

Meta-analysis: the effect of age on immunological response to hepatitis B vaccine in end-stage renal disease

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SUMMARY

Background: Patients on maintenance dialysis typically show a suboptimal immune response to hepatitis B virus vaccine compared with the non-uraemic population. A variety of inherited or acquired factors have been implicated in this diminished response. Age-associated changes in immune status may contribute to decreased vaccine efficacy in older individuals although contradictory results have been reported in individuals with normal kidney function.

Aims: To evaluate the relationship between age and immune response to hepatitis B vaccine in patients with end-stage renal disease by performing a systematic review of the literature with a meta-analysis of clinical trials.

Method: We used the random effects model of DerSimonian and Laird; sources of heterogeneity in effect estimates were explored by performing sensitivity analyses.

Results: We identified 17 clinical trials (1800 unique patients); six (35%) were controlled studies. Pooling of study results demonstrated a significantly decreased risk of response to hepatitis B vaccine among older dialysis

patients (overall risk ratio: 0.74; 95% confidence intervals: 0.70–0.79). The *P*-value was 0.0139 for our test of study heterogeneity. A lowered risk of response to hepatitis B vaccine persisted after exclusion of trials based on plasma-derived vaccines; it was present even when 'older' individuals were defined as being as 50 years (RR: 0.85, 95% CI: 0.75–0.96) or more (cut-off 60 years RR: 0.75; 95% CI: 0.66–0.85). An effect of age on seroprotection rate was present in all clinical reports, irrespective of the geographic origin of the study group: Europe (RR: 0.76; 95% CI: 0.70–0.83) North America (RR: 0.67; 95% CI: 0.60–0.74) or other countries (RR: 0.83; 95% CI: 0.71–0.97). Additional doses of vaccine did not appear to have an impact on RR of response by age.

Conclusions: Our meta-analysis showed a clear association between older age and impaired response to hepatitis B virus vaccine in end-stage renal disease patients. Such a relationship is biologically plausible. Vaccination schedules with adapted vaccine doses and frequent serum testing for loss of immunity against hepatitis B virus are recommended in elderly patients on maintenance dialysis.

INTRODUCTION

The frequency of hepatitis B virus (HBV) infection, as detected by persistent positivity for hepatitis B surface

antigen (HBsAg) in serum, is low but not negligible among end-stage renal disease (ESRD) patients on maintenance dialysis in the industrialized world.¹ In 2001, the Centers for Disease Control and Prevention (CDC; Atlanta, GA) has reported that the prevalence of HBsAg seropositivity among dialysis patients was 0.9% in the USA.² Also, outbreaks of HBV infection in haemodialysis (HD) units continue to occur.^{3, 4}

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Prevalence and incidence rates of HBV infection remain much higher within dialysis units in less-developed countries.^{1, 5-7} It is well known that patients undergoing long-term dialysis have a lower response to HBV vaccine compared with the non-uraemic population; the number of patients who develop protective antibody against HBV (anti-HBs) is lower, the antibody titres of those who do mount an antibody response are reduced and decline faster over time.⁵ The impaired efficacy of HBV vaccine in dialysis population has been attributed to a variety of inherited or acquired factors such as gender, age, immune compromise because of uraemia, nutritional status, serological positivity for antibody against hepatitis C virus (anti-HCV antibody), body weight, possession of the major histocompatibility complex aploptype HLA and blood transfusion history.⁵ Also, failure to complete a full schedule of HBV vaccination may diminish response.⁵

It has been suggested that age-associated changes in humoral and cellular immune function may decrease vaccine effectiveness in older individuals, compared with children or young adults.^{8, 9} However, recent research related to this topic has yielded contradictory findings in the general population.¹⁰⁻¹² This issue is of practical importance, as the different efficacy of the vaccine in different age groups could change the optimal vaccination policy.

The goal of this study was to investigate the available evidence on the relationship between age and immune response to HBV vaccination in ESRD population by performing a systematic review of the literature with a meta-analysis of clinical trials.

