PUBLIC HEALTH SERVICE STUDY ON REYE'S SYNDROME AND MEDICATIONS

Report of the Pilot Phase


Abstract

Between February and May 1984, we conducted a pilot study to examine the methods for a larger study of a previously reported relation between Reye's syndrome and medications. Thirty patients with Reye's syndrome, whose diagnosis was confirmed by an expert panel, and 145 controls were matched for age, race (black or not black), and antecedent illness (respiratory infection, chickenpox, or diarrhea) and selected from the same hospital, emergency room, or school, or identified by random digit dialing. Significantly more cases (93 per cent, 28 of 30) than members of each of the four control groups or all controls combined (46 per cent, 66 of 145) had received salicylates during matched antecedent illnesses (odds ratio of all 30 cases vs. all controls = 16.1; lower 95 per cent confidence limit = 4.6). The prevalence and mean severity score of signs, symptoms, and selected events during the antecedent illness tended to be lower among cases than controls. Thus, differences in the severity of this illness between cases and controls did not explain differences in medication exposures.

This pilot study suggests an association between Reye's syndrome and the use of salicylates during an antecedent illness. (N Engl J Med 1985; 313:849-57.)

In the past five years, case-control studies in Arizona, Michigan (two studies), and Ohio have reported a statistically significant excess risk of Reye's syndrome in association with ingestion of salicylates during antecedent chickenpox and respiratory illnesses. These four studies were reviewed by several groups, including an advisory panel convened by the Centers for Disease Control, the American Academy of Pediatrics Committee on Infectious Disease, and a Food and Drug Administration working group. On the basis of the findings of this review, the Surgeon General of the Public Health Service proposed an epidemiologic study of the American Academy of Pediatrics advised giving salicylates and salicylate-containing medications under usual circumstances to children with influenza or chickenpox.

As with many epidemiologic studies, concerns have been expressed regarding methodologic issues and the limitations of these four studies, including possible differences in the ability of case and control parents to recall and verify the medications administrated, differences in the severity of the matched antecedent illness for which cases and controls were receiving medications, and possible misclassification of non-cases as cases of Reye's syndrome. In an effort to address these and other concerns, a Public Health Service Task Force was formed to design and implement a new epidemiologic study concerning the nature of the possible relation between Reye's syndrome and medications. A committee of the Institute of Medicine, National Academy of Sciences, served as an advisory board to evaluate the proposed protocol, monitor the study's progress, and review the analyses and results. A pilot study was undertaken during mid-February through May 1984, to determine the feasibility and establish the methods of the main study.

The Institute of Medicine reviewed the data-collection methods for the pilot study in August 1984 and reviewed data analysis in December 1984. In view of the strength of the findings of an epidemiologic association between Reye's syndrome and salicylates, the institute recommended that the pilot study be published. This report describes the major findings of this study.

Methods

Criteria for Eligibility

All patients with Reye's syndrome who were enrolled in the study had to have received the diagnosis from a physician and to have had a respiratory, gastrointestinal, or chickenpox antecedent illness within three weeks before hospitalization, and all had to have Stage II or deeper encephalopathy as defined in a previously reported National Institutes of Health consensus conference. Guidelines for diagnosing Reye's syndrome were based on previously published criteria of the Centers for Disease Control. At the conclusion of the pilot study, the hospital records of the enrolled patients with Reye's syndrome were reviewed by an independent expert panel of physicians to confirm the diagnosis.

Study Sites and Case Enrollment

Eligible patients were identified through the cooperation of 16 participating pediatric tertiary care centers (defined as hospitals with 50 or more pediatric beds or a pediatric intensive care unit, or both) located in 11 states. In addition, we received statewide cooperation in Ohio, Oklahoma, and Minnesota. In these three states, 90 hospitals with 20 or more pediatric beds participated, including 17 pediatric tertiary care centers.

For the 16 pediatric tertiary care centers in 11 states, a hospital surveillance officer, usually a nurse or physician who was involved in the care of patients with Reye's syndrome, notified a central coordinator of all hospitalized patients with confirmed or possible Reye's syndrome (including those identified with possible Stage 0 or I) within 24 hours of hospitalization or diagnosis. These central coordinators, employed by an independent research contractor (Westat) or the state health departments (for hospitals in the three participating states), contacted hospital surveillance officers approximately twice a month to ensure prompt and continued report-
ing of all confirmed and possible cases of the syndrome. Patients hospitalized with Stage 0 or I Reye's syndrome were followed daily by telephone (for five days or until the day of discharge) to determine whether they met the study's criteria for eligibility; none of these patients had progression to Stage II or deeper encephalopathy.

