Infant Sleep After Immunization: Randomized Controlled Trial of Prophylactic Acetaminophen

WHAT'S KNOWN ON THIS SUBJECT: For adults, sleep deprivation before or after immunization is associated with decreased antigen-specific antibody formation, but little is known about infant sleep before and after immunization or the effects of prophylactic acetaminophen treatment on infant sleep.

WHAT THIS STUDY ADDS: Infants demonstrated increased sleep duration in the 24 hours after immunization, particularly if they were immunized after 1:30 PM and had elevated temperatures. Acetaminophen use was associated with smaller increases in sleep duration but not when other factors were controlled.

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KEY WORDS

immunization, infant, sleep, acetaminophen, actigraphy

ABBREVIATION

RCT—randomized controlled trial

This trial has been registered at www.clinicaltrials.gov (identifier NCT01321710).

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abstract

OBJECTIVE: To determine the effects of acetaminophen and axillary temperature responses on infant sleep duration after immunization.

METHODS: We conducted a prospective, randomized controlled trial to compare the sleep of 70 infants monitored by using ankle actigraphy for 24 hours before and after their first immunization series at ~2 months of age. Mothers of infants in the control group received standard care instructions from their infants' health care provider, and mothers of infants in the intervention group were provided with pre-dosed acetaminophen and instructed to administer a dose 30 minutes before the scheduled immunization and every 4 hours thereafter, for a total of 5 doses. Infant age and birth weight and immunization factors, such as acetaminophen use and timing of administration, were evaluated for changes in infant sleep times after immunization.

RESULTS: Sleep duration in the first 24 hours after immunization was increased, particularly for infants who received their immunizations after 1:30 PM and for those who experienced elevated temperatures in response to the vaccines. Infants who received acetaminophen at or after immunization had smaller increases in sleep duration than did infants who did not. However, acetaminophen use was not a significant predictor of sleep duration when other factors were controlled.

CONCLUSIONS: If further research confirms the relationship between time of day of vaccine administration, increased sleep duration after immunization, and antibody responses, then our findings suggest that afternoon immunizations should be recommended to facilitate increased sleep in the 24 hours after immunization, regardless of acetaminophen administration. *Pediatrics* 2011;128:1100–1108

Irritability and elevated temperature are expected reactions to infant immunizations.^{1,2} Anecdotal parent reports of infant sleep changes after immunization also are common. However, the influence of immunization on infant sleep has received little research attention. For adults, sleep deprivation before immunization³ or the night after immunization⁴ was associated with decreased antigen-specific antibody formation. Loy et al⁵ studied the effects of immunization on infant sleep and found no differences in sleep duration or numbers of awakenings for 14 infants during 5-hour observation periods the day before and the day after immunization. Parent-completed sleep diaries for 11 of the infants also showed no sleep differences.⁵

Before 2009, infants commonly received prophylactic acetaminophen treatment to prevent immunization discomfort and fever, although there is a low level of evidence for effectiveness.^{6–8} In 2009, Prymula et al⁹ published data from a randomized controlled trial (RCT) that showed reduced immunogenicity when infants (3–5 months of age) received 3 doses of acetaminophen in the first 24 hours after primary vaccines. This led some authors to reconsider the practice,¹⁰ whereas others advocated maintaining the current practice.^{11,12} All agreed, however, that additional research is needed. There are no published data on how acetaminophen affects postimmunization sleep in this age group.

Given the paucity of research regarding sleep after immunization, we examined infant sleep at the first immunization series. For this RCT, we had 3 hypotheses: (1) infants would sleep more in the 24-hour period after immunization compared with the 24-hour period before immunization; (2) a higher temperature response to immunization would be associated with

more sleep; and (3) the group assigned randomly to receive prophylactic acetaminophen treatment would have an altered temperature response and increased postimmunization sleep duration.

METHODS

Participants and Procedures

This study was approved by the institution's committee on human research. As part of a larger RCT,¹³ expectant mothers were recruited from childbirth education classes and prenatal clinics between 2004 and 2008. Eligible women were expecting their first singleton birth, were ≥ 18 years of age, and were able to read and to write English. Women were excluded if they worked nights, had a diagnosed sleep

or mood disorder, or took medication that affected sleep. Of the 198 women screened for eligibility, 152 enrolled in the study (Fig 1).