MATERIALS AND METHODS

Search strategy and data extraction

Electronic searches of the National Library of Medicine's MEDLINE database, Current Contents, and manual searches of selected speciality journals were performed to identify all pertinent literature. It has been previously demonstrated that an electronic search alone may not sensitive enough.¹³ Four MEDLINE database engines (Ovid, PubMed, Embase and GratefulMed) were used. The key words 'hepatitis B', 'vaccine', 'dialysis', 'age' and 'ESRD' were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. Our search was limited to human studies that involved individuals aged ≥ 19 years published in the

English literature. All articles were identified by a search from 1980 to December 2003. Data extraction was conducted independently by two investigators (FF, VD) and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Eligibility and exclusion criteria were prespecified.

Criteria for inclusion

We included studies evaluating patients undergoing maintenance dialysis [HD and peritoneal dialysis (PD)] or with chronic renal failure (CRF) not yet requiring dialysis. Studies restricted to students, military recruits or other cohorts that involved subjects < 19 years of age were excluded. Many studies have identified an age-related effect,¹⁴⁻⁴⁴ but only studies that (i) specified either a relative risk and a measure of variance for vaccine response among older individuals, compared with younger individuals, or (ii) presented data in a form that could be used to construct a 2×2 contingency table were considered eligible for final inclusion.

Both randomized-controlled trials and observational studies were considered eligible for inclusion in the analysis. We included trials using plasma-derived or recombinant DNA hepatitis B vaccines; we also enrolled studies based on recombinant vaccine with immune adjuvant administration. All dose schedules and routes of vaccine administration were included, as long as they involved primary vaccination regimens and not booster doses only.

Ineligible studies

Studies were excluded if they reported inadequate data on measures of response, or included individuals with positive serology for HBsAg, antibodies to HBsAg (HBsAb) or human immunodeficiency virus (HIV). Trials that were only published as abstracts or as interim reports were excluded; letters and review articles were not considered for this analysis. Trials that involved previously vaccinated patients were excluded.

End-points of interest

We evaluated the association of age with response to HB 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 HB are considered immune if protective titres of anti-HBs antibody can be demonstrated after completion of vaccination. The level of antibody production that defines immunity varied among studies; many investigators considered this 'immune threshold' to be 10 IU/mL, whereas few authors have used an immune threshold of 50 or 100 mIU/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. titre), we used 10 IU/mL as it is a titre of anti-HBs antibody considered to provide protection.⁵

Source of support

This meta-analysis was not supported by any pharmaceutical company, by any governmental agency or by other grants.

Statistical methods

Data on serological response were collected and 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% confidence intervals (95% CIs) could be approximated. A summary estimate of the relative risk of failure to respond to vaccination among older patients was generated by use of a random-effects approach, as described by DerSimonian and Laird.⁴⁵

Possible sources of heterogeneity were explored in subgroup analyses and in sensitivity analyses in which certain subgroups were excluded. Chi-square test statistics were used to test for heterogeneity across studies. Spearman correlation coefficients were used to assess the association between outcomes of interest (e.g. the reported size of the estimated intervention benefit) and variables thought to be potential sources of heterogeneity (e.g. various subjects and trial characteristics of interest). The 5% significance levels was used for alpha risk. Every estimate was given with its 95% CI.

RESULTS

Literature review

Our electronic and manual searches identified 113 manuscripts which were selected for full text review. Ninety-six (85%) studies were excluded because they did not fulfil the inclusion criteria. A list of the 96 bibliographical references is available from the authors on request. Fourteen (14.6%) papers reported an age-related effect but this information could not be used for this meta-analysis; 11 (11.4%) and three (3.1%) studies concerned HBV vaccine in prior non-responder and renal transplant (RT) patients, respectively. Two studies (2.2%) regarded HB vaccination in dialysis patients who lost natural immunity against HBV. HB vaccination in paediatric population was made in three (3.1%) clinical trials. In 63 (65.6%) studies the relationship between age and response to vaccine against HB was not adequately addressed.

