Primary seroresponses to double-dose compared with standard-dose hepatitis B vaccination in patients with chronic kidney disease: a systematic review and meta-analysis

William R. Mulley1,2, Suong T.T. Le3,4 and Kathryn E. Ives5

1Department of Nephrology, Monash Medical Centre, Clayton, VIC, Australia, 2Centre for Inflammatory Diseases, Department of Medicine, Monash University, Clayton, VIC, Australia, 3Department of Gastroenterology and Hepatology, Monash Medical Centre, Clayton, VIC, Australia, 4School of Clinical Sciences, Monash University, Clayton, VIC, Australia and 5Department of Anaesthesia, Pain and Perioperative Medicine, Barwon Health–University Hospital Geelong, Geelong, VIC, Australia

Correspondence and offprint requests to: William R. Mulley; E-mail: bill.mulley@monashhealth.org

ABSTRACT

Background. Clinical guidelines recommend double-dose hepatitis B vaccination for patients requiring dialysis, due to an increased risk of hepatitis B infection and reduced vaccine responsiveness. There are no recommendations for patients with chronic kidney disease (CKD) prior to dialysis.

Methods. We performed a systematic review and meta-analysis of randomized and quasi-randomized trials comparing efficacy (seroresponses) and harms of double-dose compared with standard-dose hepatitis B vaccination in patients with CKD, including those requiring dialysis. A systematic literature search (CENTRAL, MEDLINE and EMBASE) was performed using a predetermined search strategy. Relative risks were calculated from pooled data using a random-effects model with subgroup analysis by dialysis requirement and vaccine type.

Results. Seven studies (501 patients) fulfilled review criteria: four in patients receiving dialysis and three in patients not receiving dialysis. The incidence of seroconversion was not increased with double-dose vaccination overall [risk ratio (RR) 1.17, 95% confidence interval (CI) 0.98–1.39], by dialysis requirement or vaccine type. The incidence of seroprotection increased with double-dose vaccination overall [risk ratio (RR) 1.53, 95% confidence interval (CI) 1.17–2.00] but not by requirement or vaccine type. The incidence of seroconversion was not increased with double-dose vaccination overall [risk ratio (RR) 1.17, 95% confidence interval (CI) 0.98–1.39], by dialysis requirement or vaccine type. The incidence of seroprotection increased with double-dose vaccination overall [risk ratio (RR) 1.53, 95% confidence interval (CI) 1.17–2.00] but not by

Received for publication: 20.9.2015; Accepted in revised form: 6.12.2015
dialysis requirement. Adverse events were not reported by treatment arm, precluding comparison. The overall quality of included studies was moderate to low.

**Conclusions.** The current data do not support clinical guideline recommendations for administering double-dose vaccination for patients with CKD as seroconversion was not improved and seroprotection was inadequately assessed. Large high-quality studies are required to overcome the current evidence gap regarding vaccine dosing in CKD.

**Keywords:** hepatitis B, pre-dialysis, seroconversion, seroprotection, vaccine

**INTRODUCTION**

Chronic kidney disease (CKD) is associated with a suppressed immune phenotype including a reduced capacity to mount protective seroresponses to vaccination compared with healthy controls [1–5]. While particularly apparent for patients with end-stage kidney disease requiring dialysis, there appears to be a gradation of reducing vaccine responsiveness with increasing renal impairment [1, 5]. Hepatitis B infection is a leading cause of cirrhosis and liver cancer [6] and is spread by contact with body fluids. Patients requiring dialysis are at an increased risk of exposure to hepatitis B virus through contact with potentially contaminated equipment and surfaces [3]. While the risk of exposure has reduced with the widespread implementation of single-use equipment and greater attention to aseptic technique and sterilization, it remains a significant problem for patients with CKD [7, 8].