Each woman provided written informed consent for herself and her infant, and women were paid for participation. Women were enrolled beginning at 36 weeks of gestation; therefore, all infants had gestational ages of ≥ 37 weeks at birth. Women were assessed in their homes during late pregnancy and at 1, 2, and 3 months after the birth. The 2-month assessment was coordinated with infant immunizations and included an assessment of infant sleep.

The mother-focused sleep hygiene intervention in the larger study was not

FIGURE 1

Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow. T2 indicates the study visit 2 months after birth. ^a Actigraphic data were missing (mother declined), invalid (actigraphy error), or incomplete (<24 hours of continuous data immediately before and after immunization).

the primary interest in this analysis, but random group assignment was considered a covariate. Mothers assigned randomly to the sleep hygiene intervention group were given strategies for improving their own sleep while providing nighttime infant care in the first 3 months.¹³ Mothers assigned randomly to the control group were given dietary information for promoting sleep.

The infant-focused intervention was designed to minimize infant sleep disruption after immunization at 2 months of age (Fig 1). Each infant was weighed, and mothers of infants assigned randomly to the intervention were provided with predosed acetaminophen appropriate for weight (Table 1). Mothers were instructed to administer a dose 30 minutes before immunization and every 4 hours thereafter, for a total of 5 doses.¹⁴ Mothers assigned to the control group received standard immunization care instructions from the infant's health care provider. Some providers administered a single prophylactic dose of acetaminophen as standard care, whereas other providers recommended that mothers administer acetaminophen in the event of infant fever or discomfort after immunization.

Both mother and infant randomization sequences were generated randomly, in blocks of 6, by the project statistician. The mother-focused intervention had a 2:1 ratio (experimental group/control group) to allow for an adequately sized group eligible for the infant-focused intervention. Only in-

fant with mothers assigned to the sleep hygiene intervention were eligible for the infant-focused intervention, and they were assigned randomly in a 1:1 ratio. Research assistants were informed of randomization assignments immediately before each study visit and were responsible for implementing the intervention procedures. Participants and outcome assessors were blinded to group assignment.

Measures

Demographic and Immunization Information

Demographic information was provided through maternal report, as were infants' birth history and immunization information.

Actigraphy

For objective estimation of sleep quantity, each infant wore an actigraph (Ambulatory Monitoring, Ardsley, NY) around 1 ankle for 24 hours before and after the 2-month immunization. The actigraph provides continuous motion data by using a microprocessor with a piezoelectric linear accelerometer. Data were analyzed by using the Sadeh Infant Algorithm autoscoring program in Action4 software (Ambulatory Monitoring), with established validity and reliability for infants.^{15,16} Sleep outcomes included active sleep time, quiet sleep time, and total sleep time (active sleep time plus quiet sleep time). Measures were computed across 2 time periods, namely, 24 hours before immunization and 24 hours after immunization.

Daily Sleep Diaries

Mothers used sleep diaries to record their infants' time spent asleep, which were used to facilitate interpretation of actigraphic data. Infant medication doses, feeding type, and sleep locations also were recorded.

Infant Temperature

Mothers were given digital thermometers (Write Temp 3-in-1 digital thermometer [Safety 1st, Columbus, IN]) and instructed to record their infants' axillary temperature in the diary each morning and evening throughout the 72-hour monitoring period.

Analyses

Without previous data to estimate the sample size needed for statistical significance, we used a clinically meaningful effect size difference of 1.0 SD unit between the prophylactic acetaminophen treatment group and the control groups. This effect size (*d*) required a minimum of 17 infants per group for 80% power to test our third hypothesis with a significant difference (2-tailed $P < .05$) between infants receiving prophylactic acetaminophen treatment and infants receiving standard care.¹⁷

To evaluate the effect of immunization, paired *t* tests were used to compare sleep and temperature measurements before and after immunization. To control for individual differences in infant sleep, the main outcome variable used in subsequent analyses was the difference in total sleep time for 24 hours before and 24 hours after immunization, with positive values indicating more sleep after immunization; changes of >5 hours ($n = 3$) were truncated to 300 minutes to normalize the distribution. Morning and evening temperatures were correlated ($r = 0.46$ before immunization and $r = 0.52$ after immunization) and were not significantly different. Therefore, av-

TABLE 1 Intervention Group ($N = 25$) Predosed Acetaminophen Doses Based on Infant Weight

Weight, Range, kg	Dose to Administer, mg	Dose, Range, mg/kg
3.80–4.44	51	11.49–13.42
4.45–5.20	60	11.54–13.48
5.21–6.05	70	11.57–13.44
6.06–6.95	80	11.51–13.20
6.96–7.80	90	11.54–12.93

The target dose was 11.5 to 13.5 mg/kg, to be administered 30 minutes before the scheduled immunization and every 4 hours thereafter, for a total of 5 doses.¹⁴

erage temperatures for 24 hours before immunization and for 24 hours after immunization were used, and differences between preimmunization and postimmunization temperatures were calculated.

