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Immunization against hepatitis B – what can we expect?

Results of a survey of antibody response to immunization in persons 'at risk' of occupational exposure to hepatitis B

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SUMMARY

One thousand three hundred and twenty adults at risk of occupational exposure to hepatitis B were immunized using genetically engineered surface antigen and their antibody response (anti-HBs IU/l) assessed. Sex was known for all subjects and age for 1120 (range from 17–71 years). Seven hundred and sixty-four subjects were immunized in the local Department of Occupational Health, the remainder mainly by general practitioners.

Analysis of 'good responders' (anti-HBs > 100 IU/l) according to age and sex showed that increasing age and male sex had independent adverse effects on the likelihood of developing a satisfactory level of antibody to HBsAg. Furthermore even those most likely to respond well (young women), had a 1/5 to 1/6 failure rate to achieve > 100 IU/l anti-HBs.

Of 63 persons who received a fourth dose of vaccine, 26 developed anti-HBs titres > 100 IU/l when tested after 6 months. Subjects who had a low level of anti-HBs following primary immunization were more likely to develop > 100 IU/l anti-HBs following a booster dose than were non-responders (< 10 IU/l).

INTRODUCTION

Since the introduction of hepatitis B vaccines a great deal of information has been gained about their safety and immunogenicity. In most of the early studies an anti-HBs cut-off of 10 IU/l was used to indicate seroconversion since it was known that 10 IU/l of passively transferred antibody was protective against hepatitis B infection [1–4].

Subsequently, it has become clear that for most vaccinees, the peak titre of anti-HBs antibody is followed by a decline whose rate of fall is relatively constant between individuals. It thus follows that the length of time a vaccine recipient has > IU/l circulating antibody post-immunisation depends on the peak antibody titre achieved [5–8]. The possibility that immunological memory will ensure

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protection even after circulating antibody has reached undetectable levels is a real one, but it is suggested that the production of a brisk anamnestic response is more likely in those who initially produce a high titre of circulating anti-HBs [8, 9].

For these reasons we, and others, have regarded it as important to identify recipients of hepatitis B vaccine who mount a good initial response (antibody titre > 100 IU/l) and those who do not. Those vaccinees whose initial response was poor (10–100 IU/l) or nil (< 10 IU/l) were offered a booster (fourth) dose of vaccine and their antibody level checked 6 months later.

Early figures for seroconversion to hepatitis B vaccine have varied – patients receiving haemodialysis or who have HIV infection respond poorly. Much of the early work using hepatitis B vaccine studied groups of young, fit, adults (often medical students) [1–3] or rather special groups such as homosexuals [5, 13, 14], haemodialysis patients [15] or neonates [16, 17].

There have been some studies of health-care workers who have received hepatitis B vaccine, but the seroconversion rates and those factors which affect it have not emerged consistently – perhaps because the number of persons in these studies has been small. Also, early immunizations were performed in the gluteal region, found to be an unsatisfactory route for hepatitis B immunization [7, 8, 11, 12, 18, 19, 21–23].

During an 18-month period over 1300 health-care workers and others at occupational risk of hepatitis B infection (policemen, ambulance men, prison officers) were immunized against hepatitis B using a genetically engineered surface antigen preparation (Engerix B) according to the manufacturer's instructions. Numbers of subjects who developed a good response (anti-HBs > 100 IU/l) to vaccine and those who developed a poor response (anti-HBs < 100 IU/l) were analyzed according to age, sex and whether immunized by the Occupational Health Department or within the community. Subjects who developed anti-HBs titres of < 10 IU/l were identified separately ('non responders').

A single booster dose of vaccine was offered to all subjects whose post primary course response was < 100 IU/l. Those receiving a booster dose were asked to return 6 months later to have their antibody level rechecked to assess the value of a booster dose following primary hepatitis B immunization.