Various strategies have been investigated to improve seroresponses to hepatitis B vaccination in patients with CKD, including increased vaccine dose, additional inoculations, the use of adjuvants or adjuncts and different routes of administration [3, 9–11]. Despite these strategies, seroresponses of patients with CKD remain significantly less than those of healthy controls [3]. Clinical guidelines from the USA and Britain recommend providing double the standard vaccine dose to patients with CKD requiring dialysis [4, 12], with no recommendations for patients with CKD not requiring dialysis. Other strategies to improve responses are not currently recommended [4, 12]. Previous systematic reviews have not examined the core clinical guideline recommendation of double-dose vaccination for dialysis patients or whether it should be extended to pre-dialysis patients.

Initial hepatitis B vaccines were plasma-derived preparations composed of purified and chemically inactivated hepatitis B virus obtained from patients infected with hepatitis B [13]. Recombinant vaccines have largely replaced plasma vaccines to avoid any risk of hepatitis B virus transmission [13]. Responses to plasma and recombinant hepatitis B vaccines have been studied in patients with CKD. It is recommended that patients be vaccinated at an early stage of CKD to increase the likelihood of achieving a significant seroresponse [1, 4, 12]. Standard dosing varies by vaccine type but is generally administered by three or four intramuscular doses within a 3- to 6-month period [3, 4].

Our aim was to systematically review the benefits and harms of increased hepatitis B vaccine dosing compared with standard dosing in patients with CKD Stages 3–5 including patients on dialysis. Efficacy was assessed in terms of seroconversion and seroprotection and harms in terms of hepatitis B infection and death.

**MATERIALS AND METHODS**

**Study selection**

Randomized or quasi-randomized trials comparing increased and standard hepatitis B vaccination regimens in adults with CKD Stages 3–5 were included. There were no language restrictions. Published abstracts were included if <5 years since publication to allow time for full publication. Studies employing plasma or recombinant hepatitis B vaccines administered by any route were included. We excluded studies comparing additional inoculations with standard regimens; different routes of administration; different vaccine preparations in treatment and control arms; the addition of adjuncts. The study populations were patients with CKD Stages 3–5 without prior vaccination or hepatitis B infection determined by history and absence of hepatitis B: surface antigen or antibodies, core antigen, or antibodies or virus in blood. Studies involving patients taking immunosuppressive drugs were excluded.

The primary outcome measures were the proportion of patients achieving seroconversion and seroprotection. Seroconversion was defined as the development of detectable hepatitis B surface antibodies when previously negative. Seroprotection was defined as the development of 'protective' hepatitis B surface antibody titres when previously negative with the titre defined by the investigators. Both outcomes were assessed at 4–8 weeks after the final inoculation.

Secondary outcomes measured were the proportion of vaccinated patients who subsequently developed hepatitis B infection; adverse vaccination reactions including death, anaphylaxis and local reactions.

**Search methodology**

We systematically searched the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 18 September 2014. To allow for delay in trials being entered onto CENTRAL, we searched MEDLINE OVID SP and EMBASE OVID SP from 1 January 2011 until 18 September 2014. (For full search strategy, see Supplementary material, Appendix S2.) We searched reference lists from identified studies and review articles. Two reviewers independently assessed studies for eligibility based on the title and the abstract. Two reviewers independently performed full-text review for all studies that appeared relevant or where there was uncertainty. Studies subsequently excluded were listed with reasons (Supplementary material, Table S1). Disagreements were resolved by consensus.

**Data extraction and assessment of risk of bias**

Data extraction was performed independently by two authors using standardized data extraction forms
(Supplementary material, Appendix S3). Where duplicate studies were found, the most complete report was included. Disagreements were managed by consensus. The following information was extracted from eligible studies: first author, year of publication, country of publication, study registration, study design, inclusion and exclusion criteria, participant numbers and characteristics, vaccine type, dose, regimen and route of administration, timing of outcome assessment, seroconversion and seroprotection proportions, mean antibody titres and adverse events (Supplementary material, Appendix 3).

The risk of bias was independently assessed by two authors using the risk of bias assessment tool of Higgins and Green [14] (Supplementary material, Appendix S1).

