The Rotavirus Vaccine’s Withdrawal and Physicians’ Trust in Vaccine Safety Mechanisms

Heather A. McPhillips, MD, MPH; Robert L. Davis, MD, MPH; Edgar K. Marcuse, MD, MPH; James A. Taylor, MD

Objective: To determine how the withdrawal from the market of the rotavirus vaccine has affected physicians’ trust in vaccine safety mechanisms, future adherence to vaccine recommendations, and willingness to use a new rotavirus vaccine.

Design: National survey mailed to 1228 randomly selected pediatricians and family physicians.

Main Outcome Measures: Confidence in vaccine safety mechanisms was defined by agreement with the statements that the system for determining vaccine safety before a vaccine is licensed works well and that the system for monitoring vaccine safety after vaccine licensure works well. Physicians who indicated that they would use a new rotavirus vaccine within 1 year of licensure and recommendation by professional organizations were classified as “early adopters.” Logistic regression was used to assess the relationship between trust in vaccine safety mechanisms and future early adoption of new rotavirus vaccines.

Results: Following the withdrawal of the rotavirus vaccine, 83% of respondents believed the postlicensure surveillance system works well to monitor vaccine safety, while 22% of respondents believed the prelicensure system works well to determine vaccine safety. After adjusting for physician specialty and years in practice, respondents who believed the prelicensure vaccine safety system works well were significantly more likely to be early adopters than those with less confidence in prelicensure studies (adjusted odds ratio, 2.2 [95% confidence interval, 1.3-3.6]).

Conclusions: Physicians have different levels of trust in prelicensure studies that determine vaccine safety and postlicensure surveillance systems that monitor vaccine safety. Trust in prelicensure vaccine safety evaluations may be associated with early adherence to new vaccine recommendations.

Arch Pediatr Adolesc Med. 2001;155:1051-1056

The past decade has seen an explosion of vaccine research and development.1 Vaccines against hepatitis B, varicella, rotavirus, and pneumococcus have been added to the recommended childhood immunization schedule.2 With the addition of these new vaccines, some of which prevent diseases generally perceived as less serious (rotavirus, varicella), and with the rarity of outbreaks from vaccine-preventable diseases, more concerns are being raised in the popular press as well as the medical literature about vaccine safety.3-5

The United States has several mechanisms to ensure that licensed vaccines are safe for use in the general public. The first steps are the prelicensure clinical studies, which are designed to determine the overall safety, immune response, efficacy, and the risk of adverse effects from vaccines in the group for whom the vaccine is intended.6-8 These studies are limited in their ability to detect very rare adverse events because the studies are performed on 10000 to 20000 children. After licensing by the Food and Drug Administration (FDA), Washington, DC, vaccines are monitored for safety by the Vaccine Adverse Events Reporting System, a passive surveillance system that receives case reports from providers and parents of children who have adverse events temporally associated with vaccination.9,10 The Vaccine Adverse Events Reporting System reports raise hypotheses that can be evaluated using the Vaccine Safety Datalink, a database that collects clinical information on 2% to 4% of the nation’s children at 4 large West Coast health maintenance organizations and allows for population-based assessment of vaccine safety.11 Special epidemiologic studies are conducted by federal agencies in conjunction with states when postlicensure studies are inconclusive or require confirmation.
The rapid withdrawal of the tetravalent rhesus-human reassortant rotavirus vaccine (RotaShield; Wyeth Laboratories Inc, Marietta, Pa) only 11 months after licensing may have affected physicians’ trust in future prelicensure vaccine safety evaluations and may change the way providers make decisions regarding whether to adhere to recommendations for new vaccines. Because of the potential cost savings in the United States and the important impact on morbidity and mortality from rotavirus diarrhea globally, pharmaceutical companies are continuing to pursue development of both attenuated human and bovine-human reassortant rotavirus vaccines. The potential risk of intussusception after immunization with these types of rotavirus vaccines has not been established.

We conducted a national survey of pediatricians and family physicians to determine how the withdrawal of the RotaShield vaccine has affected physicians’ trust in vaccine safety mechanisms, future adherence to vaccine recommendations, and willingness to use a new rotavirus vaccine. We also wanted to determine if any important differences exist between family physicians’ and pediatricians’ confidence in vaccine safety or the likelihood of future utilization of new vaccines.