Independent *t* tests, analyses of variance, and χ^2 tests were used to identify group differences in infant characteristics, immunization factors, and sleep and temperature changes. Prophylactic acetaminophen use was evaluated through intention-to-treat analysis, as well as analyses of actual use and timing of administration. Because of the small sample sizes for some group comparisons, type II error was evaluated by calculating effect sizes (*d*). Pearson correlations were used to determine the relationship between sleep measures and infant immunization factors.

Logistic regression was used to identify predictors of changes in sleep times after immunization. Variables that were associated with postimmunization sleep changes in univariate analyses ($P < .10$) were included in the multivariate model. Because this study was a RCT, group assignment was included in the model regardless of its relationship to infant sleep. Analyses were conducted by using SPSS for Windows 18.0 (SPSS Inc, Chicago, IL). A 2-tailed α level of .05 was used.

RESULTS

Study Group

Of the 152 mother-infant dyads enrolled in the study, 70 infants had complete actigraphic data for 24 hours before and after immunization and were included in the analyses (Fig 1). The 82 infants not included did not differ from the final sample with respect to maternal or infant age, infant gender, birth weight, feeding type, sleep location, acetaminophen use, or group assignment. The mothers in the final sample

had a mean age of 26.8 ± 6.9 years (range: 18–47), and the sample was diverse (31% Asian, 26% white, 23% Hispanic, 11% black, and 9% mixed or other race). Most mothers (90%) had finished high school, and 29% had completed college. Approximately 36% were employed, but only 9% were working at the 2-month assessment. Infant characteristics and immunization factors are reported in Table 2. Sixty-six infants (94%) had temperatures recorded for 24 hours before immunization, 68 (97%) had temperatures recorded for 24 hours after immunization, and 65 (93%) had both.

Immunizations

The majority of infants (80%) received all recommended immunizations, including pneumococcal conjugate vaccine, diphtheria-tetanus-pertussis vaccine, *Haemophilus influenzae* type b vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine.^{18–20} Rotavirus vaccine became available in February 2006,²¹ and approximately one-half of the infants received this orally administered vaccine in addition to the injected vaccines. Of the 7 infants (10%) who did not receive 1 or 2 of the recommended immunizations, 5 did not receive hepatitis B vaccine, 2 did not receive *H influenzae* type b vaccine, 1 did not receive diphtheria-tetanus-pertussis vaccine, and 1 did not receive inactivated poliovirus vaccine. Because some vaccines were administered in combination, the number of injections ranged between 2 and 5, with 96% of infants receiving 3 or 4 injections. Seven mothers (10%) did not know which immunizations their infants had received and could not find the immunization records, but they did recall their infants receiving 3 or 4 injections, which suggests that the infants likely received most or all vaccines.

Acetaminophen Use

Most infants (80%) received acetaminophen either prophylactically at the time of immunization or to manage symptoms that appeared later, regardless of group assignment (Table 2). Infants in the prophylactic acetaminophen intervention group were more likely to have received the first dose at the time of immunization, and infants in the control group were more likely to have received the first dose after symptoms (eg, fever or discomfort) appeared. No adverse events were reported.

Infant Axillary Temperature After Immunization

There were small but significant changes in infant temperature after immunization (Table 3). The mean axillary temperature for the 24 hours after immunization was $0.23^\circ\text{C} \pm 0.41^\circ\text{C}$ higher than the mean temperature for the 24 hours before immunization. Of the 65 infants with temperature data before and after immunization, 28 received acetaminophen within 1 hour after immunization and had minimal temperature increases after immunization ($0.09^\circ\text{C} \pm 0.40^\circ\text{C}$), compared with 14 infants who received no acetaminophen ($0.38^\circ\text{C} \pm 0.31^\circ\text{C}$; effect size: 0.767) and 25 infants who received acetaminophen later ($0.31^\circ\text{C} \pm 0.44^\circ\text{C}$; effect size: 0.520). The results of a comparison of all 3 groups were not statistically significant ($F_{2,62} = 3.09$; $P = .053$); effect sizes were >0.50 SD units but less than the 1.0 SD unit on which statistical power was based.