**Statistical methodology**

We examined dichotomous outcomes and expressed results as risk ratios (RRs) with 95% confidence intervals (CI). Several studies examined multiple time points for vaccine responses; we included seroconversion and seroprotection data from the time point 4–8 weeks after the third or fourth dose of the vaccine. For studies with missing data, attempts to contact corresponding authors by mail or email were made. No responses were received. Data analysis proceeded by excluding those studies from the analysis.

Heterogeneity was assessed using the methods of Higgins and Green [14] using a $\chi^2$-test with n-1 degrees of freedom, with $P < 0.05$ for statistical significance. The $I^2$ test was used to assess the proportion of variation in vaccination responses occurring beyond chance with values of 25, 50 and 75% representing low, medium and high levels of heterogeneity, respectively [14]. Due to the limited number of included studies, funnel plots to assess reporting bias were not constructed [14].

All analyses were performed using Review Manager 5.3. When appropriate, data were pooled using a random-effects model to present a more conservative assessment of effect in the presence of heterogeneity.

Predefined subgroup analyses were conducted for seroresponses in dialysis patients separately from patients with CKD not requiring dialysis and for studies using plasma vaccines separately from those using recombinant vaccines. One study compared quadruple dose vaccination with double-dose vaccination and was considered separately [15].

Sensitivity analyses by vaccine type were performed by CKD subgroup by excluding studies using plasma vaccines as they are no longer in widespread clinical use. Sensitivity analysis excluding all studies with high or uncertain risk of bias was planned; however, it was not conducted as all studies would have been excluded.

**RESULTS**

**Characteristics of included studies**

Our search identified 731 citations. We excluded 723 citations on the basis of title and abstract (n = 712) and full-text review (n = 11) (Supplementary material, Table S1). Eight studies were included in the qualitative review and seven in the meta-analysis (Figure 1). The eight studies included 588 patients with CKD Stages 3–5 (Table 1, Supplementary material, Appendix S3) [15–22].

Seven studies (501 participants) examined double-dose compared with standard-dose vaccination [16–22]. Four studies (332 participants) included patients receiving dialysis [16–18, 21] and three studies (169 participants) pre-dialysis patients [19–21]. Two studies employed plasma-derived vaccines [16,
Hepatitis B vaccination in CKD

Double-dose vaccination compared with standard-dose vaccination.

Seroconversion. The proportion of patients who achieved seroconversion ranged from 54 to 83% for double-dose and 46 to 75% for standard-dose vaccination (Table 1). The overall RR of seroconversion was not significantly improved by double-dose compared with standard-dose vaccination (RR 1.17, 95% CI 0.98–1.39) (Figure 2). There was no significant increase in the incidence of seroconversion with double-dose relative to standard-dose vaccination for patients with CKD requiring or not requiring dialysis when considered separately (RR 1.15, 95% CI 0.93–1.44 and RR 1.16, 95% CI 0.85–1.58, respectively) (Figure 2A). There was no significant difference in the incidence of seroconversion with double-dose relative to standard-dose vaccination for plasma-derived or recombinant vaccines when considered separately (RR 1.16, 95% CI 0.53–2.52 and RR 1.1, 95% CI 0.94–1.27, respectively) (Figure 2B). Only the study of Benhamou et al. [17] demonstrated a significant increase in seroconversion with double-dose vaccination (Figure 2). There was no statistically significant heterogeneity for seroconversion by \( \chi^2 \)-test, \( P = 0.13 \) (Figure 2). The \( I^2 \) test (40%) suggests low-to-moderate variability among studies due to heterogeneity (Figure 2) [14]. When recombinant vaccines were examined separately, there was no significant heterogeneity (\( \chi^2 \)-test, \( P = 0.76 \) and \( I^2 = 81\% \)) (Figure 2).

