MAJOR ARTICLE

The Effect of Age on Immunologic Response to Recombinant Hepatitis B Vaccine: A Meta-analysis

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Hepatitis B vaccine is a key tool for the prevention of hepatitis B infection. Age-associated changes in immune function may contribute to decreased vaccine efficacy in older individuals, although research related to this topic has yielded contradictory findings. We performed a meta-analysis of 24 published trials and studies that evaluated the association of age with response to hepatitis B vaccine, using a random-effects model. Pooling of study results suggested a significantly increased risk of nonresponse to hepatitis B vaccine among older individuals (relative risk [RR], 1.76; 95% confidence interval [CI], 1.48–2.10). An elevated risk of nonresponse persisted even after exclusion of poor-quality studies (RR, 1.63; 95% CI, 1.23–2.15) and adjustment for publication bias (RR, 1.52; 95% CI, 1.26–1.83), and it was present even when "older" individuals were defined as being as young as 30 years. These findings have important implications for individuals at risk for hepatitis B infection, including health care workers and travelers.

Hepatitis B virus is a major cause of viral hepatitis, cirrhosis, and liver cancer worldwide, and it is estimated to cause 1 million deaths worldwide annually [1]. The virus is highly transmissible and can be contracted via sexual or household contact with an infected person, vertical transmission from mother to child, and blood-to-blood contact (e.g., via blood transfusion). A safe and immunogenic recombinant vaccine against hepatitis B virus has been widely available since the 1980s; the introduction of this vaccine has transformed hepatitis B virus into a potentially eradicable infectious disease [2].

It has been suggested that age-associated changes in humoral and cellular immune function may result in decreased vaccine effectiveness in older individuals, compared with children or young adults [3, 4]. Some investigators have suggested that older individuals are less likely to have a serological response to recombinant hepatitis B vaccine [5], although other investigators have failed to find such an association [6]. The issue is of practical importance, because the differential efficacy of the vaccine in different age groups could change the optimal vaccination policy.

Meta-analysis provides a statistical framework for the synthesis and interpretation of data from multiple randomized trials, and it may also be used for the synthesis of data from observational studies [7, 8]. Our objectives were (1) to use meta-analytic techniques to provide enhanced statistical power for the interpretation of published data, and (2) to generate a summary estimate of the effect of age on recombinant hepatitis B vaccine response. In addition, we aimed to identify sources of heterogeneity among studies and to ascertain factors that modify seroresponse in different age groups.

Received 7 May 2002; accepted 8 August 2002; electronically published 12 November 2002.

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Clinical Infectious Diseases 2002; 35:1368–75

1058-4838/2002/3511-0010$15.00

MATERIALS AND METHODS

Literature search. Using the search term "hepatitis B vaccine," we performed a structured search of the medical literature in the MEDLINE database and the COCHRANE Library. Our search was limited to human studies that involved individuals aged ⩾19 years and that were published in the English literature. By use of these criteria, we identified a total of 1170 abstracts. We read all the abstracts and then identified and reviewed in detail 251 articles that could not be excluded on the basis of abstract review. Where possible, we contacted the authors of publications that discussed relevant cohorts but contained data insufficient for inclusion in our meta-analysis, and we asked them to provide additional information.

We identified a total of 23 published studies that were considered appropriate for inclusion in our analysis on the basis of the inclusion and exclusion criteria described in the "Inclusion and exclusion criteria" subsection below. A 24th study was included after supplementary data were received from the principal author [9].

Inclusion and exclusion criteria. Both randomized controlled trials and observational studies were considered eligible for inclusion in the analysis. Only trials that used standard recombinant DNA hepatitis B vaccines were included; studies that used plasma-derived vaccines, combination vaccines, or recombinant vaccines with immune adjuvants were excluded. All dose schedules and routes of vaccine administration were included, as long as they involved primary vaccination regimens and not booster doses only.