Controls: Source and Matching Criteria

Four types of controls were sought: children visiting the emergency room where the case child was hospitalized (emergency room controls), children hospitalized at the same center as the matched case (inpatient controls), those attending the same school or day-care center (school controls), and those identified by random digit dialing (community controls). Only school controls and community controls were sought for cases identified through hospitals located in the three participating states.

The controls were randomly selected from children matched to cases on the basis of age group, race (black or not black), and the occurrence of the same type of antecedent illness (whether chickenpox, respiratory illness, or gastrointestinal illness) within a pre-established period. Cases under one year of age were matched to controls within six months of their age; other children were matched as follows: cases one year of age and controls six months to two years of age; cases two years of age and controls one to three years of age; cases three years and controls two to five years; cases four years and controls three to six years; cases five years and controls four to seven years; and cases six years and controls within four years of their age. Chickenpox was defined as characteristic blisters with fluid, respiratory illness as any two of the following manifestations — fever, runny nose or congestion, cough, and sore throat — lasting two or more consecutive days in the absence of chickenpox, and gastrointestinal illness as three or more loose watery stools for two or more consecutive days in the absence of either chickenpox or respiratory illness. Inpatient and emergency room controls were selected from a list of patients who were hospitalized or seen in the emergency room within two days before and seven days after hospitalization of their matched case and were required to have had the onset of their matched antecedent illness within three weeks before hospitalization or emergency room visit. School controls were matched for the occurrence of an antecedent illness within four days before or after the onset of the matched case's antecedent illness, and community controls were matched to within four days before and seven days after the onset of the matched case's antecedent illness. Seventeen percent of the parents of subjects selected refused to participate, including the parents of 15 percent of emergency room controls, 4 percent of hospital controls, 14 percent of school controls, and 21 percent of community controls.

Exclusion Criteria: Emergency Room and Hospital Controls

The protocol specified that hospital and emergency room patients with selected chronic illnesses were to be excluded as controls because of concern that patients identified from these sources might have an excessive prevalence of certain conditions or diseases not represented in the case group. In the event that patients with Reye's syndrome and these chronic illnesses were enrolled in the study, these patients and their matched hospital and emergency room controls were to be excluded from analyses. The chronic illnesses were those for which antipyretics were indicated or contraindicated, such as juvenile rheumatoid arthritis and other rheumatic diseases, and those that might require frequent visits to a physician, during which subjects might receive more advice about medications than would children without such illnesses (including children with previously diagnosed bleeding disorders or cancer). When necessary, decisions concerning illnesses to be excluded were made by one of two pediatricians who were provided only with the admitting diagnosis of the potential control.

Interviews, Questionnaires, and Visual Aids

Parents or guardians of cases and controls were screened by telephone to identify the main care provider, that is, the person who provided the most care for the child during the antecedent illness (usually a parent). During the screening interview, the date of onset and type of antecedent illness were determined for matching purposes. For subsequent interviews, the major care provider was also asked to identify other care providers, defined as persons who had taken care of the child for four or more consecutive hours on any day during the illness or had been present when the child might have taken medication.

The in-depth interviews with the main care provider included questions concerning the child's illness, such as the type and severity of symptoms and the level of activity (whether the child was in bed each day, and the number of absences from school), and the medications taken during the illness or until the day of hospitalization (for cases and hospital controls), emergency room visit (for emergency room controls), or recovery from illness, whichever occurred earliest. Information about medications included the brand name, the daily dosage, the number of times the drug was administered, and the person administering it (the interviewee, another parent, a babysitter, or someone else). Other care providers were interviewed concerning medication histories only. Information concerning medications that children self-administered was obtained from main care providers; however, after a modification of the protocol, two case and two control children were interviewed.

To facilitate the respondent's recall, a calendar of important events related to the subject's illness was completed at the beginning of the interview. Interviewees were asked to refer to this calendar when responding to questions concerning the child's illness. In addition, interviewees were asked to show the bottles or containers of medications to the interviewer for documentation; when medication containers were not available for verification, interviewees were asked to identify medications from a set of pictures, developed from the Physicians' Desk Reference, of the most commonly used nonprescription medicines.

Professional interviewers, employed and trained by the independent contractor, conducted structured and close-ended interviews according to written procedures.