The purpose of this study was to establish the efficacy of hepatitis B vaccine in inducing satisfactory anti-HBs levels in a large mixed population of individuals 'at risk' of exposure to hepatitis B in the course of their employment. We also aimed to determine the factors associated with good or poor response to the vaccine and to comment on the value of post-immunization antibody assessment and 'booster' dose administration.

MATERIALS AND METHODS

1. *Hepatitis B immunization*

Vaccinees received 'Engerix B' hepatitis B vaccine (Smith, Kline and French Laboratories Ltd). Individuals immunized by the Occupational Health Department (Royal United Hospital, Bath) received an initial course of $3 \times 20\ \mu g$ doses intramuscularly into the deltoid according to a 0-, 1- and 6-month schedule.

They were recalled to the department 6–8 weeks following the third vaccine dose and serum taken for antibody testing. Any individual whose immunization had been done elsewhere but who had presented to the Occupational Health Department for antibody testing following employment in Bath was excluded from the survey as were individuals whose post-vaccine check was more than 6 months following the third vaccine dose or whose immunization schedule had (e.g. due to pregnancy) varied widely from that recommended by the manufacturer.

Approximately 40% of the individuals included in this survey were immunized within the community, the vast majority by general practitioners and a few at a private health care clinic. Unless specifically stated otherwise it was assumed that persons administering vaccine had done so according to the manufacturer's instructions and the vaccinees were included in the survey. Individuals who were clearly stated not to have been immunized according to the schedule were excluded from the survey.

2. *Booster immunizations*

Any individual whose post primary course antibody level was less than 100 IU/l was advised to have a fourth 20 μg dose of vaccine followed by repeat antibody testing 6 months later.

3. *Measurement of antibody to hepatitis B surface antigen (anti-HBs)*

Antibody to hepatitis B surface antigen was measured using an enzyme-linked immunoadsorbent assay manufactured by Sorin Biomedica (Wokingham, Berks, UK). Some of the difficulties in quantitative assessment of anti-HBs are outlined in the Discussion. In brief, the test was performed as follows: 100 μl of standard reagents (supplied by the manufacturer) containing anti-HBs at 5, 10, 20 and 40 IU/l were added to wells of an HBsAg coated microtitre plate. Ten microlitres of specimen to be tested plus 90 μl diluting fluid were added to remaining wells – each specimen was tested once.

The plate was allowed to incubate at room temperature overnight in a moist chamber. After washing, horse radish peroxidase conjugated HBsAg was added to each well and the plate incubated at room temperature for 4 h. Binding of enzyme-conjugated HBsAg was detected by the addition of substrate plus chromogen (tetramethylbenzidine). After 30 min at room temperature colour development was stopped using 0·5 M sulphuric acid and the absorbance of each well at 450 nm measured using a Dynatech MR710 microplate reader. Calculation of the antibody level in each specimen was made by comparison with the standard curve and the amount of antibody in the undiluted serum obtained by multiplication. Specimens whose calculated antibody level (undiluted) was < 100 IU/l were re-tested without dilution.

4. *Measurement of antibody to hepatitis B core antigen (anti-HBc)*

Antibody to hepatitis B core antigen was measured using an enzyme linked immunoadsorbant assay manufactured by Sorin Biomedica. This is a competitive assay based on the same enzyme substrate/chromogen detection system described above for anti-HBs detection. Serum samples (undiluted) were incubated together with horseradish peroxidase-conjugated human anti-HBc – IgG in microtitre

Table 1. *Antibody response to hepatitis B vaccine. Antibody level (IU/l) measured following three dose vaccine course*

	Total sera examined	Good response (> 100 IU/l)	Poor response (< 100 IU/l)
All vaccinees	1320 (100%)	1009 (76·4%)	311 (23·6%)
Females	1016 (100%)	802 (78·9%)	214 (21·4%)
Males	304 (100%)	207 (68·1%)	97 (31·9%)