Changes in Infant Sleep After Immunization

Infants slept an average of 69 minutes more (95% confidence interval: 32–105 minutes) in the 24-hour period after immunization than in the 24-hour period before immunization (Table 3). Most of the additional sleep was active

TABLE 2 Infant Characteristics and Immunization Factors According to Treatment Group ($N = 70$)

	Total Sample ($N = 70$)	Standard Immunization Care ($N = 45$)	Prophylactic Acetaminophen Intervention ($N = 25$)	Statistics
Infant characteristics				
Age, wk				NS
Mean $\pm$ SD	8.7 $\pm$ 1.2	8.9 $\pm$ 1.1	8.4 $\pm$ 1.3	
Range	6.1–11.3	6.3–11.3	6.1–11.0	
Male, % (n)	57 (40)	58 (26)	56 (14)	NS
Delivery type, % (n)				NS
Vaginal	61 (43)	64 (29)	56 (14)	
Cesarean	39 (27)	36 (16)	44 (11)	
Birth weight, kg				NS
Mean $\pm$ SD	3.41 $\pm$ 0.5	3.37 $\pm$ 0.53	3.48 $\pm$ 0.47	
Range	2.49–4.99	2.49–4.99	2.66–4.88	
Feeding type, % (n)				NS
Breast milk only	47 (33)	51 (23)	40 (10)	
Combination of breast milk and formula	23 (16)	20 (9)	28 (7)	
Formula only	30 (21)	29 (13)	32 (8)	
Usual sleep arrangement ($N = 69$), % (n)				NS
Parent/infant bed-sharing	45 (31)	41 (18)	52 (13)	
Parent/infant room-sharing	51 (35)	52 (23)	48 (12)	
Separate room	4 (3)	7 (3)	0 (0)	
Immunization factors				
Vaccines received, % (n)				NS
All recommended vaccines ^a	80 (56)	80 (36)	80 (20)	
All except 1 or 2 recommended vaccines	10 (7)	11 (5)	8 (2)	
Unsure of specific vaccines received	10 (7)	9 (4)	12 (3)	
No. of injections ($N = 69$)				NS
Mean $\pm$ SD	3.42 $\pm$ 0.58	3.38 $\pm$ 0.54	3.50 $\pm$ 0.66	
Range	2–5	3–5	2–5	
Time of immunization				NS
Mean $\pm$ SD	1:21 PM $\pm$ 145 min	1:18 PM $\pm$ 140 min	1:27 PM $\pm$ 157 min	
Range	9:00 AM to 7:30 PM	9:00 AM to 6:30 PM	9:00 AM to 7:30 PM	
Acetaminophen use				
Any acetaminophen administered, % (n)	80 (56)	71 (32)	96 (24)	$\chi^2_1 = 6.22$; $P = .013$
Timing of first dose, % (n)				$\chi^2_2 = 27.0$; $P < .001$
None	20 (14)	29 (13)	4 (1)	
Within 1 h of immunization	43 (30)	20 (9)	84 (21)	
>1 h after immunization	37 (26)	51 (23)	12 (3)	
Total No. of doses				$t_{69} = 3.89$; $P < .001$
Mean $\pm$ SD	2.80 $\pm$ 2.11	2.13 $\pm$ 2.09	4.00 $\pm$ 1.58	
Range	0–9	0–9	0–6	

NS indicates nonsignificant.

^a At the time the study data were collected, the vaccines recommended at 2 months of age were diphtheria-tetanus-pertussis vaccine, *H influenzae* type b vaccine, pneumococcal conjugate vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine. An oral rotavirus vaccine was added to the immunization schedule in February 2006.**TABLE 3** Comparison of Infant Sleep Measures and Temperature Readings Before and After Immunization