Onset of Reye's Syndrome

In comparisons of symptoms and events during the antecedent illness among cases and controls and before the onset of Reye's syndrome among cases, the onset of the syndrome was defined as the first day when any of a series of symptoms (alone or in combination) occurred for more than one consecutive day, including nausea, vomiting, dry heaves, hyperactivity, excitability, disorientation or confusion, delirium, combativeness, and coma. The onset was designated as one calendar day earlier if headache, dizziness, lethargy, or severe loss of appetite first occurred on that day.

Comparisons of Antecedent Illnesses among Cases and Controls

A measure of the severity of illness was developed to allow case-control comparisons of selected signs, symptoms, and events of the respiratory antecedent illnesses (before the onset of Reye's syndrome) that might explain differences in exposure to medications. The measure of severity included a mean overall severity score based on parents' daily perception of the illness (zero points for no illness, one point for mild, two for moderate, and three for severe) averaged over the entire illness; the overall prevalence of specific symptoms, including headache, cough, sore throat, and muscle aches; the mean daily severity of fever (zero points for no fever, one point for mild, two for moderate, and three for severe); and the occurrence of selected events or actions, including remaining in bed or absence from school, and contact or visit with a health care professional. The potential confounding role of these variables in explaining differences in medication use was assessed with a conditional multiple logistic regression procedure that incorporated these variables.

Study Modifications

Since this was a pilot study, several modifications in the study protocol and questionnaires were implemented during the study to improve the quality of the data on medications, including expansion of the number of drug pictures used for visual verification, efforts to
identify and interview additional care providers who might have administered medications (as well as teenagers who self-medicate), and attempts to interview more parents of inpatient controls while their child was still hospitalized.

Analyses of Medication Exposures

Analyses of exposure to medications were based on the medications reported to have been administered by the main care provider and all other care providers during the antecedent illness, before the clinically defined onset of Reye’s syndrome for cases and on any day during the matched antecedent illness for controls. Odds ratios were estimated with use of univariate and multivariate conditional logistic-regression models for matched sets. In the logistic models, the exposure status was the dependent variable, and the case status, symptoms, actions, and events included as measures of severity were the independent variables. Unadjusted odds ratios refer to models that do not include the measures of severity; adjusted models include these measures. One-tailed (95 per cent) confidence limits are given.

RESULTS

Case Review

Thirty-two patients who met the criteria for eligibility were initially enrolled as cases in the study. The physician review panel excluded two patients (one with apparent valproate toxicity and one whose hepatic pathological findings were not characteristic of Reye’s syndrome). Thus, 30 cases, 26 with respiratory antecedent illnesses and 4 with chickenpox, and their matched controls were used for the analysis. Two of the 30 cases had chronic illnesses — juvenile rheumatoid arthritis and Kawasaki’s syndrome. Because inpatient and emergency room controls with these illnesses were excluded, these cases and their inpatient and emergency room controls were not included in estimates of odds ratios for cases versus inpatient controls, emergency room controls, or all controls.

The ages of the 30 cases ranged from 5 months to 18 years, with a median of 13 and a mean of 11.5. The majority of cases (22, or 73 per cent) were between 10 and 18 years of age (Table 1), five (17 per cent) were 5 to 9, and three (10 per cent) were under 5, including two who were under 2. Twenty-seven (90 per cent) were white, one (3 per cent) was black, 1 (3 per cent) was Asian, and one (3 per cent) was “other.” Seventeen (57 per cent) were female. Eighteen (60 per cent) were hospitalized at pediatric tertiary care centers outside the three states; the remaining cases were hospitalized in the three states, all but one at pediatric tertiary care centers. Six cases were hospitalized in February, 13 in March, 10 in April, and 1 in May.

The mean levels of serum aspartate aminotransferase, alanine aminotransferase, and ammonia in the cases were 935 IU per liter, 980 IU per liter, and 313 mg per deciliter, respectively. Biopsy or autopsy confirmation of the diagnosis was obtained for seven patients. Twelve patients had Stage II disease; 18 had progression to Stage III or deeper. Six patients died — a case-fatality rate of 20 per cent.

A total of 145 controls were enrolled in the study — 25 emergency room controls (obtained for 14 cases), 22 inpatient controls (obtained for 13 cases), 41 school controls (obtained for 23 cases), and 57 community controls (obtained for 28 cases). The age and racial distribution of controls were similar to those of cases (Table 1). The plurality of inpatient and emergency room controls (36 per cent each) were admitted or seen in the emergency room because of acute infectious processes such as pneumonia or urinary tract infections; other reasons for hospitalization or emergency room visit included trauma, non-elective or elective surgery, abdominal pain, and seizures.