Table 2. *Antibody response to hepatitis B vaccine – effect of age on post-immunization antibody titre in female vaccinees*

Age (years)	Total sera examined	Good response	Poor response
11–20	27	21 (77·8%)	6 (22·2%)
21–30	290	242 (83·5%)	48 (16·5%)
31–40	182	148 (81·3%)	34 (18·7%)
41–50	217	153 (70·5%)	64 (29·5%)
51–60	124	94 (75·8%)	30 (24·2%)
61–70	16	10 (62·5%)	6 (37·5%)
> 70	0	0	

wells coated with HBcAg. Positive and negative control sera were provided with the kit and the results calculated according to the manufacturer's instructions.

5. *Statistical analysis*

Results were calculated using a statistical calculator software package for 2×2, $2 \times N$ stratified tables produced by EpiInfo 'Statcalc' USD Incorporated. For a single table this produced Mantel–Haenszel χ^2 values, P values and Greenland/Robins 95% confidence limits [27]. Stratification produced Mantel–Haenszel weighted relative risk values.

RESULTS

Antibody titre to HBsAg was determined post immunization in 1320 adults 'at risk' of occupational exposure to hepatitis B. Date of birth was available for 1120 vaccinees. A post-immunization antibody level of greater than 100 IU/l was deemed to be satisfactory, a titre less than 100 IU/l was regarded as a poor response [6, 8, 10–12, 18, 23]. As shown in Table 1, 76·4% of subjects developed satisfactory post-immunization anti-HBs titres and 23·6% did not. More women than men were immunized, perhaps reflecting the preponderance of women working in health-care services.

Table 1, indicates that more men (31·9%) than women (21·4%) responded poorly to hepatitis B vaccine. (Relative risk of poor response if male = 1·51 (95% confidence limits 1·24–1·86, $P < 0{\cdot}0001$).)

In Tables 2 and 3, vaccinees have been grouped according to age (by decade) and sex, with the number and percentage of good and poor responders in each group. Tables 2 and 3 demonstrate that women respond better to hepatitis B vaccine than men but that the response to vaccine deteriorates with increasing age

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Table 3. *Antibody response to hepatitis B vaccine – effect of age on post-immunization antibody titres in male vaccinees*

Age (years)	Total sera examined	Good response (> 100 IU/l)	Poor response
11–20	3	3	0
21–30	76	60 (78·9%)	16 (21·1%)
31–40	86	61 (70·9%)	25 (29·1%)
41–50	54	29 (53·7%)	25 (46·3%)
51–60	38	22 (57·9%)	16 (42·1%)
61–70	6	4	2
> 70	1	0	1

in both sexes. If all vaccinees (men and women) are grouped according to age above or below 40 years of age, the relative risk of poor response if over 40 years old is 1·63 (95% confidence limits 1·32–2·00, $P < 0·00001$). For women the relative risk of poor response if over 40 years of age is 1·59 (95% confidence limits 1·23–2·04, $P < 0·003$), for men the relative risk of over 40 years old is 1·79 (95% confidence limits 1·27–2·53, $P < 0·001$). When the results are stratified for sex (thereby removing any anomalies due to the unequal number of men and women tested) the Mantel–Haenszel weighted relative risk of poor response if over 40 years of age is 1·65 (95% confidence limits 1·34–2·02). Furthermore the difference due to sex is demonstrable for vaccinees below 40 years of age (relative risk of poor response if male is 1·41 [95% confidence limits 1·02–1·95, $P < 0·05$]) and above 40 years of age (relative risk of poor response if male is 1·59 [95% confidence limits 1·20–2·09, $P < 0·002$]). If the data are stratified for age (removing anomalies due to uneven age distribution between the groups of male and female vaccinees) the difference due to sex is preserved and the Mantel–Haenszel weighted relative risk of poor response if male is 1·5 (95% confidence limits 1·21–1·85).