We included studies that evaluated both healthy recipients and individuals with comorbid illnesses. Studies restricted to students, military recruits, or other cohorts that involved subjects <30 years of age were excluded. Many studies suggested an age-related effect, but only studies that (1) specified either a relative risk and a measure of variance for vaccine response among older individuals, compared with younger individuals, or (2) presented data in a form that could be used to construct a 2×2 contingency table were considered eligible for final inclusion.

Exposures and end points of interest. We evaluated the association of age with response to recombinant hepatitis B vaccine in trials and observational studies. The definition of older age varied among studies. We considered subjects to be "older" if they met the definition used in the study in which they participated. When multiple age strata were presented or when data on age and vaccine response were available on an individual basis, age ⩾40 years was used as a default definition of "older age" for study participants.

Individuals vaccinated against hepatitis B are usually considered immune if high titers of antibody against hepatitis B surface antigen can be demonstrated >1 month after the completion of vaccination. However, the level of antibody production that defines immunity has varied among studies; some authors consider this "immune threshold" to be 10 IU/mL, whereas other authors have used an immune threshold of 100 IU/mL. We considered study subjects to be "immune" if they met the definition of immunity used in the study in which they participated. When several immune thresholds were presented or when data were presented in the form of a scatter-plot (e.g., age vs. titer), we used 10 IU/mL as the default threshold, because this is the threshold advocated by the World Health Organization and the US Centers for Disease Control and Prevention [10].

Data analysis. Data on vaccination regimen, serological response, and population characteristics were abstracted using a standardized data-collection form. When studies presented sparse data, we added a value of 0.5 to all cells of the contingency table, so that relative risks and 95% CIs could be approximated. We generated a summary estimate of the relative risk of failure to respond to vaccination among older individuals by use of a random-effects approach, as described by DerSimonian and Laird [11].

We assessed the heterogeneity of study results by use of the Q statistic of DerSimonian and Laird [11]. Possible sources of heterogeneity were explored in subgroup analyses and in sensitivity analyses in which certain subgroups were excluded, as well as through creation of meta-regression models. These models make use of a recursive algorithm to estimate between-study variance after adjustment for study covariates [12, 13].

Studies included in the analysis were variable in quality. We considered studies to be of poor quality if they failed to provide adequate documentation of vaccine schedules, routes of vaccine administration, or definitions of response to vaccination, or if <90% of participants had completed the entire vaccine schedule. We performed a sensitivity analysis of quality by excluding all studies considered to be of poor quality.

Finally, we anticipated publication bias, because studies in which a statistical association between age and vaccine response was present were expected to be more likely to present these data than were studies that found no such association. We explored the presence of publication bias graphically by constructing a "funnel plot" of relative risk and study variance and by statistically using Egger's regression asymmetry plot [14]. We attempted to adjust for the extent of publication bias by use of a "trim-and-fill" approach, as described by Duval and Tweedie [15]. This approach assumes that each study asymmetrically distributed around the pooled effect estimate has an unpublished counterpart that has been kept out of the medical literature because of failure to find the association of interest. The likely variance and effect size of these "mirror-image" studies was calculated and was added to the pooled relative risk

Table 1. Studies identified through systematic review of the English literature and used in a meta-analysis evaluating the association of age with vaccine response.