Sleep Outcome	Before Immunization	After Immunization	Statistics
Infant sleep over 24 h, N	70	70	—
Total sleep, mean $\pm$ SD, h	11.8 $\pm$ 2.2	13.0 $\pm$ 2.6	$t_{69} = 3.77$; $P < .001$
Active sleep, mean $\pm$ SD, h	7.1 $\pm$ 1.3	7.9 $\pm$ 1.8	$t_{69} = 4.07$; $P < .001$
Quiet sleep, mean $\pm$ SD, h	4.7 $\pm$ 1.6	5.0 $\pm$ 1.8	NS
Infant axillary temperature, N	65	65	—
Temperature, mean $\pm$ SD, $^{\circ}$ C	36.60 $\pm$ 0.32	36.84 $\pm$ 0.46	$t_{64} = 4.55$; $P < .001$

NS indicates nonsignificant.

sleep, whereas quiet sleep time increased only slightly. To verify that these results were not influenced by the prophylactic acetaminophen intervention, analyses were repeated with

only the 45 infants assigned to the control group, and results were the same. Although most infants slept more in the 24 hours after immunization, compared with the 24 hours before immu-

nization, 37% slept less after immunization.

Predictors of Increased Sleep Duration After Immunization

The change in infant sleep duration was unrelated to infant age ($r = 0.081$), birth weight ($r = 0.018$), or number of acetaminophen doses ($r = -0.189$). Postimmunization sleep increase was significantly correlated with higher mean temperature in the 24 hours after immunization ($r = 0.315$; $P = .009$). There was a significant correlation between the

time of day of immunization and changes in infant sleep quantity ($r = 0.303$; $P = .011$). Infants immunized later in the day had larger increases in sleep duration in the 24 hours after immunization. Infants immunized earlier in the day not only had smaller increases in sleep, many of them slept less than they had in the previous 24 hours (Fig 2).

Group comparisons were conducted to evaluate the effects of group assignment (mother and infant), categorical infant characteristics, and categorical immunization factors (Table 4). Three immunization-related factors were significantly related to changes in infant sleep duration in univariate analyses, namely, acetaminophen use, axillary temperature, and time of immunization. Infants who received acetaminophen had smaller increases in total sleep duration after immunization, compared with infants who did not receive acetaminophen, regardless of whether the first dose was administered prophylactically or given later in response to symptoms such as fever or discomfort (Table 4). Infants with a mean axillary temperature above the median of 36.85°C during the 24 hours after immunization had larger increases in sleep quantity. Infants who were immunized after the median time of 1:30 PM had greater increases in sleep quantity than did infants who were immunized earlier in the day. Neither of the group assignments and none of the infant characteristics was significantly associated with changes in sleep quantity in the 24-hour period after immunization.

Multivariate logistic regression analysis then was conducted to explore predictors of increased sleep after immunization, with controlling for the effects of other variables (Table 5). Acetaminophen use, postimmunization temperature (split at the median of 36.85°C), and timing of immuniza-

tion (split at the median of 1:30 PM) were all included in the model on the basis of univariate associations ($P < .10$) with postimmunization sleep changes, and group assignments were also included in the model. Higher postimmunization axillary temperatures and afternoon immunizations were the only significant predictors of increased sleep time in the final model. The final model accounted for 32.5% of the variance in increased sleep duration after immunization.

DISCUSSION

To our knowledge, this is the first study to investigate the effects of immunization and acetaminophen use on infant sleep duration and temperature changes over a 24-hour period after immunization. Our first hypothesis was supported by the finding that infants slept longer in the first 24 hours after immunization, compared with the 24 hours before immunization. This was particularly true for infants who received their immunizations after 1:30 PM. The increased sleep time was primarily in active sleep rather than quiet sleep.

Our second hypothesis also was supported. Infants who had elevated temperatures in response to vaccines also slept longer in the 24 hours after immunization than in the 24 hours before immunization. Temperature increase is considered a marker of immune responses and is thought to be related to release of endogenous pyrogens (eg, interleukin 1 and tumor necrosis factor α) associated with increased T cell activity, enhanced antigen recognition, and immune responses.²² Therefore, longer sleep duration and increased temperature after immunization may be indicators of the degree of antibody responses.⁹ Studies have suggested that sleep quantity is a potential mediator of antibody responses to vaccines in adults, perhaps through stress-related modulation of cytokine production by activated T cells.^{23,24} Although antibody development can take several weeks, 2 studies demonstrated that even relatively brief periods of sleep restriction could disrupt adult antibody responses.^{4,24} It was beyond the scope of this study to determine whether infant sleep quantity on a sin-

FIGURE 2

Changes in infants' 24-hour sleep quantities after immunization as a function of time of day of immunization.

