

Understanding and enhancing compliance with the second dose of hepatitis B vaccine: a cohort analysis and a randomized controlled trial

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Abstract

Objective: To determine the predictors and extent of noncompliance with a second dose of hepatitis B vaccine and the effectiveness of a compliance enhancement strategy.

Design: Cohort analysis and randomized clinical trial.

Subjects: A total of 256 consecutive adults attending a sexually transmitted diseases clinic from October 1992 to July 1993 who were seronegative for hepatitis B virus and agreed to receive hepatitis B vaccination.

Setting: Hamilton, Ont.

Intervention: Subjects were followed up for 4 months. Those who did not return for the second dose of vaccine by 6 weeks after the first (2 weeks overdue) were randomly assigned to the enhanced intervention group (telephone and mail reminders) or the regular intervention group (mail reminder only). Subjects were considered noncompliant if they did not return for the second dose by 4 months after the first.

Results: The risk of not returning for the second dose of vaccine within 4 months after the first was strongly and linearly associated with level of education ($p = 0.004$). The noncompliance rate among those with less than a grade 10 education was 50%, grade 10–13 education 34%, some college education 15% and some university education 9%. In the randomized controlled trial the enhanced intervention group had twice the compliance rate of the regular intervention group (48% v. 25%; $p = 0.008$). Subjects with no postsecondary education were highly responsive to the enhanced intervention (relative risk 2.1; $p = 0.02$) compared with those with a higher level of education (relative risk 1.0; $p = 1.0$).

Conclusion: Hepatitis B vaccine recipients with lower educational levels are at increased risk of noncompliance with the second dose of vaccine but are highly responsive to telephone reminders.

Résumé

Objectif : Déterminer les prédicteurs et l'étendue de l'inobservance en ce qui concerne une deuxième dose de vaccin contre l'hépatite B, ainsi que l'efficacité d'une stratégie d'amélioration de l'observance.

Conception : Analyse de cohorte et étude clinique randomisée.

Sujets : Au total, 256 adultes consécutifs qui se sont présentés à une clinique sur les maladies transmissibles sexuellement, d'octobre 1992 à juillet 1993, qui n'étaient pas porteurs du virus de l'hépatite B et qui ont consenti à être vaccinés contre l'hépatite B.

Contexte : Hamilton (Ont.).

Intervention : Le suivi des sujets a duré jusqu'à 4 mois. Ceux qui n'étaient pas revenus recevoir la deuxième dose de vaccin 6 semaines après la première (2 semaines de retard) ont été répartis au hasard entre le groupe des sujets visés par



Evidence

Études

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des interventions plus poussées (rappels téléphonique et postal) ou celui des sujets visés par intervention ordinaire (rappel postal seulement). On a considéré que les sujets étaient en situation d'inobservance s'ils n'étaient pas revenus recevoir la deuxième dose 4 mois après la première.

Résultats : On a établi un lien solide et linéaire entre le niveau d'éducation ($p = 0,004$) et le risque que les intéressés ne reviennent pas recevoir la deuxième dose de vaccin dans les 4 mois suivant la première. Le taux d'inobservance s'est établi à 50 % chez ceux qui avaient moins d'une 10^e année, 34 % chez ceux qui avaient d'une 10^e à une 13^e année, 15 % chez ceux qui avaient fait des études collégiales et 9 % chez ceux qui avaient fait des études universitaires. Au cours de l'étude contrôlée randomisée, les sujets visés par une intervention plus poussée présentaient un taux d'observance 2 fois plus élevé que les sujets visés par une intervention ordinaire (48 % c. 25 %; $p = 0,008$). Les sujets qui n'avaient pas fait d'études postsecondaires ont très bien réagi aux interventions plus poussées (risque relatif 2,1; $p = 0,02$) comparativement à ceux qui avaient fait des études plus poussées (risque relatif 1,0; $p = 1,0$).

Conclusion : Les sujets qui reçoivent un vaccin contre l'hépatite B et ont fait des études moins poussées risquent davantage de ne pas se présenter pour recevoir la deuxième dose de vaccin, mais ils réagissent très bien aux rappels téléphoniques.

Hepatitis B is unique among sexually transmitted diseases (STDs) because vaccination is both available and effective.¹⁻³ Nevertheless, the rates of hepatitis B infection in Canada continue to rise among heterosexual men and women and among people in other risk groups such as men who have sex with men.⁴ About 30%–40% of cases of acute hepatitis B infection in the US occur in people with no identifiable risk factors other than possible exposure through sexual activity or household contacts.³

Even though hepatitis B vaccines are safe and efficacious, at least 3 doses are needed to induce protective levels of antibodies in 90% of adult recipients.¹⁻³ Some investigators have shown that although 95% of mothers bring their children for the first dose, this figure drops to about 30% for subsequent doses.² Studies of compliance with vaccine schedules at STD clinics in the US have shown that 43% of patients return for a subsequent dose after telephone and mail reminders.¹

Since October 1991 the Ontario Ministry of Health has provided hepatitis B vaccine free of charge to people at high risk of infection, including those attending STD clinics. Since little is known about the predictors of noncompliance with the vaccine schedule and the effectiveness of methods to enhance compliance, we studied compliance behaviour and conducted a randomized clinical trial of a method to enhance compliance with the second dose.