RESULTS

Of the 1228 surveys mailed, 49 were returned unopened with no forwarding address (32 pediatricians and 17 family physicians). Of the 1179 physicians contacted, 740 responded for an overall response rate of 63%. Among the 582 pediatricians contacted, 394 (68%) responded; 328 completed questionnaires, while 66 responded that they

SUBJECTS AND METHODS

SUBJECTS

We obtained a list of 614 pediatricians and 614 family physicians randomly selected from the American Medical Association’s Physician Masterfile of licensed physicians in the United States. We limited our sample to currently practicing pediatricians and family physicians living in the United States who completed residency training in their specialty, were listed as general or primary care physicians, and stated that their practice site was office- or hospital-based. In addition to names and addresses, the database provided information on each physician’s age, sex, birthplace, medical school and year of graduation, residency training and training dates, and practice specialty.

In February 2000, we sent each physician a questionnaire that required approximately 10 minutes to complete and included return postage. A $1 bill was included in the first mailing as an incentive to respond. Nonrespondents received up to 3 additional questionnaires spaced approximately 1 month apart. The final mailing was completed in June 2000. The University of Washington, Seattle, institutional review board approved this study.

SURVEY INSTRUMENT

The survey instrument had questions designed to determine (1) how confident physicians are about the prelicensure studies in determining vaccine safety; (2) how confident physicians are about the postlicensure surveillance system to monitor vaccine safety; (3) whether a new rotavirus vaccine would be accepted by physicians if the American Academy of Pediatrics (AAP), Advisory Committee on Immunization Practices (Centers for Disease Control and Prevention) (ACIP), and the American Academy of Family Physicians (AAFP) were to recommend the new vaccine; (4) how soon after recommendations physicians would adopt a new vaccine; and (5) the perceived importance of a rotavirus vaccine in the United States. The survey instrument also contained questions on demographic information, including physician practice location, practice type, number of children seen per week, subspecialty training, patients’ insurance status, and years since completion of residency. Finally, the survey contained questions to determine the physician’s experience with rotavirus disease and the RotaShield vaccine.

OUTCOMES

Confidence in vaccine safety mechanisms following withdrawal of the RotaShield vaccine was assessed by asking physicians if they believed the current system for determining new vaccine safety before the FDA approves a vaccine works well and whether the system for monitoring new vaccine safety after a vaccine is approved by the FDA works well. For purposes of this analysis, answers were dichotomized to “Yes” or “No/Undecided.” Physicians were also asked to agree or disagree with 4 statements assessing the effect of the RotaShield vaccine withdrawal on physicians’ trust in new vaccines and physicians’ opinions about the impact of the vaccine withdrawal on their patients’ trust in vaccines. Answers to this section were dichotomized to “strongly agree/agree” or “neutral/disagree/strongly disagree.”

We defined future “early adopters” of a new rotavirus vaccine as physicians who said they would feel comfortable using a new rotavirus vaccine based on FDA approval and AAP/ACIP/AAFP recommendation alone and would personally recommend the vaccine within 1 year of its inclusion into the recommended immunization schedule.

STATISTICAL ANALYSIS

Physicians who responded but were ineligible because they did not administer vaccines to children were excluded from the analyses. The Pearson $x^2$ test was used for categorical and dichotomous variables, and the Wilcoxon rank-sum test was used to compare nonparametric means. A separate analysis was performed using multiple logistic regression to determine what factors were associated with future early adopters of a new rotavirus vaccine. Variables were included in the final regression model if they were significantly associated with early adoption on bivariate analysis, or were important confounding factors or effect modifiers of the relationship between early adoption and confidence in vaccine safety mechanisms. Stata version 6 computer software (Stata Corp, College Station, Tex) was used for all analyses.
did not provide immunizations to children. Five hundred ninety-seven family physicians were contacted, and 346 (58%) responded; 230 completed questionnaires, and 116 responded that they did not provide immunizations to children. The final sample size was 358 physicians.

Respondents stratified by specialty type did not differ significantly from nonrespondents in any variable available to us in the address database, including age, sex, type of practice, or country of birth. No significant differences were observed in physicians who responded to the first, second, or third mailing.

Characteristics of eligible respondents are summarized in Table 1. Forty-eight percent of physicians reported practicing in a private group setting, and 26% reported practicing in solo private practice. Physicians who responded had been practicing for slightly longer on average than family physicians, were more likely to practice in an urban setting, and reported seeing more children per week for preventive care.