Seroconversion. The proportion of patients who achieved seroconversion ranged from 54 to 83% for double-dose and 46 to 75% for standard-dose vaccination (Table 1). The overall RR of seroconversion was not significantly improved by double-dose compared with standard-dose vaccination (RR 1.17, 95% CI 0.98–1.39) (Figure 2). There was no significant increase in the incidence of seroconversion with double-dose relative to standard-dose vaccination for patients with CKD requiring or not requiring dialysis when considered separately (RR 1.15, 95% CI 0.93–1.44 and RR 1.16, 95% CI 0.85–1.58, respectively) (Figure 2A). There was no significant difference in the incidence of seroconversion with double-dose relative to standard-dose vaccination for plasma-derived or recombinant vaccines when considered separately (RR 1.16, 95% CI 0.53–2.52 and RR 1.1, 95% CI 0.94–1.27, respectively) (Figure 2B). Only the study of Benhamou et al. [17] demonstrated a significant increase in seroconversion with double-dose vaccination (Figure 2). There was no statistically significant heterogeneity for seroconversion by \( \chi^2 \)-test, \( P = 0.13 \) (Figure 2). The \( I^2 \) test (40%) suggests low-to-moderate variability among studies due to heterogeneity (Figure 2) [14]. When recombinant vaccines were examined separately, there was no significant heterogeneity (\( \chi^2 \)-test, \( P = 0.76 \) and \( I^2 = 81\% \)) (Figure 2).

Effects of interventions

Double-dose vaccination compared with standard-dose vaccination.

Seroconversion. The proportion of patients who achieved seroconversion ranged from 54 to 83% for double-dose and 46 to 75% for standard-dose vaccination (Table 1). The overall RR of seroconversion was not significantly improved by double-dose compared with standard-dose vaccination (RR 1.17, 95% CI 0.98–1.39) (Figure 2). There was no significant increase in the incidence of seroconversion with double-dose relative to standard-dose vaccination for patients with CKD requiring or not requiring dialysis when considered separately (RR 1.15, 95% CI 0.93–1.44 and RR 1.16, 95% CI 0.85–1.58, respectively) (Figure 2A). There was no significant difference in the incidence of seroconversion with double-dose relative to standard-dose vaccination for plasma-derived or recombinant vaccines when considered separately (RR 1.16, 95% CI 0.53–2.52 and RR 1.1, 95% CI 0.94–1.27, respectively) (Figure 2B). Only the study of Benhamou et al. [17] demonstrated a significant increase in seroconversion with double-dose vaccination (Figure 2). There was no statistically significant heterogeneity for seroconversion by \( \chi^2 \)-test, \( P = 0.13 \) (Figure 2). The \( I^2 \) test (40%) suggests low-to-moderate variability among studies due to heterogeneity (Figure 2) [14]. When recombinant vaccines were examined separately, there was no significant heterogeneity (\( \chi^2 \)-test, \( P = 0.76 \) and \( I^2 = 81\% \)) (Figure 2).

Seroprotection. Four studies (372 patients) reported seroprotection. The proportion achieving seroprotection ranged from 51 to 69% for double-dose and 24 to 42% for standard-dose (Table 1). The overall RR for seroprotection was increased by double-dose compared with single-dose vaccination (RR 1.54, 95% CI 1.17–2.04) (Figure 3). There was a significant increase in the incidence of seroprotection for patients with CKD requiring dialysis (RR 1.74, 95% CI 1.02–2.96) but not for pre-dialysis patients (RR 1.72, 95% CI 0.98–3.03) when considered separately (Figure 3A). There was a significant increase in the incidence of seroprotection with double-dose relative to standard-dose vaccination for plasma-derived vaccine (\( n = 1 \)) and recombinant vaccines (\( n = 3 \)) when considered separately (RR 2.32, 95% CI 1.43–3.77 and RR 1.35, 95% CI 1.05–1.74, respectively) (Figure 3B). The direction of effect was the same for the four studies reporting this outcome.