TABLE 4 Group Differences in Infant Sleep Changes After Immunization

Infant and Immunization Characteristics	<i>n</i>	Change in Sleep Quantities in 24 h Before and After Immunization, Mean $\pm$ SD, min ^a	Statistics	Effect Size (<i>d</i>) ^b
Randomization 1			NS	0.175
Nutrition (control)	21	47.4 $\pm$ 133.3		
Sleep hygiene (experimental)	49	73.1 $\pm$ 151.8		
Randomization 2			NS	0.153
Standard care (control)	45	57.4 $\pm$ 140.6		
Acetaminophen (experimental)	25	79.8 $\pm$ 157.2		
Infant gender			NS	0.296
Boys	40	46.9 $\pm$ 144.1		
Girls	30	90.0 $\pm$ 147.3		
Delivery type			NS	0.398
Vaginal	43	87.5 $\pm$ 156.2		
Cesarean	27	30.1 $\pm$ 122.7		
Feeding type			NS	0.190
Breast milk only	33	75.2 $\pm$ 149.4		
Combination	16	67.8 $\pm$ 162.7		
Formula only	21	48.0 $\pm$ 132.2		
Sleeping arrangement (<i>N</i> = 69)			NS	0.287
Bed-sharing	31	42.7 $\pm$ 151.4		
Separate beds	38	84.8 $\pm$ 142.5		
No. of injections (<i>N</i> = 69)			NS	0.203
2 or 3	41	52.1 $\pm$ 157.3		
4 or 5	28	81.9 $\pm$ 130.4		
Time of immunization			$t_{68} = 1.84; P = .070$	0.441
Before or at median of 1:30 PM	36	34.6 $\pm$ 142.1		
After median of 1:30 PM	34	97.9 $\pm$ 145.1		
Acetaminophen use			$t_{68} = 2.05; P = .044$	0.613
Yes	56	47.9 $\pm$ 140.4		
No	14	135.4 $\pm$ 152.4		
Timing of first acetaminophen dose			NS	0.003
Within 1 h of immunization	30	47.7 $\pm$ 150.8		
>1 h after immunization	26	48.1 $\pm$ 130.2		
Mean temperature after immunization (<i>N</i> = 68)			$t_{66} = 2.30; P = .024$	0.559
Below median of 36.85°C	34	23.7 $\pm$ 153.1		
At or above median of 36.85°C	34	103.6 $\pm$ 132.2		

NS indicates nonsignificant.

^a Difference between total sleep times in the 24 hours before and after immunization, with positive values indicating more sleep after immunization.^b The effect size for feeding type is based on comparisons of the breast milk-only and formula-only groups.**TABLE 5** Logistic Regression Analysis of Increased Sleep Quantities After Immunization (*N* = 68)

Predictors	Value	<i>P</i>	ΔR^2
Step 1: group assignments, OR (95% CI)			0.032
Sleep hygiene intervention	2.82 (0.67–11.81)	NS	
Acetaminophen intervention	1.73 (0.39–7.74)	NS	
Step 2: acetaminophen, OR (95% CI)			0.061
Acetaminophen administered	0.32 (0.62–1.60)	NS	
Step 3: temperature, OR (95% CI)			0.095
Mean temperature in 24 h after immunization of at least median of 36.85°C	5.97 (1.58–22.62)	.009	
Step 4: timing of immunization, OR (95% CI)			0.137
Immunization after median of 1:30 PM	5.86 (1.63–21.16)	.007	
Full model, χ^2_6	18.59	.002	0.325

The dependent variable was increased infant sleep in the 24 hours after immunization, compared with the 24 hours before immunization. NS indicates nonsignificant. ΔR^2 is the change in the coefficient of determination resulting from this step; χ^2_6 is the χ^2 statistic for the goodness of the model fit.

gle night after immunization was associated with antibody responses. Future research should address this impor-

tant question by assessing infant sleep and antibody responses over longer time frames. If relationships between

time of day of vaccine administration, increased sleep, and antibody responses are substantiated, then our findings suggest that afternoon immunizations should be recommended, to facilitate increased infant sleep after immunization.