Eight to 12 months following the withdrawal of the RotaShield vaccine, physicians expressed a high level of confidence in postlicensure vaccine surveillance mechanisms but reported a low level of confidence in the effectiveness of prelicensure studies to ensure vaccine safety (Table 2). Overall, 22% of physicians reported that the prelicensure system works well, while 83% of physicians reported the postlicensure system works well. Forty-three percent of respondents reported reluctance to use any new rotavirus vaccine, while 28% of physicians reported that the withdrawal of the RotaShield vaccine has made them more reluctant to use any new vaccine. Nearly 40% of physicians felt their patients were more concerned about vaccine safety than ever before, but only 30% of physicians felt that the withdrawal of the RotaShield vaccine has increased distrust of new vaccines among their patients.

Physician attitudes regarding a new rotavirus vaccine are summarized in Table 3. Only a slight majority of respondents (57%) indicated that a rotavirus vaccine is needed. Once a new rotavirus vaccine is recommended, 34% of physicians responded that they would utilize the immunization within 6 months of the recommendation, while 64% would use it within 12 months. When asked what type of recommendation would be needed to allow clinicians to feel comfortable using a new rotavirus vaccine, the most common response was recommendation by organizations such as the AAP, AAFP, and ACIP; widespread use of the rotavirus vaccine has made me more reluctant to use any new vaccine in the future (pneumococcal, RSV, etc).

Events Reporting System; and RSV, respiratory syncytial virus. All values given as percentages.†Pediatricians differ significantly from family physicians, P<.05 (χ² analysis).

Agree With Statement | Pediatrists (n = 328) | Family Physicians (n = 230)
--- | --- | ---
Prelicensce studies prior to FDA approval work well to determine vaccine safety | 21 | 23
Postlicensure surveillance (VAERS and other safety mechanisms) works well to monitor vaccine safety† | 87 | 78
The withdrawal from the market of the rotavirus vaccine has made me reluctant to use any new vaccine in the future | 27 | 30
Patients are more concerned than even before about vaccine safety† | 43 | 34
The withdrawal from the market of the rotavirus vaccine has made my patients distrustful of new vaccines | 32 | 24

*FDA indicates Food and Drug Administration; VAERS, Vaccine Adverse Events Reporting System; and RSV, respiratory syncytial virus. All values given as percentages.†Pediatricians differ significantly from family physicians, P<.05 (χ² analysis).
CI, 0.3-0.7). Pediatric specialty and completion of residency more than 5 years ago were also more likely to be associated with early adoption of a future rotavirus vaccine.

Pediatricians consistently ranked the importance of vaccines higher than family physicians for 5 vaccine-preventable infections (Figure). However, both groups of physicians ranked the measles vaccine as most important, followed by vaccines against pneumococcus, varicella, rotavirus, and hepatitis A. Despite seeing significantly fewer children for preventive care, family physicians did not differ significantly from pediatricians in how likely they were to report having had a patient experience with severe/fatal rotavirus disease, belief that patients are more concerned about vaccine safety, and belief in need for a rotavirus vaccine.

Results of this study indicate that physicians make an important distinction between prelicensure and postlicensure surveillance systems such as the Vaccine Adverse Events Reporting System and Vaccine Safety Datalink that monitor vaccine safety. Following the withdrawal of the rotavirus vaccine, trust in prelicensure studies was low, whereas trust in the postlicensure surveillance system to monitor vaccine safety was high. Furthermore, nearly half of physicians reported some reluctance to use a new rotavirus vaccine if one is released, and more than one fourth of physicians stated that the withdrawal of the RotaShield vaccine has increased their reluctance to use other new vaccines. The observed difference in confidence between prelicensure and postlicensure vaccine safety mechanisms in this study likely reflects events surrounding the release and rapid withdrawal of the rotavirus vaccine. While prelicensure studies did not detect a significant association between the rotavirus vaccine and intussusception, postlicensure surveillance rapidly detected a strong, statistically significant signal, and this information was acted on quickly by federal agencies.

