Importance of Attributable Risk in Monitoring Adverse Events After Immunization: Hepatitis B Vaccination in Children

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A B S T R A C T

Objectives. Most vaccine safety data present only the postvaccination incidence of all adverse events rather than an estimate of attributable risk. This study sought to illustrate the difference between the 2 estimates with data from a hepatitis B immunization program.

Methods. The incidence of health problems occurring before and after each dose of hepatitis B vaccine in a cohort of 1130 children were compared.

Results. Although 47.5% of all children reported an adverse event during the 4 weeks following each of the 3 doses, adverse events attributable to immunization occurred in only 10.6% of children.

Conclusions. Postimmunization incidence systematically overestimates the risk of adverse events. Estimating actual attributable risk is necessary to avoid false beliefs regarding immunization. (*Am J Public Health.* 2001;91:313–315)

When an illness develops even weeks after a vaccination, some providers and most vaccinees intuitively incriminate the vaccine as a possible or probable cause. Adding to this confusion, pharmaceutical companies' publications and packaging inserts most often present a summary of all adverse events ever reported after vaccination. This also applies to most of the information on adverse events given by public health authorities to providers and parents.

To hold a vaccine responsible for all adverse events occurring after it is administered overestimates the risk, because events with other etiologies frequently arise coincidentally after a vaccination. These other etiologies cause a significant background incidence of health problems.[1] To calculate the incidence of adverse events really attributable to the vaccine—that is, the attributable risk—it is necessary to remove the background incidence of health events from the incidence observed after vaccination. To illustrate the importance of attributable risk, we analyzed data from a preadolescent universal hepatitis B immunization program and compared estimates of the attributable risk with estimates of the incidence of all adverse events occurring after immunization.

Methods

Participants were recruited from fourth-grade elementary school children (aged 8–10 years) in Quebec City, Canada, who were to be vaccinated in the school-based universal hepatitis B immunization program.[2] The children were given Engerix-B (SmithKline Beecham

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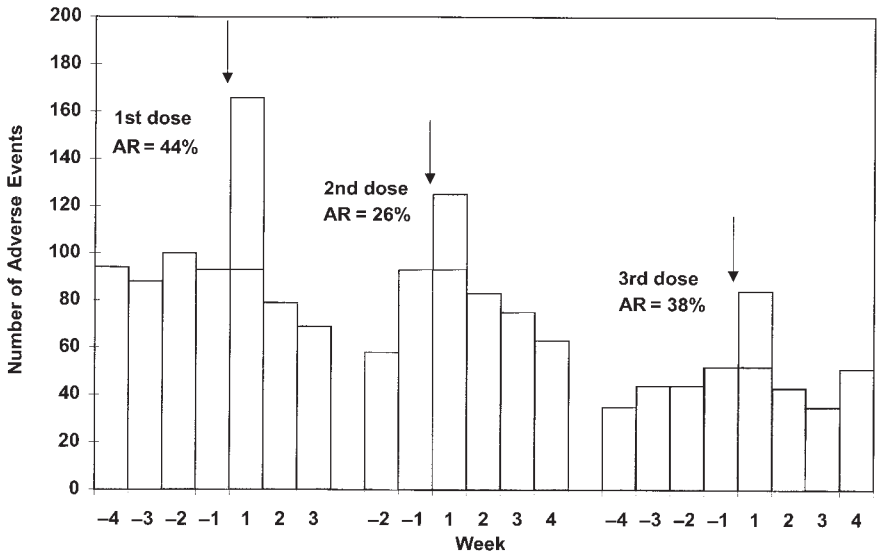
This brief was accepted May 23, 2000.



Note. White bars represent relative attributable risk (AR). Arrows indicate vaccination.

FIGURE 1—Total number of adverse events in the weeks preceding and following each of the 3 doses of hepatitis B vaccine and the proportion of these events attributable to the vaccine (compared with the incidence during the week preceding vaccination).

Pharmaceuticals, Rixensart, Belgium) intramuscularly in the deltoid according to the pediatric dosage (10 μg of hepatitis B surface antigen in 0.5 mL of Engerix-B) and schedule (0, 1, and 6 months). The first and second doses were given between October and December 1995 and the third in April to May 1996.

Open-ended diaries were provided to the parent(s) or guardian of the child before the vaccination program began in which to record any health problems that occurred 1 month before and 1 month following each of the 3 doses of vaccine, whether or not a health professional was consulted.

An adverse event was counted once whatever its duration, but a recurrence was considered a new event if it happened after 6 days during which no symptoms occurred. Events were classified in broad categories such as respiratory tract infections or gastrointestinal problems, which are not very precise but avoid classification errors. Attributable risk was estimated by computing the difference between the incidence of adverse events following the vaccination and the incidence of similar health events identified during the equivalent time interval before vaccination.