Seroprotection. Four studies (372 patients) reported seroprotection. The proportion achieving seroprotection ranged from 51 to 69% for double-dose and 24 to 42% for standard-dose (Table 1). The overall RR for seroprotection was increased by double-dose compared with single-dose vaccination (RR 1.54, 95% CI 1.17–2.04) (Figure 3). There was a significant increase in the incidence of seroprotection for patients with CKD requiring dialysis (RR 1.74, 95% CI 1.02–2.96) but not for pre-dialysis patients (RR 1.72, 95% CI 0.98–3.03) when considered separately (Figure 3A). There was a significant increase in the incidence of seroprotection with double-dose relative to standard-dose vaccination for plasma-derived vaccine (\( n = 1 \)) and recombinant vaccines (\( n = 3 \)) when considered separately (RR 2.32, 95% CI 1.43–3.77 and RR 1.35, 95% CI 1.05–1.74, respectively) (Figure 3B). The direction of effect was the same for the four studies reporting this outcome.
four studies, and overall heterogeneity was minimal ($\chi^2$-test $P = 0.2, I^2 = 31\%$) (Figure 3).

Sensitivity analyses. Given the small number of included studies, a limited sensitivity analysis was performed by excluding the studies using plasma-derived vaccines, given their limited current use. The outcomes for seroconversion and seroprotection were unaltered (RR 1.10, 95% CI 0.94–1.27 and RR 1.35, 95% CI 1.05–1.74, respectively). Both studies using plasma-derived vaccines were conducted in patients requiring dialysis. Seroconversion in dialysis patients was not improved with double-dose compared with standard-dose vaccination when analysis was restricted to recombinant vaccines (RR 1.05, 95% CI 0.86–1.28).

Secondary outcomes. Insufficient reporting of our pre-specified secondary outcomes of death, subsequent hepatitis B infection and incidence of other adverse events precluded meta-analysis. The incidence of minor adverse events per injection was reported by three studies [18, 19, 22] but not by treatment arm, so differences could not be determined (Supplementary material, Table S3). Minor adverse events complicated 9–15% of injections.

Quadruple dose vaccination compared with standard-dose vaccination. One study compared quadruple dose vaccination with double-dose vaccination and was included for completeness. The study included 87 patients on dialysis and showed no improvement in the incidence of seroconversion.
DISCUSSION

The risk of hepatitis B infection in patients with CKD is substantially reduced by vaccination [23]; however, it is not eliminated, with those with poor vaccine responses remaining at increased risk of infection [24] and its ensuing complications. Poor vaccine responsiveness to standard vaccines in dialysis patients has prompted the use of novel vaccines by some clinicians in Israel and Europe. These include ‘third generation’ vaccines with very limited efficacy data [25] and second generation vaccines employing novel adjuvants, with reports of increased protective antibody persistence with similar early efficacy to standard vaccines in patients with CKD [26]. The use of newer vaccines may increase over time with mounting supportive evidence. We examined evidence relating to current clinical guidelines recommending double-dose vaccination using standard recombinant vaccines [4, 12].

Using pooled data from the seven included studies, double-dose vaccination with plasma-derived or recombinant vaccines was associated with a similar incidence of seroconversion as standard-dose vaccination for pre-dialysis and dialysis patients. The incidence of seroprotection was significantly improved by double-dose vaccination combining data from the four studies assessing this outcome. The results were not significant for patients not requiring dialysis considered separately. For recombinant vaccines, when data from the single, quasi-randomized study in patients requiring dialysis are combined with the two studies in pre-dialysis patients, a benefit for double-dose vaccination is maintained. This suggests that double-dose vaccination may increase antibody titres in those who seroconvert; however, mean antibody titres reported or
Both our study and that of Schroth et al. demonstrated that increasing antigenic load did not improve seroconversion; McNulty et al. [28] found no significant increase in seroconversion in a meta-analysis of data from studies examining additional inoculations compared with usual vaccine regimens. Similar to double-dose vaccination, extra inoculations provide an increased dose of antigen, albeit with potentially different immune dynamics, which seems to be a logical strategy to increase seroresponses. Both our study and that of Schroth et al. demonstrate that provision of an increased antigen load did not improve seroconversion. Furthermore, a quadruple dosing strategy resulted in a similar incidence of seroprotection and seroconversion to double-dose vaccination, suggesting that there is a ceiling to the efficacy of increasing antigenic load [15].