The remaining 17 studies,¹⁴⁻³⁰ representing a total of 1800 unique patients, were included in our meta-analysis. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria.

There were six (35%) prospective, controlled trials; two used a double-blind method. Eleven (65%) were prospective, cohort studies; three provided adequate randomization to assign patients in at least two vaccination schedules.

Patient characteristics

Shown in Table 1 are some salient demographic characteristics of subjects enrolled in the included clinical trials. The majority (13 of 17, 76%) of studies were from centres in Europe and North America.

As listed in Table 2, recombinant HB vaccine was used in 10 (58.9%) clinical trials. Vaccine adjuvants were used in one report:³⁰ granulocyte-macrophage colony-stimulating factor (GM-CSF) was given on day 1 followed by the vaccination schedule, as reported below (Table 2). HBV vaccine was administered by intramuscular route in most (15 of 17, 88%) clinical trials; it was given by subcutaneous route in two studies.^{16, 22} The mean time after dialysis prior to initiation of vaccination treatment varied from 21 to 61 months, although nine (53%) studies did not report data on this characteristic (Table 3).

Table 1. Characteristics of clinical trials: demographic data and vaccination schedule

Authors	Patients (n)	Country of origin	Vaccine dose (μ g)	Control group
Crosnier <i>et al.</i> ¹⁴	138	France	40	Yes
De Graeff <i>et al.</i> ¹⁵	37	The Netherlands	40	Yes
Jungers <i>et al.</i> ¹⁶	111	France	5	No
Lelie <i>et al.</i> ¹⁷	227	The Netherlands	3	No
			27	
Bruguera <i>et al.</i> ¹⁸	80	Spain	40	No
Schmid <i>et al.</i> ¹⁹	52	Germany	40	Yes
Steketee <i>et al.</i> ²⁰	444	USA	40	No
Guan and Choong <i>et al.</i> ²¹	32	Singapore	40	No
Lombardi <i>et al.</i> ²²	35	Italy	5	No
Jaiswal <i>et al.</i> ²³	40	India	40	Yes
Fabrizi <i>et al.</i> ²⁴	118	Italy	40	No
Khan <i>et al.</i> ²⁵	97	USA	40	No
Mitwalli <i>et al.</i> ²⁶	42	Saudi Arabia	10	No
			20	
			20	
Peces <i>et al.</i> ²⁷	80	Spain	40	Yes
Jadoul and Goubau <i>et al.</i> ²⁸	31	Belgium	20	No
DaRoza <i>et al.</i> ²⁹	165	Canada	40	No
Singh <i>et al.</i> ³⁰	71	India	40	Yes

The mean age of subject cohorts ranged from 39.9 to 73 years of age. The gender distribution ranged from 38 to 79% male. Most (15 of 17, 88%) clinical trials included patients undergoing maintenance dialysis (Table 3).

Summary estimates of outcome

Table 4 lists the risk ratios (RR) for seroprevention by age (old vs. young) and the corresponding 95% CI for each study. The overall RR is 0.74, the 95% CI were 0.70–0.79. The test for heterogeneity is significant ($P = 0.0139$).

We explored some of the possible sources of study heterogeneity. The subset of studies using recombinant vaccine, in particular, appears to represent a relatively homogeneous population of studies. Table 5 summarizes the RR and the 95% CI for each subset listed. Some studies have been eliminated from these analysis based on the criteria given for the categorization. Table 6 lists the P -values for each comparison. Within each subset different categories are being compared with each other. The differences are significant in the following categories: age cut-off of 40 vs. 50 ($P = 0.0065$), country of origin