Author(s) [reference]	Year	Country	No. of patients studied	Vaccine used	Booster	Schedule, month	Population studied	Route of injection
Zajac et al. [16]	1986	United States	509	Other	No	0, 1, 6	Healthy volunteers	im
Dahl-Hansen et al. [17]	1989	Norway	139	Engerix B and Recombivax	No	0, 1, 6	Health care workers	im
Morris et al. [6]	1989	United Kingdom	215	Engerix B	Yes	0, 1, 6	Health care workers	id
Promjunyakul and Limsuwan [18]	1989	Thailand	15	Engerix B	No	0, 1, 2	Health care workers	im
Westmoreland et al. [19]	1990	United Kingdom	1120	Engerix B	Yes	0, 1, 6	Health care workers	im
Guan et al. [20]	1990	Singapore	29	Engerix B	No	0, 1, 2, 6	Patients with chronic renal failure	im
CDC [21]	1991	United States	226	NS	No	0, 1, 6	Police and fire department employees	im
Wismans et al. [22]	1991	Holland	20	Other	Yes	0, 1, 6	Diabetics and healthy control subjects	im
Van Thiel and Gavaler [9]	1992	United States	132	Recombivax	No	0, 1, 2	Liver clinic patients	im
Dentico et al. [23]	1992	Italy	195	Other	No	0, 1, 6	Healthy volunteers	im
Bayas et al. [24]	1993	Spain	111	Engerix B	No	Variable	Prisoners	NS
Roome et al. [25]	1993	United States	526	Recombivax	No	NS	Public safety personnel	NS
McMaster et al. [26]	1993	United States	411	Engerix B	No	0, 1, 2, 6	Health care workers	id
Clements et al. [5]	1994	United States	73	Recombivax	No	0, 1, 6	Healthy volunteers	im
Wistrom et al. [27]	1995	Sweden	38	Recombivax	No	0, 1, 6	Health care workers	id
Jaiswal et al. [28]	1995	India	44	Engerix B	No	0, 1, 6	Patients with chronic renal failure	im
Cumberland et al. [29]	1995	United Kingdom	2729	Engerix B	Yes	Variable	Health care workers	im
Bock et al. [30]	1996	Germany	852	Engerix B	No	0, 1, 6	Health care workers and their relatives	im
Mitwali [31]	1996	Saudi Arabia	32	NS	Yes	0, 1, 6	Patients with chronic renal failure	im
Havlichek et al. [32]	1997	United States	112	Engerix B and Recombivax	Yes	Variable	Health care workers	im
Peces et al. [33]	1997	Spain	80	Engerix B	No	0, 1, 2, 6	Patients with chronic renal failure	im
Averhoff et al. [34]	1998	United States	1754	Engerix B and Recombivax	Yes	0, 1, 6	Health care workers	im
Louther et al. [35]	1998	United States	269	Recombivax	No	0, 1, 6	Health care workers	im
Cardell et al. [36]	1999	Sweden	1406	Engerix B	Yes	0, 1, 6	Health care workers	id

NOTE. CDC, Centers for Disease Control and Prevention (Atlanta, GA); id, intradermal; NS, not stated.

calculation to provide a publication bias-adjusted estimate of effect.

RESULTS

The 24 studies included in the analysis are presented in table 1. Studies used for analysis were published from 1986 through 1999, and they included a total of 11,037 subjects. Eleven of the studies were conducted in Europe; 9, in the United States; and 4, in Asia. Nineteen of 24 studies evaluated the efficacy of Engerix B (GlaxoSmithKline), Recombivax (Merck), or some combination of these preparations, whereas the remaining 5 studies used either an alternate vaccine preparation or did not identify the specific preparation used. A 3-dose vaccine schedule was used in 20 studies, although 8 studies that used a 3-dose regimen provided an additional booster dose to subjects who failed to respond to the 3-dose schedule. Approximately one-half of the studies (13 of 24) found a significant decrease in the rate of response to recombinant hepatitis B vaccine among older study participants.

Using a random-effects model, we estimated that, for older individuals, the pooled relative risk of failure to have an ade-

quate response to hepatitis B vaccination, compared with that for younger individuals, was 1.76 (95% CI, 1.48–2.10; $P < .001$). A Forrest plot of these data is presented in figure 1. We found evidence of significant heterogeneity in effect estimates among studies (Q statistic, 61.94 with 23 degrees of freedom; $P < .001$).