**Table 3. How Important Is a New Rotavirus Vaccine for Use in the United States and How Soon Would Physicians Use a New Vaccine Once Approved by the FDA?**

<table>
<thead>
<tr>
<th>Question</th>
<th>Pediatricians</th>
<th>Family Physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>If there a need for a safe, effective rotavirus vaccine?†</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>What level of recommendation is needed to feel comfortable using a new rotavirus vaccine?†</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>FDA approval alone</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>FDA approval and AAP/ACIP/AAP recommendation</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Wait for local experts to recommend</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Wait until vaccine is in widespread use for months to years</td>
<td>Never will use</td>
<td>1</td>
</tr>
<tr>
<td>Personal practice: How soon would you use a new vaccine once it was recommended?†</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>Within 6 mo</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>6 mo to 1 y</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>1-2 y</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;2 y/never</td>
<td>Other (only if schools required, only for high-risk patients, only if parent requested, etc)</td>
<td>19</td>
</tr>
<tr>
<td>Will you be a future early adopter of a new rotavirus vaccine?†</td>
<td>41</td>
<td>31</td>
</tr>
</tbody>
</table>

*FDA indicates Food and Drug Administration; AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; and AAP, American Academy of Family Physicians. All values given as percentages. †Pediatricians differ significantly from family physicians, P < .05 (χ² analysis).

**Table 4. Responses Associated With Early Adoption of a New Rotavirus Vaccine**

<table>
<thead>
<tr>
<th>Survey Response</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Believe the current system for determining vaccine safety prior to FDA approval works well</td>
<td>2.2</td>
<td>1.3-3.6</td>
</tr>
<tr>
<td>Believe the current system for monitoring vaccine safety after FDA approval works well</td>
<td>1.8</td>
<td>1.0-3.4</td>
</tr>
<tr>
<td>Agree with statement “The withdrawal of the RotaShield vaccine has made me more reluctant to use any new vaccine in the future (pneumococcal, respiratory syncytial virus, etc)”†</td>
<td>0.4</td>
<td>0.3-0.7</td>
</tr>
<tr>
<td>Pediatrician†</td>
<td>1.9</td>
<td>1.0-3.7</td>
</tr>
<tr>
<td>Completed residency more than 5 years ago†</td>
<td>1.8</td>
<td>1.0-3.1</td>
</tr>
</tbody>
</table>

*Adjusted for number of children seen per week, subspecialty training, experience with severe/fatal rotavirus disease, belief that patients are more concerned about vaccine safety, and belief in need for a rotavirus vaccine.
†Final model logistic regression z statistic for odds ratio, P < .05.
FDA indicates Food and Drug Administration.
‡RotaShield; Wyeth Laboratories inc, Marietta, Pa.

Percentage of family physicians and pediatricians who responded that a vaccine was very important for universal use in children for 6 vaccine-preventable infections. The differences between specialty type for each vaccine-preventable disease except hepatitis A was P < .01 (χ² analysis).
there had been a greater time lag in detecting the increased risk of intussusception after vaccine licensure, there may have been lower confidence in the postlicensure vaccine safety mechanisms. This study does not allow any general conclusions about physician confidence in prelicensure and postlicensure vaccine safety efforts with regard to other vaccines.

The disparity in trust between prelicensure vaccine safety mechanisms and postlicensure safety surveillance could potentially lead to continued support by physicians for vaccines once in widespread use but reluctance to adopt new vaccine recommendations. In our study, those physicians who would use a new rotavirus vaccine within 1 year following a recommendation by professional organizations were also twice as likely to trust in prelicensure vaccine safety mechanisms. However, one third of respondents indicated they would not use a rotavirus vaccine until it had been in widespread use for months to years. Based on the results of our study, we do not know if the introduction of other new recommended vaccines would face similar obstacles. Future studies could attempt to determine why, given the same level of safety information, some physicians trust in vaccine safety studies and are willing to rapidly adopt new recommendations for vaccines, while other physicians have a “watch-and-wait” attitude toward new vaccines.

Despite the association between RotaShield and intussusception and its rapid withdrawal from the market, the majority of physicians believe we need a vaccine against rotavirus; fewer than 2% of physicians responded they would never use a rotavirus vaccine in children. In our survey, most physicians reported they would wait longer than 6 months after recommendation by the AAP/ACIP/AAFP before administering a new rotavirus vaccine to their patients. If a new rotavirus vaccine is approved by the FDA and recommended by the AAP/ACIP/AAFP, strong efforts will need to be made to assure physicians and parents that adequate prelicensure studies were conducted to determine vaccine safety.