Authors	Vaccine used	Vaccine type	Schedule (months)
Crosnier <i>et al.</i> ¹⁴	Plasma-derived	IP	0–2
De Graeff <i>et al.</i> ¹⁵	Plasma-derived	MSD	0, 1, 6
Jungers <i>et al.</i> ¹⁶	Plasma-derived	Hevac-B	0–2, 4
Lelie <i>et al.</i> ¹⁷	Plasma-derived	CLB	0–2
Bruguera <i>et al.</i> ¹⁸	Recombinant	Engerix-B	0–2 ($n = 36$) 0, 1, 6 ($n = 44$)
Schmid <i>et al.</i> ¹⁹	Plasma-derived	Heptavax-B	0, 1, 6
Steketee <i>et al.</i> ²⁰	Plasma-derived	Heptavax-B	0, 1, 6
Guan and Choong ²¹	Recombinant	Engerix-B	0–2, 6
Lombardi <i>et al.</i> ²²	Plasma-derived	IP	0–5
Jaiswal <i>et al.</i> ²³	Recombinant	Engerix-B	0, 1, 6
Fabrizi <i>et al.</i> ²⁴	Recombinant	Engerix-B	0–2
Khan <i>et al.</i> ²⁵	Recombinant	Engerix-B	0–2, 6
Mitwalli <i>et al.</i> ²⁶	Recombinant	N.S.	0–2 ($n = 15$) 0–2 ($n = 17$) 0, 1, 6 ($n = 10$)
Peces <i>et al.</i> ²⁷	Recombinant	Engerix-B	0–2, 6
Jadoul and Goubau ²⁸	Recombinant	Engerix-B	0–7
DaRoza <i>et al.</i> ²⁹	Recombinant	N.S.	0, 1, 6
	Plasma-derived		0–2, 6
Singh <i>et al.</i> ³⁰	Recombinant	Enivac-HB	0–2, 6

Table 2. Vaccination schedule

N.S., not specified; IP, Institute Pasteur production; MSD, Merck, Sharp and Dohme production; CLB, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service production.

Table 3. Characteristics of trials: clinical data

Authors	Age (years)	Sex, male (%)	Time on dialysis (months)	Therapy
Crosnier <i>et al.</i> ¹⁴	48.3 ± 13.1	80 (58)	NA	HD
De Graeff <i>et al.</i> ¹⁵	49 (18–77)	20 (54)	NA	HD
Jungers <i>et al.</i> ¹⁶	46.5 ± 2.8	61 (55)	0	CRF
Lelie <i>et al.</i> ¹⁷	56.0 ± 10.3	128 (56)	NA	HD
Bruguera <i>et al.</i> ¹⁸	53 ± 14	49 (61)	33 ± 26	HD
Schmid <i>et al.</i> ¹⁹	52.7 ± 16.7	NA	NA	HD (n = 30) PD (n = 22)
Steketee <i>et al.</i> ²⁰	56 (2–90)	251 (57)	30	HD (n = 374) PD (n = 70)
Guan and Choong <i>et al.</i> ²¹	40 ± 77	11 (34)	28.7 ± 10	HD
Lombardi <i>et al.</i> ²²	56.5 ± 14.5	15 (79)	NA	HD
Jaiswal <i>et al.</i> ²³	40	29 (72.5)	NA	HD
Fabrizi <i>et al.</i> ²⁴	63.4 ± 13.9	58 (49)	21 (2–208)	HD
Khan <i>et al.</i> ²⁵	51 ± 18.4	51 (52.5)	38.6 ± 58	HD (n = 50) PD (n = 47)
Mitwalli <i>et al.</i> ²⁶	39.9 ± 14.6	24 (57)	NA	HD (n = 27) PD (n = 15)
Peces <i>et al.</i> ²⁷	58.5 ± 1.5	36 (45)	61 ± 6	HD
Jadoul and Goubau ²⁸	73 (35–95)	15 (48)	NA	HD
DaRoza <i>et al.</i> ²⁹	59.8 ± 14.9	106 (64)	0	CRF
Singh <i>et al.</i> ³⁰	45.8 ± 15	40 (62.5)	NA	HD (n = 32) CRF (n = 39)

NA, not available; HD, haemodialysis; PD, peritoneal dialysis; CRF, predialytic chronic renal failure.