We thus conclude that older age and male sex have *independent* adverse effects on the likelihood that an individual will respond satisfactorily to hepatitis B immunization.

It is of note that even in the group of vaccinees most likely to develop good post-immunization antibody titres (i.e. young women) between 1/5 and 1/6 fail to do so.

Table 4 compares antibody responses achieved by individuals immunized by staff of the Occupational Health Department (Royal United Hospital, Bath) with those immunized in the community, predominantly by general practitioners but some by a senior nurse at a private health care clinic. The table shows the number and percentage of good responders and the proportion of men and women in each group. The relative benefit of immunization in the hospital Occupational Health Department compared with immunization within the community is 1·07 (95% confidence limits 1·01–1·14, $P = 0·02$), a small but just significant difference. However, if the same analysis is performed after the data have been stratified for sex there is no significant difference in response rate between those immunized in the hospital and those immunized in the community. The apparent difference was accounted for by the disproportionate number of women immunized by the Occupational Health Department.

Table 4. *Antibody response to hepatitis B vaccine – individuals immunize Hospital Occupational Health Departments and individuals immunized withi community*

Occupational Health Department		Good response (> 100 IU/l)
Total immunized	764	614 (80·3%)
Females	626	528 (84·3%)
Males	138	86 (62·3%)

82% vaccinees were female

Community Immunization (GPs and private sector)		Good response (> 100 IU/l)
Total immunized	556	417 (75·0%)
Females	386	297 (76·9%)
Males	170	120 (70·6%)

69·4% vaccinees were female

Table 5. *Distribution of non-responders (< 10 IU/l) to hepatitis B vaccine according to age and sex*

	Total vaccinees with < 10 IU/l)...	
Total records with date of birth...	Antibody response 1120	< 10 IU/l (%) 107 (9·6%)
Age (years)	Male	Female
11–20	0 of 3 (0%)	2 of 27 (7·4%)
21–30	6 of 76 (7·9%)	14 of 290 (4·8%)
31–40	9 of 86 (10·5%)	10 of 182 (5·5%)
41–50	12 of 54 (22·2%)	26 of 217 (12·0%)
51–60	10 of 38 (26·3%)	12 of 124 (9·7%)
61–70	2 of 6 (33·3%)	3 of 16 (18·8%)
> 70	1 of 1	

Previous studies have evaluated the number of 'non responders' to vaccine, i.e those whose post-primary anti-HBs titre was < 10 IU/l. In our population, as shown in Table 5, overall 9·5% individuals produced < 10 IU/l antibody following a three dose course of hepatitis B vaccine – a level comparable with that described by others. 'Non response' is also related to increasing age and male sex. Applying the same statistical analysis to these data as for Tables 2 and 3 produced a relative risk of producing < 10 IU/l of 2·97 if male (95% confidence limits 2·08–4·24, $P = < 0{\cdot}0001$) and a relative risk of producing < 10 IU/l of 2·34 if over 40 years of age (95% confidence limits 1·62–3·40, $P < 0{\cdot}00003$). If the results are stratified for sex the relative risk for non response if over 40 years of age is preserved (relative risk 1·40, 95% confidence limits 1·66–3·47), again inferring that increasing age and male sex have an independent adverse effect on the outcome of immunization.

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Table 6. *Response to a booster (fourth) dose of hepatitis B vaccine*

Number of post-booster sera tested	63	Number of sera with > 100 IU/l	26 (41·26%)
Number of post-booster sera initially < 10 IU/l	30	Number of sera reaching > 100 IU/l	6 (20·0%)
Number of post-booster sera initially > 10 IU/l	33	Number of sera reaching > 100 IU/l	20 (60·6%)
Number of males receiving booster	19	Number of males achieving > 100 IU/l	8 (42·1%)
Number of females receiving booster	44	Number of females achieving > 100 IU/l	18 (40·9%)