One main care provider was interviewed for each of the 30 cases and 145 controls. One other care provider was identified and interviewed for 30 per cent of cases and 23 per cent of controls, and two or more such persons were interviewed for 17 per cent of cases and 6 per cent of controls. The interviews for 77 per cent of the main care providers for cases took place in the hospital as compared with 6 per cent of such interviews for all controls and 36 per cent of those for inpatient controls.

Interviews of main care providers were completed a mean of 9.4 days (range, 5 to 24) after the onset of matched antecedent illnesses in cases, as compared with a mean of 12.9 days (range, 5 to 28) after the onset in all controls. Interviews for 93 per cent of cases and 72 per cent of controls were conducted within 14 days of the onset of the antecedent illness, and those for 97 per cent of cases and 92 per cent of controls were conducted within 21 days.

Generic Components of Medications

We analyzed the generic components of medications reported to have been administered by either the main care provider or other care provider before the clinically defined onset of Reye’s syndrome in cases and at any time during the matched antecedent illness in controls. The analysis revealed that 10 compounds were used by at least 20 per cent of cases or members

| Table 1. Characteristics of 30 Patients with Reye’s Syndrome (Cases) and 145 Controls.* |
|-----------------------------------------------|---------------|---------------|
| Age (yr)                                      |               |               |
| <5                                            | 3 (10)        | 17 (12)       |
| 5-9                                           | 5 (17)        | 26 (18)       |
| 10-18                                         | 22 (73)       | 102 (70)      |
| Mean ± S.D.                                   | 11.5±4.4      | 10.9±4.3      |
| Race                                          |               |               |
| White                                         | 27 (90)       | 138 (95)      |
| Black                                         | 2 (1)         | 21 (15)       |
| Asian                                         | 1 (3)         | 1 (1)         |
| Other                                         | 1 (3)         | 4 (3)         |
| Sex                                           |               |               |
| Male                                          | 13 (43)       | 69 (48)       |
| Female                                        | 17 (57)       | 76 (52)       |
| Antecedent illness                            |               |               |
| Respiratory                                   | 26 (87)       | 134 (92)      |
| Chickenpox                                    | 4 (13)        | 11 (8)        |

*Except where otherwise indicated, values are numbers of patients with percentages shown in parentheses.
of any of the four control groups (Table 2). Among all generic components, only two had been used with a significantly different frequency among cases and all four control groups: salicylates were given to more cases than controls (93 vs. 46 per cent), and acetaminophen was given to more controls than cases (67 vs. 27 per cent).

On the basis of these frequencies, the unadjusted matched odds for cases (n = 30) receiving salicylates were found to be significantly greater than the odds for all matched controls (odds ratio = 16.1, lower 95 per cent confidence limit = 4.6). The odds ratios for the four control groups were 9.5, lower limit = 1.9 (school controls); 12.6, lower limit = 3.5 (community controls); 49.4, lower limit = 8.6 (emergency room controls); and 57.5, lower limit = 8.4 (inpatient controls). Cases were also found to have significantly lower odds for receiving acetaminophen during the antecedent illness than all controls (odds ratio = 0.22, upper limit = 0.44). Similar trends were noted for each control group; the odd ratios were 0.16 (emergency room), upper limit = 0.65; 0.20 (community), upper limit = 0.44; 0.25 (inpatient), upper limit = 1.09; and 0.26 (school), upper limit = 0.92.

Ninety-three per cent of cases, 92 per cent of emergency room controls, 93 per cent of community controls, 90 per cent of school controls, and 77 per cent of inpatient controls were exposed to either salicylates or acetaminophen at some time during the antecedent illness. The majority (90 per cent of cases and 85 per cent of all controls) were first exposed on or before the third day of illness (with inpatient controls having the lowest exposure rate) (Fig. 1). Differences in cumulative percentages of cases and controls exposed to these medications were apparent by the first days of illness; 70 per cent of cases, as compared with 30 per cent of controls, were exposed to salicylates by the first day, and 7 per cent of cases, as compared to 41 per cent of controls, were exposed to acetaminophen. Twenty-seven per cent of cases, 8 per cent of emergency room controls, 18 per cent of inpatient controls, 32 per cent of school controls, and 26 per cent of community controls received both salicylates and acetaminophen.

**Brands of Medications**

Interviewers were able to verify medications by seeing the bottles or containers for 55 per cent of the medicines reported for cases, 72 per cent of those reported for emergency room controls, 51 per cent for inpatient controls, 79 per cent for school controls, and 80 per cent for community controls. Interviewees for cases were able to identify an additional 10 per cent of medications from the pictures provided, as compared with 5 per cent, 20 per cent, 7 per cent, and 7 per cent identification among interviewees for emergency room, inpatient, school, and community controls, respectively.