In this RCT, infants were assigned randomly to 3 groups, namely, control mothers with infants who received usual care, intervention mothers with infants who received usual care, and intervention mothers with intervention infants, who were instructed to provide prophylactic and continuing doses of acetaminophen. Although group assignment had no effect on postimmunization sleep in intent-to-

treat analysis, 71% in the usual-care group received acetaminophen and 20% received it prophylactically, which made it more difficult to detect group differences. Nevertheless, the findings support one aspect of our third hypothesis regarding the effects of prophylactic acetaminophen treatment on infant temperature. The large effect sizes (with $P = .053$) suggest that the study was underpowered for an intent-to-treat analysis to detect large differences, when effects of group contamination with acetaminophen administration are considered. These differences would require 64 infants per group for statistical significance.¹⁷

In comparison with the few infants who did not receive any acetaminophen ($n = 14$), the 56 infants who received ≥ 1 dose had smaller increases in postimmunization sleep duration, regardless of acetaminophen administration timing. The rationale for postimmunization administration of acetaminophen cannot be completely explained by group assignment, which suggests that these infants might have experienced more symptoms, for which they received acetaminophen. However, acetaminophen use was not significant in the regression analysis, which suggests that the primary

mechanism for increased sleep time may involve higher temperature.

Our findings are consistent with those of Prymula et al⁹ and, taken together, suggest that antipyretic agents should not be given prophylactically for infant immunization. Therefore, research on alternative pain-management strategies for immunization discomfort is urgently needed. As immunization practices shift from single-antigen to multiple-antigen vaccine delivery, sleep duration should be measured in future studies of combination vaccine products, because of the potential for fever or pain responses to such products and sleep implications.²⁵

These findings were limited to term firstborn infants receiving their first immunization series, and they may not be applicable to premature or older infants and children. The small number of infants who did not receive acetaminophen ($n = 14$) and the likelihood that acetaminophen often was used for symptom relief also may limit the generalizability of these findings; larger, placebo-controlled trials are warranted. Findings should be interpreted with caution because of the limited study period (ie, 24 hours before and after immunization) and the use of ankle movements to estimate infant sleep. Infants mature at a rapid rate, however, and comparisons of more-

proximal times around the immunization protocol are critical for understanding how sleep is influenced. Differences in active and quiet sleep times should be explored further by using polysomnography, and longitudinal studies of sleep and responses to immunization are needed for a better understanding of the interactions between immunization time of day, active and quiet sleep, temperature, and antibody responses.

CONCLUSIONS

Our findings provide new data about infant sleep after immunization. Given the importance of sleep for a healthy immune response, our findings suggest that the time of day of vaccine administration and sleep duration after immunization are important variables to consider when evaluating infant antibody responses. If further research confirms relationships between the time of day of vaccine administration, increased sleep, and antibody responses, then our findings suggest that afternoon immunizations should be recommended, to facilitate increased infant sleep in the 24 hours after immunization.

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THE GOOD DIVORCE: A friend of ours drove our daughter home recently. After talking in the driveway for a few minutes, we invited her into the house for a glass of wine. During our conversation, I noticed that she was no longer wearing her engagement or wedding rings. Also, she had started working again after a long absence from the work force. We learned a few weeks ago that she and her husband, both good friends of ours, may be divorcing. I had seen him several times over the summer, and although never with his wife, he seemed fine and had never said anything about her. Similarly, she seemed fine and never said a word about him. This prompted me to wonder, is there such a thing as a good divorce? As reported in *The New York Times* (Fashion: October 28, 2011), it could be that Generation X, those born between 1965 and 1980, approach divorce a bit differently than previous generations. After all, Generation X entered marriage in a different way as 60% chose to live with their future spouse before marriage and almost 80% stay married for more than 10 years. Moreover, all states now uphold joint custody of children, whereas 30 years ago only three states did. Maybe this generation is more clear-eyed both about entering and leaving a marriage. With many divorced couples sharing parental duties, energy has to be directed on the children rather than lobbing bombs at each other. Another explanation may be that divorce is easier when couples fall out of love. If there is no passion left in the marriage, is there likely to be passion in the divorce? While “good” and “divorce” may not be a natural pairing, for our friends the dyad may apply. As for our friends, we saw them drift apart over the years. Both seem happier and more animated now. They have enough financial power so that while not as well off as previously, they are both doing okay. They share schedules and pick-ups for the kids and both children seem to be adjusting without any major difficulties. Still, I can’t help but wonder, what happened to the passion? I am sad for that loss.

Noted by WVR, MD