Sources of heterogeneity. We explored sources of heterogeneity in effect estimates by performing stratified and sensitivity analyses and by creating a series of meta-regression models. The results of stratified and sensitivity analyses are presented in figure 2. The risk of failing to respond to the vaccine appeared to be diminished (1) when individuals were given 4 doses of vaccine or were given a booster if they failed to have seroconversion, and (2) when vaccine was given intradermally rather than intramuscularly. Among older individuals, decreased response was seen with both Engerix B and Recombivax vaccine preparations. The effect of age on seroconversion was less marked in studies of individuals with comorbid medical illnesses than in studies of subjects without comorbid illnesses.

Sensitivity analysis was performed after exclusion of studies that were considered to be of poor quality. On the basis of our quality criteria, we excluded 11 of 24 studies. The pooled relative risk among the remaining studies was 1.63 (95% CI, 1.23–2.15)

We attempted to further identify and quantify sources of heterogeneity by creating a series of random-effects meta-regression models. An initial random-effects model suggested that the between-study variance (τ^2) in log relative risk was 0.116. Covariates that had appeared to be associated with heterogeneity in stratified analyses were individually added to the model. The addition of route of vaccination (intradermal vs. intramuscular) to the model (2 studies that did not report the route of administration were excluded) resulted in a substantial decrease in between-study variance ($\tau^2 < .001$), which suggests that the majority of between-study heterogeneity was due to differences in route of vaccine administration. No other covariate resulted in a notable change in between-study variance.

Publication bias. We postulated that the investigators who found a statistical association of age with failure to have an adequate response to vaccination would be likely to comment on such a finding in published manuscripts, whereas investigators who failed to find such an association would be less likely to comment on the absence of such an association. We explored the possibility of such publication bias by creating a