The predetermined secondary outcomes for this review were not reported adequately to provide a meaningful synthesis. The major areas of data omission related to mortality, hepatitis B infection and adverse events such as anaphylaxis and local and systemic reactions. Clinical trial data for recombinant vaccines in the general population report an incidence of 24% for local side effects, 8% for systemic side effects and 13% for both. The rate of local reactions doubled with double-dose vaccination (https://www.gsksource.com/gskprm/htdocs/documents/ENGEXIX-B.PDF, www.merck.com/product/usa/pi.../recombivax.../recombivax_pi.pdf). We therefore anticipated a higher incidence of adverse events with double-dose vaccination in CKD patients; however, the rates, when reported, were lower and did not indicate significant mortality or morbidity (Supplementary material, Table S3).

Reasons for attrition of participants after randomization were reported in less than half the studies. Only patients who completed the full course of vaccination were analysed, amounting to 89% of the initial pooled study population. We are therefore unable to exclude attrition bias; however, for the most part, attrition was balanced between treatment arms where described.

The overall quality of the included studies was classified as low using the GRADE schema [29], which implies limited confidence in the effect estimates and that the true effect may be quite different [29]. All studies were assessed as having an unclear risk of bias. The randomization process was unclear or not specified in four studies. Due to the age of the studies (seven were published prior to 2010), there is potential for an impact of study era on outcomes if other parameters affecting immune responses such as dialysis efficacy changed over time. There was clinical heterogeneity in the type of vaccine administered (plasma and recombinant) and the timing of the primary outcome measure across some studies. Plasma-derived vaccines are currently used infrequently, but were included as they still address immune responsiveness. Overall, there was sufficient consistency between studies for us to believe that pooling of results was appropriate; this was supported by a low degree of statistical heterogeneity.

Most included studies were underpowered to detect a true difference in seroresponses; McNulty et al. calculated that 125 patients were required to detect a 25% increase in seroconversion with 80% power [20]. Using these parameters, only the studies of Bruguera (n = 153) and Benhamou (n = 139) were sufficiently powered; hence, the potential for Type II error is significant, and a true beneficial effect may have been missed [17, 18]. The alternative explanation is a true lack of efficacy of double-dose vaccination. Other limitations of the current evidence include the use of subcutaneous vaccine administration in one study [17], which does not reflect current practice, and the predominant (70%) male representation in the included studies.

The current evidence has significant qualitative and quantitative deficiencies such that we cannot confidently support the current clinical guideline recommendations for double-dose vaccination for dialysis patients or an extension of this policy to pre-dialysis patients. Due to inadequate reporting of adverse events, we are unable to determine the balance of benefit and harm of a double-dose vaccination strategy irrespective of dialysis status. Another significant limitation to adopting double-dose hepatitis B vaccination for CKD patients is the additional cost, which has not been explored in any of the studies. Currently, therefore, the clinician cannot be clearly advised on the dose of hepatitis B vaccine to offer to their patients with moderate-to-severe CKD.
Hepatitis B vaccination in CKD

The significant evidence gap identified by this review suggests the need for appropriately powered randomized clinical trials of double-dose compared with single-dose recombinant hepatitis B vaccination among patients with CKD both prior to and after commencing dialysis. Such studies should measure vaccine efficacy as well as adverse events. The fundamental question of whether the incidence of hepatitis B infection is reduced by an increased vaccine dose would ideally be addressed by long-term follow-up studies performed in endemic territories. Given these initiatives are unlikely to be undertaken, the use of surrogate markers such as seroconversion and seroprotection is necessary. Trials in patients with CKD prior to commencing dialysis are critical as this group constitutes the majority of CKD patients and has more robust vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1]. Cost-effectiveness analyses of double-dose vaccination in areas of low vaccine responses than patients requiring dialysis [1].

REFERENCES

24. Lewis-Ximenez LL, Oliveira JM, Mercadante LA et al. Serological and vaccination profile of hemodialysis patients during an outbreak of hepatitis B virus infection. Nephron 2001; 87: 19–26

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

None declared.

THE COCHRANE LIBRARY

Received for publication: 3.9.2015; Accepted in revised form: 7.12.2015