Individuals who produced < 100 IU/l of anti-HBs following the primary three dose course of vaccine were advised to receive a fourth 20 μg dose and have their antibody level checked 6 months thereafter. During the 18 months of this study 63 people whose primary response was < 100 IU/l received a booster dose and presented for 6-month follow up. As shown in Table 6 26 subjects developed satisfactory antibody titres. Again using the Mantel–Haenszel χ^2 test it is calculated that the relative benefit of female sex when receiving a booster dose of hepatitis B vaccine is insignificant. A favourable outcome following boosting is, however associated with post primary antibody levels of 10–100 IU/l rather than post-primary titres of < 10 IU/l. The relative benefit is 3·03 (95% confidence limits 1·41–6·52, $P < 0·018$). It is of note however that six subjects who produced no detectable anti-HBs following primary immunization, developed > 100 IU/l 6 months following the booster dose.

Serum specimens from poor and non-responders were tested for the presence of antibody to hepatitis B core antigen. Of 251 sera examined only 8 (3·19%) were positive for anti-HBc. We thus conclude that the majority of poor responders have not previously been infected with hepatitis B.

DISCUSSION

Now that immunization against hepatitis B has become widespread among health-care workers and others occupationally 'at risk' of exposure to the virus it is important to establish reasonable expectations for individual vaccinees and employing authorities with regard to the development of protective immunity.

Because occupational exposure to hepatitis B is rare in the UK (and indeed elsewhere) there is a paucity of data linking previous immunization with protection against subsequent infection in this very large group of vaccine recipients. Because, however, it is possible to measure anti HBs in serum following immunization and it is known that passively transferred antibody to HBsAg at a level of 10 IU/l is protective if given post-exposure to hepatitis B virus, initial studies regarded a successful outcome following immunization against HBsAg as development of 10 IU/l or more of antibody [1–4].

It has however become clear that antibody level declines during the months and years following immunization and moreover that an initial response producing only 10 IU/l is very low, mean titres in some of the pilot studies were reported as > 1000 IU/l or even > 10000 IU/l [1, 2]. The possibility that even when antibody

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is no longer detectable, a previously immunized individual will have sufficiently primed immunological memory to mount an anamnestic response and therefore be protected against hepatitis B infection has gained some support – again however, it is believed that those individuals who mount a good primary response to immunization are more likely to have protective secondary immunological capacity than those who do not [6, 8, 9, 13].

Consequently there has been a movement away from setting the cut off for satisfactory antibody response at 10 IU/l. A level of 50 IU/l has been suggested but the higher level of 100 IU/l is preferred by others and we chose to conform to this standard [6, 8, 10–12, 18, 23].

The selection of testing method for antibody to HBsAg has been a subject of recent concern, most commercial kits do not give accurate quantitative results in the range 10–200 IU/l – no doubt because they were designed at an earlier period when the range of interest was around 10 IU/l. The six standards provided by Sorin for use in their kit include two (80 and 160 IU/l) which produce absorbance values greater than the capacity of the spectrophotometer to quantify. To achieve reliable quantitation of anti-HBs levels, both sera and standards were tested after 1 in 10 dilution and without dilution as described in the Materials and Methods.

In contrast to some of the pilot studies [1, 2, 13] and in common with many subsequent reports [12, 20–22] we found a significant number of poor responders (< 100 IU/l) in all groups tested. It has been suggested [24, 25] that post-immunization antibody assessment be confined to older vaccinees and that young vaccine recipients can safely be regarded as almost all immune. The work presented here cannot support this view. Even young women (the most responsive group) had a 1/5 to 1/6 failure rate to develop > 100 IU/l antibody following a three-dose vaccine course.

In addition to the clinical problems associated with hepatitis B infection, the disease, if acquired by occupational exposure is reportable to the Health and Safety Executive under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulation (1985) and the sufferer may also be able to claim compensation; both under the Prescribed Industrial Diseases Regulation and also possibly from his/her employer. It is thus of considerable importance both to the individual and to their employer that poor responders to hepatitis B immunization are identified. If, after attempts to boost their immune response, these subjects still have unsatisfactory levels of antibody to hepatitis B they should be aware of their lack of protection despite immunization and should receive passive protection from specific anti-HBs immunoglobulin (HBIG) if exposed to hepatitis B.