Prelicensure clinical evaluation of the rhesus-human reassortant vaccine lasted longer than 15 years, cost hundreds of millions of dollars, involved multiple agencies and investigators, and involved administration to more than 10,000 children. Careful retrospective evaluation of the prelicensure data after the vaccine withdrawal determined that the prelicensure studies did not reveal an association between the vaccine and intussusception because the risk of intussusception was approximately 1 per 5000 vaccinated children, too rare to be identified in a trial of 10,000 children. Tremendous resources are needed to conduct very large prelicensure trials, so a balance must be struck between enrolling enough children in a randomized trial to determine the efficacy and safety of a vaccine and the cost of vaccine trials, which translates into the cost of the vaccine after licensure. Enrolling more children in prelicensure vaccine studies to determine the risk of rare adverse events would not only drive the cost of the vaccine up, potentially beyond affordability for universal use in children, but also substantially delay the availability of the vaccine.

There were some important differences between family physicians and pediatricians in this survey, consistent with other studies. Results from a recent national immunization survey indicated that children aged 19 to 35 months) who receive immunizations solely from family physicians are significantly less likely to be up-to-date on their immunizations. We found that family physicians were less likely to believe that a vaccine against rotavirus is needed and were less likely to trust postlicensure vaccine safety mechanisms. Overall, family physicians rated vaccines against 5 vaccine-preventable diseases as less important than pediatricians did. Fewer than half of family physicians reported following recommendations for universal varicella vaccination of children. Family physicians did not differ significantly from pediatricians in reporting serious adverse events associated with vaccines in their patients, despite seeing far fewer pediatric patients for preventive care. This may reflect differences in their confidence about vaccine safety; differences in the way they define a serious adverse event associated with a vaccine, or differences in the incidence of serious adverse events given different patient populations. Although family physicians immunize considerably fewer children than pediatricians, approximately 23% of impoverished children receive their immunizations solely from family medicine physicians. These same children are at highest risk for poor outcomes from vaccine-preventable diseases. Efforts are needed to determine why family physicians have different attitudes and practices toward immunizations than pediatricians. Family physicians may require additional or different information than pediatricians in their decision-making process.

There are limitations to this study. Although we were able to determine there was no significant difference in age, sex, or board certification, we do not know if nonrespondents differed from respondents in any way that would change our results. Nonresponse bias is an important limitation of mail surveys; however, our response rate of 63% is in keeping with most other published studies involving national surveys of physicians.
As found in previously published surveys on immunization practices, pediatricians had a higher response rate than family physicians. The most plausible explanation for this difference is the higher proportion of family physicians who do not immunize children. Among our respondents, only 17% of pediatricians did not immunize children compared with 34% of family physicians. Physicians who do not immunize children are likely to have less incentive to return a survey on immunizations. Another important limitation of this study is that it was conducted within 10 months of the withdrawal of the RotaShield vaccine. It is not known if the responses that physicians gave are consistent with what their attitudes will be about new rotavirus vaccine recommendations and trust in vaccine safety mechanisms after more time has passed.

Despite these limitations, our data strongly suggest that most physicians believe that we need a safe and effective vaccine against rotavirus for use in the United States. Physician trust in vaccine safety mechanisms is mixed. There is skepticism about the ability of prelicensure studies to determine vaccine safety; however, trust in postlicensure surveillance systems that ensure vaccine safety is high. If physicians are able to trust prelicensure studies to determine vaccine safety, they may be more likely to rapidly adopt new vaccine recommendations. Future research could determine if these opinions are stronger given the circumstances of the RotaShield vaccine withdrawal or are consistent beliefs that will affect future new vaccine uptake of any new rotavirus vaccine as well as any other new vaccines against childhood illness.

Accepted for publication April 10, 2001.

This study was funded by the Ambulatory Pediatric Association’s Special Project Grant for Immunization-Related Research, McLean, Va (Drs McPhillips, Davis, and Taylor).

Corresponding author and reprints: Heather McPhillips, MD, MPH, Department of Pediatrics, University of Washington, 4800 Sand Point Way NE, PO Box 5371, Mail stop CH-30, Seattle, WA 98105 (e-mail: hmcphall@u.washington.edu).

REFERENCES