Table 4. Risk ratios (RR) for seroprevention by age (old vs. young) in dialysis patients and the corresponding 95% confidence intervals (CI) for each study

Authors	Risk ratio	Lower bound of 95% CI for RR	Upper bound of 95% CI for RR	Cut-off age
Crosnier <i>et al.</i> ¹⁴	0.54	0.32	0.90	50
De Graeff <i>et al.</i> ¹⁵	1.02	0.69	1.51	50
Jungers <i>et al.</i> ¹⁶	0.53	0.40	0.71	40
Lelie <i>et al.</i> ¹⁷	0.97	0.81	1.17	50
Bruguera <i>et al.</i> ¹⁸	0.77	0.48	1.23	40
Schmid <i>et al.</i> ¹⁹	0.64	0.48	0.86	50
Steketee <i>et al.</i> ²⁰	0.51	0.42	0.62	40
Guan <i>et al.</i> ²¹	0.82	0.59	1.13	40
Lombardi <i>et al.</i> ²²	0.61	0.44	0.84	60
Jaiswal <i>et al.</i> ²³	1.00	0.54	1.86	40
Fabrizi <i>et al.</i> ²⁴	0.95	0.69	1.30	50
Khan <i>et al.</i> ²⁵	0.66	0.40	1.06	50
Mitwalli <i>et al.</i> ²⁶	0.83	0.58	1.19	40
Peces <i>et al.</i> ²⁷	0.75	0.65	0.85	40
Jadoul and Goubau ²⁸	0.81	0.28	2.40	60
DaRoza <i>et al.</i> ²⁹	0.78	0.68	0.90	60
Singh <i>et al.</i> ³⁰	0.82	0.66	1.02	40
Overall	0.74	0.70	0.79	

Table 5. Sources of study heterogeneity

Variable	Categories	Sample size	Risk ratio	95% CI
Age	Cut-off 40	8	0.69	0.64–0.75
	Cut-off 50	6	0.75	0.75–0.96
	Cut-off 60	3	0.66	0.66–0.85
Vaccine used*	Plasma-derived	7	0.68	0.61–0.75
	Recombinant	9	0.79	0.72–0.87
Continent	Asia and others	4	0.83	0.71–0.97
	Europe	10	0.76	0.70–0.83
Number of doses*	North America	3	0.67	0.60–0.74
	Three doses	9	0.75	0.68–0.82
Dialysis†	Four or more doses	7	0.72	0.66–0.79
	No	2	0.72	0.64–0.82
	Yes	14	0.74	0.69–0.80

Risk ratio and the 95% confidence interval (CI) for each subset listed.

* Eliminated DaRoza *et al.* study.²⁹

† Eliminated Singh *et al.* study.³⁰

Asia and others vs. North America ($P = 0.0226$) and Europe vs. North America ($P = 0.0507$), and type of vaccine used plasma-derived vs. recombinant ($P = 0.0266$).

Table 6. *P*-values for each comparison

Variable	Categories	<i>P</i> -value
Age	Cut-off 40 vs. 50	0.0065
	Cut-off 40 vs. 60	0.3223
	Cut-off 50 vs. 60	0.1543
Continent	Asia and others vs. Europe	0.3548
	Asia and others vs. North America	0.0226
	Europe vs. North America	0.0507
Vaccine used*	Plasma-derived vs. recombinant	0.0266
Number of doses*	Three vs. four or more doses	0.6281
Dialysis†	No vs. yes	0.7343

* Eliminated DaRoza *et al.* study.²⁹

† Eliminated Singh *et al.* study.³⁰

As shown in Figure 1, no association was found on the RR for seroprevention by age vs. gender ($r = 0.104$, $t = 0.392$, $P = 0.701$). No relationship was found between RR for seroprevention by age and vaccination route [logRR, -0.25488 ± 0.2 (im) vs. -0.5668 ± 0.09 (sc), N.S.], and vaccination year [logRR, -0.3556 ± 0.27 (before 1990) vs. 0.2346 ± 0.158 (after 1990), $P = 0.253$]. We did not observe association between RR for seroprevention by age and average age ($r = 0.013$, $t = 0.051$, $P = 0.960$).