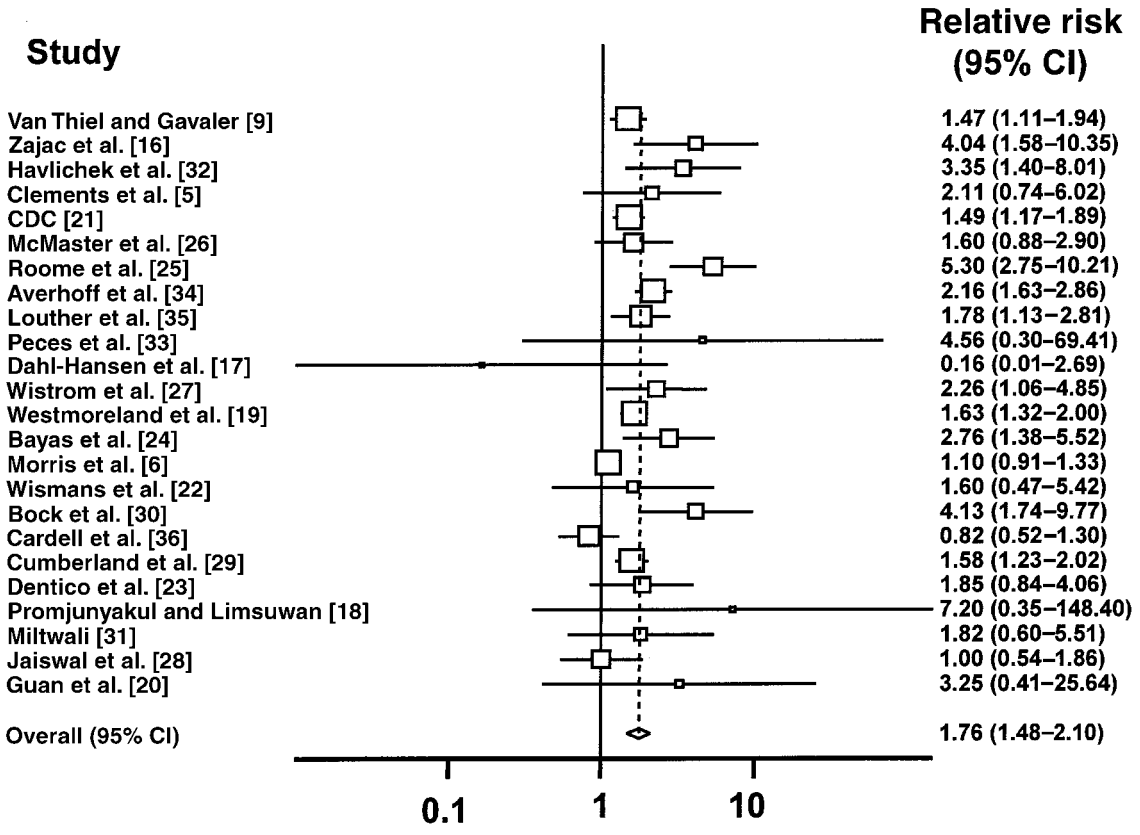

Figure 1. Forrest plot of the association between older age and the relative risk of nonresponse to recombinant hepatitis B vaccine in 24 studies. Principal authors are listed on the *Y*-axis. Block sizes are proportional to the precision of the study, and the horizontal lines denote 95% CIs. The diamond denotes the summary relative risk and 95% CI. CDC, Centers for Disease Control and Prevention (Atlanta, GA).

