, respiratory syncytial virus.

* Calculated as outpatient, emergency department, and inpatient visits combined, and matched by managed care organization site and infant birth date within the same week.

† Study periods are described in the footnotes to Table 2.

‡ Maternal high-risk status is explained in the “Health Services Data” subsection of the “Methods” section.

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tion compared with the second 6 months of life. Glezen et al\textsuperscript{20} reported that 58\% of influenza illness among infants younger than 6 months were afebrile, compared with 28\% among infants aged 6 to 11 months. Parents of afebrile infants with an upper respiratory infection may be less likely to seek medical care, and these infants would be missed in our study. Higher MAARI incidence rates among infants aged 6 to 11 months compared with 0 to 5 months could explain our finding of similar incidence rates of MAARIs for infants during the peak influenza (mean age, 2½ months) and the summer weeks (mean age, 7 months). Work by the New Vaccine Surveillance Network Group\textsuperscript{21} confirms this lower rate of influenza illness among infants younger than 6 months. Outpatient surveillance of all children younger than 5 years at 2 study sites, in which viral culture or reverse transcriptase polymerase chain reaction testing for influenza virus was performed on nasal and throat swabs, found low rates of influenza infection—that is, less than 10\% of acute respiratory infections occurring among infants aged 0 to 5 months during the 2002-2003 and 2003-2004 influenza seasons were due to influenza virus.\textsuperscript{21} Any study of the effect of maternal influenza vaccination on acute respiratory tract infection in infants faces a number of challenges. A randomized placebo-controlled trial would best control for unknown imbalances in confounders; however, given the current national recommendation that all pregnant women be vaccinated against influenza, it would be unethical to randomly assign women to vaccination or placebo. Any controlled trial allowing mothers to select vaccination could potentially suffer from confounding. The restrictive period studied reduces the number of mother-infant pairs available to study: the VSD files have more than 200 000 newborns during the study years, yet only 40 000 contributed to this work. The small number of peak influenza weeks during the winter months (average, 9.5 weeks per influenza season) means that even with large numbers of children, there will be limited person-time experience for analysis. A mismatch between the circulating strains of wild influenza virus and the strains used for vaccine development could explain the absence of an effect of maternal vaccination on MAARI visits. However, only 1 of the 6 seasons (1997-1998) was considered a fair rather than a good match. Finally, influenza cohort studies are challenged by the vagaries of the influenza season: the 2 influenza seasons after our study (2001-2002 and 2002-2003) were both unusually mild, whereas the 2003-2004 season was early (November to January), eliminating much opportunity for maternal influenza to protect infants born during that season against moderate to severe influenza infection. Future work should include multiple influenza seasons, use accurate tools such as viral culture and reverse transcriptase polymerase chain reaction to diagnose influenza, and focus on hospitalization as the outcome of interest. Small effect sizes, such as a reduction in hospitalization of 10\% to 30\%, will require large numbers of subjects to detect. Although this vaccination did not appear to have an effect on the rates of infant health care visits, vaccination is still important and is primarily recommended to protect the health of the mother.
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REFERENCES


When Is the Right Time for Toilet Training?

Only a child can decide when the time for toilet training has come. Any pressure parents may feel from grandparents, nursery schools, or helpful friends had better be disregarded. It’s got to be his achievement, not theirs.

—From Touchpoints by Dr T. Berry Brazelton, 2004

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