Among study subjects exposed to salicylate-containing medications, brand names were reported for 93 per cent of cases (26 of 28) and 92 per cent of controls (61 of 66). No differences were identified in the brands of salicylates administered to cases or controls; the brand reported most commonly was mentioned for 36 per cent of the exposed cases and controls, and the second most common was reported for 14 per cent of both cases and controls.

The 28 cases exposed to salicylates received an estimated 3 to 183 mg of salicylates per kilogram of body weight per day, with a mean dose of 34 mg per kilogram per day and median dose of 26, during the antecedent illness (before the onset of Reye’s syndrome). Only two subjects were exposed to more than 65 mg per kilogram per day, the recommended antipyretic daily pediatric dose — the case with Kawasaki’s syndrome and the case with juvenile rheumatoid arthritis. No dose–response relationship was observed with the deepest stage of Reye’s syndrome used as the response. (No information concerning weights was obtained for controls.)

**Antecedent Illnesses of Cases and Controls**

Twenty-four of the 26 cases with a respiratory antecedent illness and their matched controls were analyzed to assess differences in the antecedent illness as a possible explanation for differences in medication exposure. (The cases with juvenile rheumatoid arthritis and Kawasaki’s syndrome and their matched controls were excluded from these analyses.) The duration, prevalence, severity of symptoms, level of activity (ab-
The mean duration of the antecedent illness for cases (before the onset of Reye's syndrome) was shorter (3.8 days) than it was for controls (range, 8.5 days, for emergency room controls, to 9.9 days, for inpatient controls); none of the cases had an illness with a duration of 10 days or longer, compared with 34 per cent of all controls (43 of 125). This shorter duration for cases would be expected, since the antecedent illness of cases was truncated on the day before the onset of Reye's syndrome. Similarly, the mean duration of each symptom used as a measure of severity, including fever, cough, headache, muscle aches, and sore throat, was shorter for cases than controls.

The highest mean scores for overall severity and fever and the highest overall prevalence of symptoms and associated actions occurred in school controls, followed by community controls; the scores and prevalence of symptoms in emergency room and inpatient controls tended to be lower.

The mean overall severity score for cases (1.3) was comparable to that for controls (range, 1.4 to 1.8); the highest mean score was reported by parents of school controls. Fever during the antecedent illness was reported less frequently for cases (54 per cent) than for any of the four control groups (range, 59 per cent, for inpatient controls, to 89 per cent, for school controls). Among controls, the mean severity score for fever was comparable to or higher than that among cases.

Only 7 (29 per cent) of the 24 cases with an antecedent respiratory illness reported a measured temperature on any day of the illness, as compared with 72 (58 per cent) of the 125 controls (range, 41 per cent of inpatient controls to 67 per cent of school controls). Among those reporting, the mean peak temperature for seven cases was 37.8°C, as compared with 39°C for 11 emergency room controls, 39.2°C for 7 inpatient controls, 38.8°C for 24 school controls, and 38.6°C for 30 community controls; 2 of the 7 cases (29 per cent) and 40 of the 72 controls (56 per cent) had a peak measured temperature ≥38.9°C (102°F).

Adjustment for the Severity of the Antecedent Illness

Using a multivariate conditional logistic-regression model to adjust for the observed differences in symptoms and associated actions selected to characterize the antecedent illness (Appendix), the case-control odds ratio for receiving salicylates increased from an unadjusted estimate of 12.2 (lower limit = 3.5) (for cases and controls with a respiratory antecedent illness) to an adjusted estimate of 19.0 (lower limit = 4.8). This increase in the odds ratio indicated that the higher prevalence of symptoms and associated actions among controls tended to reduce the strength of the relationship. The adjusted odds ratios according

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**Figure 1.** Cumulative Percentage of Study Subjects Exposed to Salicylates or Acetaminophen or Both, According to Day of Illness.
Table 3. Symptoms and Associated Actions Reported during Antecedent Respiratory Illnesses for 24 Cases and 125 Matched Controls.