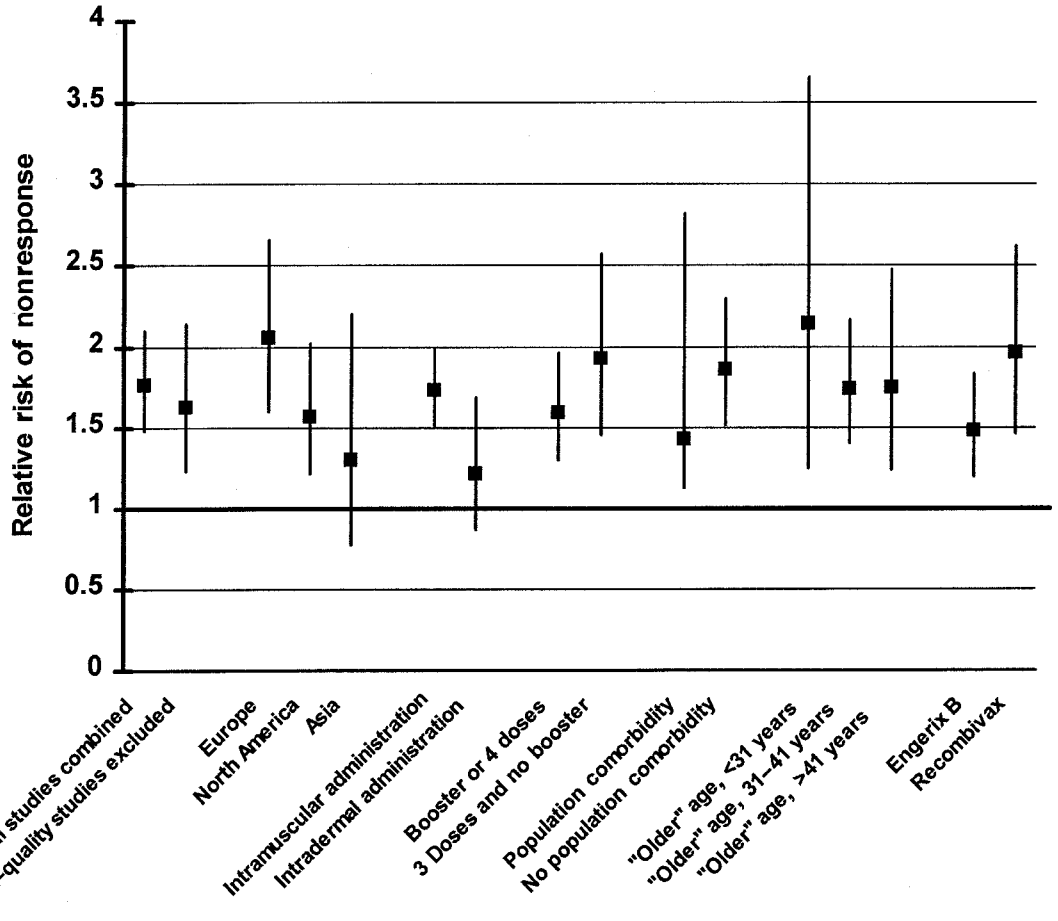

Figure 2. Subgroup and sensitivity analyses exploring possible sources of heterogeneity in effect estimates. Each block denotes the pooled estimated of relative risk of nonresponse to recombinant hepatitis B vaccine in older individuals, in studies in which factors listed on the *X*-axis were present. Vertical lines denote 95% CIs.

"funnel plot," which is presented in figure 3. Visual inspection of the plot revealed asymmetry in the distribution of smaller studies, with most small studies suggesting a relative risk larger than that predicted by the summary estimate. Statistical testing with Egger's regression asymmetry test [33] suggested that the degree of asymmetry seen in the funnel plot was greater than would be expected by chance alone ($P = .049$).

We used a trim-and-fill [34] approach to estimate a summary relative risk, which was adjusted for publication bias. This approach identified asymmetries in the distribution of published studies and counterbalanced asymmetrically distributed studies through the generation of simulated "mirror image" studies that were equal in variance but opposite in effect. The resulting "publication bias–corrected" estimate of relative risk was 1.52 (95% CI, 1.26–1.83).

DISCUSSION

We performed a systematic review of the medical literature that described the impact of age on response to recombinant hepatitis B vaccine. We found that studies that noted a decrease in serological response in association with age were approximately equal in number to the studies that did not note such a response. Although such simple "vote counting" would create the impression of conflicting data regarding the effect of age on hepatitis B vaccine response, the use of meta-analysis suggests that the absence of such an association in studies with negative results is due to insufficient statistical power.

In our pooled estimate of effect, we found a significant decrease in vaccine response among older individuals. This was a robust finding that persisted after the exclusion of poor-quality studies and after attempts to adjust for publication bias. This finding is biologically plausible, given the changes in cellular and humoral immune responses described in older individuals [3, 37, 38].

Of surprise, we found that the association between age and nonresponse to vaccine remained fairly constant, regardless of the age cutoff used. Even age cutoffs as low as 30 years predicted an increased risk of nonresponse among older individuals. Thus, the increased risk of nonresponse to vaccine may apply