Results

A total of 1130 children agreed to participate; 93% were 9 years old at the beginning of the study, and a diary was completed for all of them. For the 3 doses, during the 7 and 28 days after immunization, 24.2% and 47.5% of children, respectively, suffered at least 1 adverse event. For all doses, when pre- and postvaccination periods were considered, the incidence of health problems was higher only during the first week after vaccination (Figure 1). In the first week, 44%, 26%, and 38% of all adverse events were attributable to the first, second, and third dose of the vaccine, respectively (Figure 1). All local reactions were attributable to immunization. During the first week after immunization, the attributable risks of headaches, gastrointestinal problems, and respiratory tract infection were 2.8%, 1.8%, and 0%, respectively, which represent 57% (2.8/4.9) of the headaches, 35% of the gastrointestinal problems, and none of the respiratory tract infections. Because the increased incidence occurred only during the first week, the absolute value of the attributable risk remains identical with longer follow-up (Table 1), but the proportion of adverse events attributable to immunization decreases from 44% (10.6/24.2) during the first week to 22% (10.6/47.5) with a 4-week follow-up.

Discussion

A previous review of studies on Engerix-B had shown that this vaccine was very safe in neonates and adults.[3] In the present study, Engerix-B was also safe in preadolescents, with a low but significant frequency of headaches and gastrointestinal problems attributable to the vaccine. Even if parents were instructed to record every health problem, the information was dependent on their subjective appraisal of what constitutes a health problem and on how diligently they recorded data. They probably had a greater sensitivity for adverse events after vaccination, a bias that would overestimate the risk due to vaccination. In spite of that, we observed only a minimal increase in the incidence of adverse events during the week after vaccination compared with that of the week preceding it, confirming the safety of this vaccine.

In this study, 47.5% of the children experienced at least 1 adverse event in the 4 weeks following each of their 3 doses of hepatitis B vaccine; while this figure is remarkably high, less than a quarter of the adverse events were attributable to the vaccine. This result clearly demonstrates the overestimation of the risk of vaccine that occurs when only postvaccination data are collected. Paradoxically, the safer the vaccine, the greater will be this overestima-

TABLE 1—Percentage of Children Who Sustained an Adverse Event After Each Dose of Vaccine By Follow-Up Period and Absolute Attributable Risk

Adverse Event	Incidence Postvaccination Only				Attributable Risk[a] (95% CI)
	7 Days	14 Days	21 Days	28 Days	
Local reaction	3.0	3.0	3.0	3.0	3.0 (2.0, 4.0)
Isolated fever	0.9	1.2	1.4	1.8	0.4 (–0.2, 1.1)
Isolated headache	4.9	5.8	5.9	6.2	2.8 (1.3, 4.4)
Gastrointestinal problems	5.1	6.9	8.3	10.2	1.8 (0.7, 3.5)
Respiratory tract infections	11.1	20.9	30.5	38.2	–0.1 (–2.9, 2.7)
All others	4.7	7.2	8.1	9.3	2.7 (1.2, 4.2)
Total[b]	24.2	34.4	41.7	47.5	10.6 (6.5, 14.7)

Note. CI = confidence interval.
[a]Calculated only for the first week after vaccination.
[b]With at least 1 adverse event.

tion: with a perfectly safe vaccine, all adverse events would have another etiology. This relation also illustrates the greatest vulnerability of universal vaccination: even with a perfectly safe vaccine, with the systematic vaccination of the whole population, a temporal association with every existing disease will ultimately be found.

While the concept of attributable risk represents basic epidemiologic knowledge,[4] very few published vaccine studies include information about it; most of them present total postimmunization events in vaccinees. As an example, in a search in MEDLINE in April 1999 that used the keywords "Hepatitis B vaccine," "safety," and "safe," we retrieved 365 papers with an abstract, but in only 7 of them (2%) were there sufficient data for attributable risk to be calculated (although the attributable risk was not calculated in most of these papers).

Safety has always been an important issue for vaccines because they are administered to healthy persons to prevent disease, and tolerance for adverse events following vaccines is lower than for medications.[5] An overstated frequency of adverse events is likely to have an impact on public health decisions weighing the risks and benefits of vaccination. A high priority should be given in the future to presenting the frequency of adverse events both in the placebo (or control) group and in the vaccine group in all reference documents. This practice is already being followed for many new drugs in the *Physicians' Desk Reference* in the United States[6] and in the *Compendium of Pharmaceutical Specialty* in Canada,[7] and the same approach should be applied to vaccines. □

Contributors

G. De Serres, B. Duval, N. Boulianne, and R. Massé were the designers and investigators of the larger study on long-term immunogenicity of hepatitis B vaccine[2] and also prepared the design, analyzed the data, and participated in the writing of the manuscript. M. Rochette, M. Dionne, and M. Douville Fradet participated in the analysis and writing of this study; M. Rochette also participated in the study's design.

Acknowledgments

This study was financially supported by SmithKline Beecham Pharmaceuticals, the Ministère de la santé et des services sociaux du Québec, and the Direction de la santé publique du Québec. G. De Serres is supported by a scholarship from the Fonds de la recherche en santé du Québec.

We want to acknowledge and express our profound thanks to Colette Couture, Sophie Auger, Louis Rochette, Claude Boulianne, France Lavoie, Ramak Shadmani, and Martyne Nadeau from the Centre de santé publique du Québec, who contributed to this project. We would also like to thank the public health nurses who met with the parents and the children enrolled in this study. We want to acknowledge Robert Pless for revising the manuscript.

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