<table>
<thead>
<tr>
<th>Symptom or Action</th>
<th>Cases (n = 24)</th>
<th>Emergency Room (n = 21)</th>
<th>Inpatient (n = 17)</th>
<th>School (n = 36)</th>
<th>Community (n = 51)</th>
<th>All Controls (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (mean no. of days)</td>
<td>3.8</td>
<td>8.5</td>
<td>9.9</td>
<td>8.7</td>
<td>9.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Overall severity score (mean)*</td>
<td>1.3</td>
<td>1.5</td>
<td>1.4</td>
<td>1.8</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Fever score (mean)*</td>
<td>1.0</td>
<td>1.3</td>
<td>1.1</td>
<td>1.8</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Mean temperature (°C)†</td>
<td>37.8</td>
<td>39</td>
<td>39.2</td>
<td>38.8</td>
<td>38.6</td>
<td>38.8</td>
</tr>
<tr>
<td>Fever†</td>
<td>54% (1.3)</td>
<td>71% (2.3)</td>
<td>59% (1.4)</td>
<td>89% (3.7)</td>
<td>80% (2.6)</td>
<td>78% (2.7)</td>
</tr>
<tr>
<td>Cough‡</td>
<td>71% (1.8)</td>
<td>76% (5.1)</td>
<td>82% (4.5)</td>
<td>85% (5.0)</td>
<td>86% (5.9)</td>
<td>83% (5.3)</td>
</tr>
<tr>
<td>Headache‡</td>
<td>46% (1.0)</td>
<td>71% (1.9)</td>
<td>41% (1.2)</td>
<td>86% (4.1)</td>
<td>76% (2.5)</td>
<td>74% (2.7)</td>
</tr>
<tr>
<td>Muscle aches†</td>
<td>21% (0.4)</td>
<td>29% (1.1)</td>
<td>29% (0.8)</td>
<td>81% (3.3)</td>
<td>33% (1.4)</td>
<td>46% (1.8)</td>
</tr>
<tr>
<td>Sore throat‡</td>
<td>54% (1.3)</td>
<td>67% (2.0)</td>
<td>59% (2.8)</td>
<td>83% (4.6)</td>
<td>67% (2.7)</td>
<td>70% (3.1)</td>
</tr>
<tr>
<td>Absent from school/in bed‡</td>
<td>63% (1.6)</td>
<td>86% (2.3)</td>
<td>71% (3.1)</td>
<td>97% (4.9)</td>
<td>86% (3.2)</td>
<td>87% (5.5)</td>
</tr>
<tr>
<td>Consult/see health care provider‡</td>
<td>17%</td>
<td>57%</td>
<td>65%</td>
<td>61%</td>
<td>45%</td>
<td>54%</td>
</tr>
</tbody>
</table>

*Based on parent’s report of none = 0, mild = 1, moderate = 2, and severe = 3.
†Shown only if fever was indicated and measured (7 cases, 11 emergency room controls, 7 inpatient controls, 24 school controls, and 30 community controls).
‡Values are per cent of patients with mean number of days for each symptom or action shown in parentheses.

The odds ratio for cases versus controls receiving acetaminophen, based on the same model and adjusted for clinical severity, increased from 0.21 to 0.41 (upper limit = 1.07). The adjusted odds according to type of control were 0.23 (emergency room control), 0.31 (community control), 0.44 (inpatient control), and 0.81 (school control).

**Discussion**

This pilot study suggests an epidemiologic association between ingestion of salicylates during antecedent illnesses and the subsequent development of Reye’s syndrome. High odds ratios were observed when cases were compared with all controls combined and with each individual control group.

Four previous studies have also demonstrated an association between Reye’s syndrome and salicylates. In all prior studies, as in the current pilot study, more than 90 per cent of the patients received salicylates; 96 per cent (24 of 25), 97 per cent (94 of 97), 100 per cent (7 of 7), and 100 per cent (14 of 14) of children with Reye’s syndrome had received salicylates in studies conducted in Michigan, Ohio, Arizona, and Michigan (a second study), respectively. The prevalence of salicylate use during antecedent illnesses among controls ranged from 44 to 71 per cent. As was observed in the Ohio study, the majority of patients with Reye’s syndrome in our study were exposed to only moderate doses of salicylates (mean, 34 mg per kilogram per day in the current study versus 47 in the Ohio study).

The data collected in this pilot study can be used to address several important issues raised in this and prior studies, including the possible differential recall of illness, events, and particularly medications by case and control parents; the possible misclassification of medications by case or control parents; the misclassification of non-cases as cases of Reye’s syndrome or the failure to recognize and enroll patients with the syndrome at participating centers; the possibility of exposure to salicylates after the onset of Reye’s syndrome and not during the matched antecedent illnesses; and differences in the severity of the antecedent illness between cases and controls.