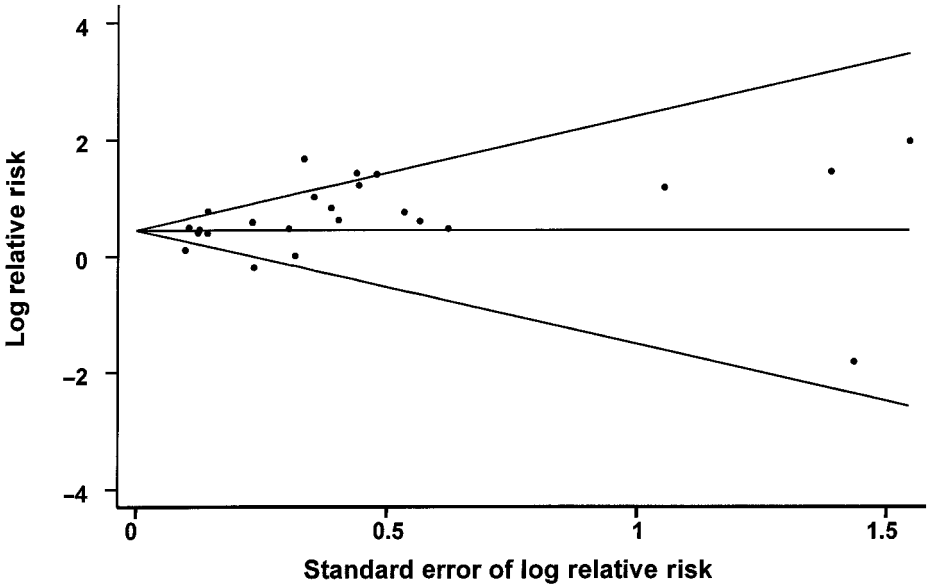

Figure 3. Funnel plot, with the log of the relative risk of nonresponse to recombinant hepatitis B vaccine in individual studies plotted against study precision. Each dot denotes a single study. Smaller, less-precise studies appear to be asymmetrically distributed around the line that denotes the overall summary of relative risk, suggesting possible publication bias.

to individuals young enough to be at risk for the long-term complications of chronic hepatitis B infection, including cirrhosis and hepatocellular carcinoma, and to individuals of childbearing age. The relevance of the latter point relates to the high degree of vertical transmissibility of the virus. More generically, the implication that adults aged >30 years are immunologically different from younger individuals has important implications for the vaccination of adults for travel to the developing world [39] and for vaccination to prevent occupationally acquired illnesses [40].

Statistical testing and visual inspection of study results suggested that much of the variation between studies could be explained by the route of vaccine administration used, with the risk of nonresponse among older adults apparently ameliorated by the use of intradermal vaccination. However, these findings should be interpreted with caution, because trials that have directly compared the efficacy of intradermal and intramuscular vaccination have yielded contradictory findings [41–44]. Further exploration of the association between age, route of vaccination, and immune response is warranted.

We were unable to find convincing evidence that either of the 2 most commonly used vaccine preparations was more immunogenic in older individuals or that the routine use of a fourth dose of vaccine or booster would substantially decrease the risk of nonresponse among older individuals. We did not find evidence of a synergistic increase in risk among older individuals with comorbid illnesses (e.g., diabetes or renal failure). Indeed, the relative risk of nonresponse among older individuals in populations with comorbid illness was smaller than that seen in apparently healthy populations, perhaps because of an increased risk of nonresponse to vaccination among younger individuals in populations with diabetes or renal failure.

As expected, we found graphical and statistical evidence for publication bias. The graphical evidence presented in our funnel plot suggests that small studies are likely to report an association between age and nonresponse to vaccine only if this association is found to be positive. This is of particular concern, given that evaluation of vaccine response according to age was not a primary objective of any of the studies included in our analysis. After adjusting for publication bias, we would still estimate that there is a 1.5-fold increased risk of nonresponse to vaccine among older individuals. However, trim-and-fill methodology makes use of strong assumptions about the size and distribution of unpublished studies [36]. As a consequence, we cannot be certain that the true association between age and vaccine response is not null.

Our attempts to limit the impact of poor-quality studies through sensitivity analysis resulted in a decrease in our estimate of relative risk from 1.76 to 1.63. This finding may be closely related to our finding of publication bias, in that editors may be more ready to forgive authors for flaws in study design when statistically significant associations are reported. Our analysis is also limited by the fact that we limited our literature search to English-language journals [45]. If the studies that were thus omitted were systematically different in their findings from those that we included, then this would have been a source of bias.

Nonetheless, using the best available data, we found evidence for a robust association between older age and risk of nonresponse to hepatitis B vaccine and for modification of this risk by route of vaccination. Such a relationship is biologically plausible and, for the reasons noted in this report, clinically important. These findings can serve to inform both vaccination policy and the direction of future research.

Acknowledgments

We thank Professor Graham Colditz, for his teaching and guidance, and Drs. William Toffler, David Van Thiel, and Erik Back, for their assistance in locating supplemental data from published studies. We also thank Lydia Napper for her expert assistance in manuscript preparation.

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