Figure 2 shows the estimated logRR for each study ± 2 S.E., i.e. the 95% CIs. We use the logRR scale since the CIs are only symmetric on this log scale. The test for heterogeneity is significant ($P = 0.0139$), meaning that at least one of the studies' 95% CI does not overlap with the common overall logRR value as indicated by the solid vertical line. The following three studies' 95% CIs do not overlap with the common overall value: Jungers *et al.*,¹⁶ Lelie *et al.*,¹⁷ Steketee *et al.*²⁰ and this result (lack of heterogeneity) is also consistent with our finding of significant differences by age, continent or vaccine.

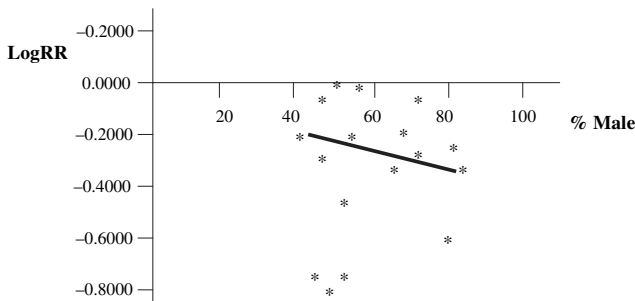


Figure 1. Sensitivity analysis: relationship between influence of age on response rate to hepatitis B virus (HBV) vaccine and gender.

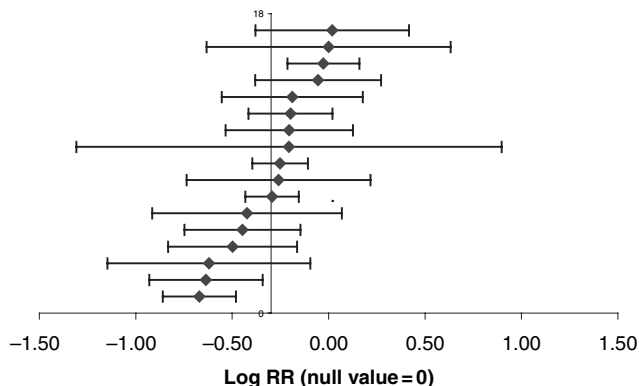


Figure 2. Estimated log risk ratio (logRR) for each study and 95% confidence intervals – the upper bar represents the last study shown in the tables (Singh *et al.*³⁰), the bar at the bottom represents the first study (Crosnier *et al.*¹⁴). The vertical line represents the summary logRR.

DISCUSSION

We have performed a systematic review of the medical literature that described the impact of age on response to HBV vaccine among dialysis patients. Many studies noted a decrease in serological response in association with age; our meta-analysis suggested that the absence of such an association in studies with negative results is related to insufficient statistical power.

In our pooled estimate of effect, older dialysis patients have a significantly decreased response to HB vaccine – the overall RR was 0.74 (95% CI: 0.7–0.79). However, the test for heterogeneity is significant ($P = 0.0139$), so one must be cautious in accepting this as an absolute value. Despite this, it seems quite clear that older dialysis patients have a significantly decreased risk of response to HBV vaccine.

Moreover, we found that the relationship between age and non-response to vaccine in dialysis population occurred irrespective of the age cut-off used. Even an age cut-off as low as 40 years predicted an increased risk of non-response among older patients on maintenance dialysis. We were unable to find convincing evidence that the recombinant or plasma-derived HB vaccine was more immunogenic in older patients on maintenance dialysis or that the routine use of an additional vaccine dose would substantially decrease the risk of non-response among older dialysis patients. The association between age and non-response to HB vaccine remained fairly constant, regardless of the country of origin or the type of renal replacement therapy.