Several features were incorporated into the study design to diminish or address concerns about possible differential recall among case and control parents, including interviewing them as quickly as possible after the onset of matched illnesses, obtaining brand names of medications; and visual verification of medications. A group of controls hospitalized or seen in the emergency room was also included to allow comparisons between subjects interviewed after more comparable events under more similar circumstances. To reduce the possibility of interviewer bias, which might have resulted from knowledge of case–control status, a structured interview with closed-ended questions was employed.

No evidence of differential recall of medications between case and control parents was observed. Analysis of the frequency of exposure to almost all generic components of medications (Table 2), to combination products not containing salicylate or acetaminophen, and to antibiotics (Fig. 2), revealed that a comparable or lower percentage of cases than controls received these medications. In these analyses, cases and controls differed significantly only in frequency of exposure to salicylate and acetaminophen products. This would not be expected if recall of case parents was uniformly greater for all medications.

Analyses of medication exposures were based on reports of main care providers (usually parents), who indicated what medications they and others administered (as well as what their children self-administered) and reports of other care providers (e.g., a second par-
ent or a babysitter), who indicated what medications they administered. Although more cases than controls were found to have other care providers (who were subsequently interviewed), this difference was largely attributable to other persons who cared for the case child after the onset of Reye's syndrome; the percentage of subjects with one or more other care providers who administered medications during the antecedent illness was similar for cases and controls (during the antecedent illness, 37 per cent of cases and 29 per cent of controls had one or more other care provider, but 20 per cent of cases and 23 per cent of controls had one or more other care provider who administered medications). Furthermore, the difference in the number of other care providers for cases and controls did not account for the differences in salicylate use. When the definition of medication exposure was restricted to drugs that the main care providers reported having themselves given, 67 per cent of cases as compared with 32 per cent of controls were found to have received salicylates, and significant differences in exposure to salicylates were observed (odds ratio for salicylates = 4.4, unadjusted [n = 30], lower 95 per cent limit = 2.1).

Care providers of both cases and controls were usually able to recall the specific brands of salicylate-containing medications administered; brand names of these medications were reported for 93 per cent of cases and 92 per cent of controls. Furthermore, the distribution of brands of salicylates reported by parents of cases and controls was similar. Thus, there did not appear to be a differential tendency between case and control parents to report analgesic/antipyretic preparations as "aspirin" or simply to report well-known brand-name products. Although the care providers for cases were less frequently able to verify medications by showing interviewers the bottles than were the care providers for control groups (with the exception of inpatient controls), this difference is consistent with the fact that persons interviewed in the hospital less frequently had containers available for verification. The parents of both cases and controls who were interviewed at home were able to show the interviewers the containers for approximately 80 per cent of the medications they reported.

Pathological confirmation of the diagnosis of Reye's syndrome is infrequently obtained at most pediatric centers; seven (23 per cent) of the cases diagnosed in this study were confirmed at biopsy or autopsy. Consequently, to reduce concerns about possible misdiagnosis of non-cases as cases of Reye's syndrome, all patients enrolled as cases were required to have the clinical picture of encephalopathy of at least Stage II Reye's syndrome (in which the patient is combative or stuporous and may verbalize inappropriately). Twenty-nine (97 per cent) of the patients enrolled as cases were hospitalized and diagnosed at major pediatric centers. In addition, a panel that conducted an independent review of the hospital records determined that 30 of 32 patients meeting the criteria for eligibility

![Figure 2. Percentage of Study Subjects Exposed to Medication in Four Categories.](image-url)
were appropriately diagnosed and that 2 should be excluded because another diagnosis was considered more likely. The high index of suspicion for patients presenting with Stage II or greater encephalopathy (which would routinely result in studies of liver function) also helped to ensure that all such patients hospitalized at the participating centers were promptly recognized and appropriately diagnosed, regardless of the history of salicylate exposure.

Although this was not a requirement of the pilot study, a second panel from the Institute of Medicine advisory committee also reviewed the hospital records of the 32 eligible patients. The second panel concurred with the first panel on all but one of the patients, a child exposed to salicylates who they thought might not have had Reye’s syndrome. Analysis of the remaining 29 cases, for which there was total agreement, revealed similar odds that remained significantly elevated: 93 per cent of the cases (27 of 29) as compared with 47 per cent of the controls (66 of 139) were exposed to salicylates; odds ratio for cases versus all controls = 10.4, lower limit = 3.0, unadjusted, and 16.7, lower limit = 4.2, adjusted.