Failure to identify and inform poor and non-responders will inevitably produce a false sense of security in many at occupational risk, often over a period of many years.

The observed difference between men and women in the ability to mount a satisfactory immune response to hepatitis B vaccine is of considerable interest. Early reports suggested that women respond less well to vaccine than men [11] but other studies have suggested a similar pattern to that we describe in which women are consistently better responders. This was particularly marked in studies where vaccine was given as a low dose intradermally. That women respond better to

hepatitis B immunization is perhaps a reflection of some true difference in ability to respond to hepatitis B surface antigen. It is known that the carrier state is more common in men than women following acute infection, also that hepatoma and other chronic complications of hepatitis B infection are more common in men – but these data may be biased by the inclusion of male homosexuals who have a particularly high probability of becoming hepatitis B carriers after infection. It has also been reported that following neonatal hepatitis B infection reversion to e antibody-positive/e antigen-negative carrier status and ultimate elimination of HBsAg is more likely to occur in girls than boys [29].

The decline in proportion of 'good responders' to vaccine with age may also reflect decreased immunological competence with increasing years. Acute hepatitis B in the older patient is associated with slow clearing of surface antigen. Much has been published on immunological insufficiency in the elderly but it should be recognised that the decline in ability to respond to hepatitis B immunization with age was observed as a continuum throughout life. It would seem very prudent therefore to immunize people entering 'high risk' occupations as early in their career as possible, when they have the best chance of developing a good immune response.

Much has been written about the importance of correct administration of hepatitis B vaccine to the development of a satisfactory immune response. Although stated practices contrary to the manufacturer's instructions (gluteal or intradermal inoculation, broken primary courses) were exclusion criteria from the survey, practices adopted by the many general practitioners in the Wessex region might have varied more widely than those adopted in the Hospital Occupational Health Department. It was reassuring therefore to find that response rates achieved in the hospital and in the community were similar when the data were corrected for the disproportionate number of women (mainly nurses) immunized by occupational health staff.

During the period of this study, 63 'poor responders' to hepatitis B vaccine received a fourth dose and donated a serum specimen for antibody testing 6 months later. Six months was chosen to allow for 'slow responders' to the vaccine [26] to be detected and at the same time to enable assessment of brisk responders before their antibody levels underwent substantial decline.

It is perhaps not surprising that subjects who made a small but detectable antibody response to primary immunization were more likely to develop > 100 IU/l anti-HBs following a booster dose. Nevertheless, six individuals who initially produced undetectable levels of antibody developed a good response following a single booster dose. Overall, the proportion of good responders to 'booster' immunization with a single 20 μg dose was 1 in 2·4; a not unreasonable level, and similar to the 38% response to a single 20 μg booster recently reported from the Netherlands [28].

In conclusion, this survey of response to Hepatitis B vaccine in adults age 17–71 demonstrates the following points:

(i) Post-immunization antibody testing is most important regardless of age or sex.

(ii) The ability to mount a satisfactory response to hepatitis B immunization is adversely affected by increasing age and male sex (as independent variables).

(iii) Administration of hepatitis B vaccine by general practitioners or occupational health department staff produced similar response rates.

(iv) A single booster 20 μg dose of hepatitis B vaccine followed by antibody testing 6 months later led to satisfactory antibody levels in more than one in three previously poor responders. (Of previous 'non responders' 1 in 10 developed good post booster antibody levels.)

These points should be helpful to microbiologists, Occupational Health Departments, general practitioners and vaccinees themselves in the development of realistic expectations from hepatitis B immunization of groups at risk of exposure by virtue of their occupation.

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