The conclusions of this meta-analysis appear to confirm the results of HBV vaccination in patients with normal renal function. The relationship between age and response to hepatitis B vaccine in the general population had been addressed by several authors with conflicting results;^{10, 11} however, a recent review¹² noted a consistent association between older age and risk of non-response to HB vaccine. This finding is biologically plausible, as numerous changes in cellular and humoral immune responses have been described in older individuals.^{8, 9}

As with all meta-analyses, this study has the potential limitation of publication bias. We postulated that the investigators who found a statistical association of age with failure to show an adequate response to HB vaccine 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. This is of particular concern, given that evaluation of vaccine response according to age in ESRD population was not a primary objective of any of the studies included in our analysis.^{14–30} Our systematic review of the literature on the relationship between age and response rate to HB vaccine in ESRD population [$n = 113$ clinical trials (reviewed in Ref⁵)] showed that this association was not addressed ($n = 63$),⁵ or a significant relationship was observed ($n = 31$).^{14–44} Also, numerous trials ($n = 19$) gave no association between age and response rate to HB vaccine;^{46–64} however, they did not respect inclusion criteria as involved paediatric patients, the data presentation did not allow the construction of contingency tables, or a direct relationship between age and immune response to HB vaccine was noted. In other words, we found 31 clinical trials^{14–44} showing a significant association between age and the response rate to HB vaccine in ESRD: 17^{14–30} were included in the current analysis according to the inclusion criteria, 14 clinical trials^{31–44} showed a negative influence of ageing on the response rate to HB vaccine but they were not included as did not otherwise fulfil our inclusion criteria. In these 14 clinical trials, the mean age in responder dialysis patients was lower than non-responders;^{33, 35, 37, 40–43} the frequency of responders was higher among younger patients,^{38, 39} the mean anti-HBs titres were higher among younger responders patients,⁴⁴ the number of vaccine doses necessary to obtain an immune response increased significantly with age;³⁴ alternatively, responders with

persistent anti-HBs titres after primary vaccination were younger than those responders with a 'transient' response to HB vaccine.^{31, 32} Also, the relative risk of failure to have an adequate response to HB vaccination in older patients was shown but no information was provided in order to create contingency tables.³⁶

Among those studies included in our meta-analysis, some authors²⁴ noted that the seroprotection rate was similar in 'older' and 'younger' patients; however, responder patients on dialysis with persistent anti-HBs titres had significantly lower age than responders with transient anti-HBs antibody after primary HB vaccination schedule.

As listed in Table 6, we did not find significant difference in the relationship between ageing and response rate to HB vaccine according to the renal function (i.e. dialysis patients vs. CRF patients in the predialysis stage); however, only two clinical trials concerned ESRD patients not yet receiving maintenance dialysis, this prevents definitive conclusions.

We have not selected in this meta-analysis abstracts and non-English literature in order to include clinical trials having good methodological quality. The possibility of biased estimates with use of language restricted meta-analyses is controversial.⁶⁵ We observed a strong relationship between ageing and response to HB vaccine; we believe that the inclusion of non-English literature would not change our findings.

The HBV vaccination with three double doses (40 mcg each dose) of recombinant vaccine by intramuscular route as early in the course of the renal disease as possible is currently recommended by the CDC for dialysis patients;⁶⁶ the data of the current meta-analysis support reinforced vaccination schedules (supplementary vaccine shots and/or increased doses) in elderly patients on maintenance dialysis.

In conclusion, we observed a consistent association between older age and increased risk of non-response to hepatitis B vaccine among dialysis patients. Our test for heterogeneity was significant, thus caution is required to accept this association as an absolute value. The relationship between ageing and higher risk of non-response to hepatitis B vaccine remained fairly constant, regardless of the age cut-off used. Such a relationship is biologically plausible and clinically relevant. These results are useful to address both vaccination policy and the direction of future research.

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