There is no evidence that differences in exposure to salicylates between cases and controls occurred because some patients received salicylates for the treatment of symptoms of Reye’s syndrome rather than symptoms of the antecedent respiratory or chickenpox illness. Analyses were based on exposures to medications during the matched antecedent respiratory or chickenpox illness of study subjects. For cases, this period was before the clinically determined day of onset of Reye’s syndrome. Similar odds for salicylates and acetaminophen were found when a statistically determined date of onset of Reye’s syndrome was used. Furthermore, differences in exposure to salicylates were apparent even on the first day of the antecedent illness, when 70 per cent of cases and 30 per cent of controls had received salicylates; and most cases (93 per cent, 26 of 28) and controls (91 per cent, 60 of 66) who received salicylates took their first dose by the third day of their matched illness.

Analyses indicated that differences in the severity of the antecedent illness between cases and controls did not explain the higher prevalence of salicylate use among cases. The duration (mean number of days) and prevalence of symptoms and associated actions, as well as the reported severity and fever scores, tended to be lower for cases than controls. Though not reported here, in analyses comparing cases and controls over the same number of days of illness, and thereby controlling for the duration of illness, similar differences in severity of illness and odds ratios associated with the use of salicylates were observed. Most of the measures of severity of illness, including severity score and fever score, were based on parents’ reported perception; however, more objective information concerning absence from school, number of days in bed, and peak temperature (as well as the percentage of subjects with temperatures above 38.9°C [102°F]), though limited, also suggested that the antecedent illnesses of cases tended to be less severe than those of controls. Further evidence that the matched antecedent illnesses of cases were not more severe than those of controls is the fact that cases received a comparable number of medications or fewer in several categories (Fig. 2), including combination products (primarily cold preparations) and antibiotics.

This pilot study demonstrated a strong association between Reye’s syndrome and the use of salicylates during the antecedent illness of Reye’s syndrome, consistent with the results reported in earlier studies. Evaluation of epidemiologic issues of concern did not explain the significant differences in salicylate use between cases and controls. The main study of Reye’s syndrome and medications, involving more than 50 pediatric tertiary care centers throughout the United States, is currently under way.

We are indebted to Reye Syndrome Task Force Members Lowell T. Harmiss, Ph.D., Joel N. Kuritsky, M.D., Ann Rose, Ph.D., and former member Stanley Edlavitch, Ph.D., for their contributions to this study; to Vaughn Trader for assistance; to Martha Berlin, Project Manager, for assistance; to Mort Robins, Project Director, and to other study personnel of Westat, Inc., as well as study participants from the Ohio, Oklahoma, and Minnesota State Health Departments and from Cardinal Glennon Memorial Hospital for Children, St. Louis Children’s Hospital, Birmingham, Ala., Children’s Hospital of Philadelphia, Children’s Hospital of Pittsburgh, Children’s Hospital Medical Center, Boston, Children’s Hospital National Medical Center, Washington, D.C., Children’s Medical Center of Dallas, Denver Children’s Hospital, James Whitcomb Riley Hospital for Children, Indianapolis, Ind., Lubbock General Hospital, Medical College of Virginia, Methodist Hospital of Indiana, Primary Children’s Medical Center, Salt Lake City, Utah, St. Christopher’s Hospital for Children, Philadelphia, St. Louis Children’s Hospital, and University Hospital of Upstate Medical Center, Syracuse, N.Y.

Appendix

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\text{Log odds ratio} = 2.95X_1 - 0.50X_2 + 0.73X_3 - 1.32X_4 \\
+ 0.03X_5 + 0.70X_6 + 0.34X_7 + 0.18X_8 + 1.32X_9
\]

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>VARIABLE</th>
<th>POSSIBLE VALUES</th>
<th>RELATIVE ODDS* OF SALICYLATE EXPOSURE (CONTROLLING FOR OTHER VARIABLES)</th>
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<tbody>
<tr>
<td>1</td>
<td>Case status</td>
<td>Case/control</td>
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<tr>
<td>2</td>
<td>Average daily severity</td>
<td>Mild/moderate/severe</td>
<td>0.60</td>
</tr>
<tr>
<td>3</td>
<td>Average daily fever</td>
<td>None/mild/moderate/severe</td>
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<td>4</td>
<td>Contact any health care provider</td>
<td>Yes/no</td>
<td>0.27</td>
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<tr>
<td>5</td>
<td>In bed/absent</td>
<td>Yes/no</td>
<td>1.03</td>
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<tr>
<td>6</td>
<td>Headache</td>
<td>Yes/no</td>
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<td>7</td>
<td>Muscle aches</td>
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<td>8</td>
<td>Sore throat</td>
<td>Yes/no</td>
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<td>9</td>
<td>Cough</td>
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</table>

*Exponentiation of coefficient given for log odds ratio.

REFERENCES