Methods

Sample selection

From October 1992 to July 1993, 385 consecutive, self-

referred people attending the STD clinic in Hamilton, Ont., were counselled regarding hepatitis B infection and offered hepatitis B vaccination free of charge. Demographic characteristics and risk data were recorded by the nurses on standard forms approved by the Institutional Review Board of the Hamilton Civic Hospitals; the forms incorporated a statement of the rationale for vaccination, contraindications and possible adverse reactions. If the subject consented to be vaccinated, the person and the nurse signed the form. All subjects were given a printed summary of facts concerning hepatitis B for later reference.

Serologic testing was carried out routinely for all subjects at the time of first vaccination. Of the 385 subjects, 256 (66.5%) who consented to receive vaccination and who were seronegative for hepatitis B surface antigen and antibody to hepatitis B surface antigen were included in this study.

Vaccine was administered intramuscularly in the deltoid area, and each recipient was given a wallet-sized record of vaccination and a return appointment card for the second dose, 1 month later.

Randomized trial of compliance enhancement

Subjects who did not return for the second dose of vaccine within 6 weeks after the first (2 weeks overdue) were entered into this portion of the study. They were stratified by sex and randomly assigned to 1 of 2 intervention groups: an "enhanced" or a "regular" method of encouragement to return for the second dose within 4 months after the first dose (the time frame recommended by the National Advisory Committee on Immunization⁵). Randomization was accomplished by using sequentially num-



bered envelopes containing the group assignment generated with the help of a random number table. The clinic receptionist opened the next envelope in sequence for each new eligible subject.

With the enhanced method, the clinic receptionist attempted to contact the subject by telephone at least 3 times, if necessary, over the course of 2 weeks. If this was unsuccessful, the person's name was given to the public health nurse, who then tried to contact the person by telephone at least 3 times over the next 2 weeks. Having the receptionist attempt to contact all subjects initially was considered cost-effective, since the hourly wage was considerably less than that of a nurse.

With the regular method, no attempt was made to contact the subject by telephone. If people in either group did not return for the second dose by about 3 months after the first dose, an appointment reminder letter was mailed to them. Those who did not return for the second dose by 4 months after the first dose were assessed as noncompliant, since they would have been unlikely to receive the vaccine free of charge elsewhere.

Statistical analysis

Data were analysed using the continuity-corrected χ^2 test, the 2-tailed Fisher's exact test or the Student's *t*-test, as required; the probability of a Type I (α) error was chosen to be 0.05. Stepwise multiple logistic regression analysis (BMDPLR computer program, 1988 version, BMDP Statistical Software Inc., Los Angeles) was used to determine the relative importance of variables found to be statistically significant by single variable analysis.

Table 1: Characteristics of subjects at an STD clinic randomly assigned to receive either a regular or an enhanced method of ensuring compliance with the second dose of hepatitis B vaccine*

Characteristic	Group; % (and no.) of subjects		<i>p</i> value
	Regular intervention <i>n</i> = 69	Enhanced intervention <i>n</i> = 67	
Male sex	71 (45/63)	76 (50/66)	0.69
Age > 25 yr	41 (28/68)	37 (25/67)	0.73
Postsecondary education	25 (16/63)	34 (22/65)	0.30
Previous chlamydial infection	15 (9/61)	17 (10/59)	0.94
Previous gonorrhoea	13 (8/61)	15 (9/61)	1.00
Previous genital herpes	5 (3/61)	8 (5/61)	0.71
Previous genital warts	10 (6/60)	15 (9/60)	0.58
Current bacterial vaginosis	5 (3/60)	2 (1/66)	0.35
Current chlamydial infection	25 (15/60)	20 (13/66)	0.62
Current gonorrhoea	3 (2/60)	8 (5/66)	0.52
Current genital herpes	3 (2/66)	2 (1/66)	0.93
Current genital warts	12 (7/60)	18 (12/66)	0.33
Intravenous drug use ever	5 (3/62)	3 (2/65)	0.68
> 1 sexual partner in past year	79 (50/63)	77 (49/64)	0.83

*Subjects were included in the randomized trial if they had not returned for the second dose within 6 weeks after the first dose. Regular intervention = mail reminder only, enhanced intervention = telephone and mail reminder (see Methods section).

Results

Sample description

The mean age of the 256 study subjects was 25.6 (standard deviation 8.1) years; 67.5% were men (8.0% of whom were homosexual or bisexual), 37.9% had a postsecondary education, and 16.8% were born outside of Canada. Having more than 1 sexual partner in the previous year was reported by 63.6%; the median number of sexual partners in the previous year was 2. Condom use during the last time of vaginal intercourse was reported by 27.4%, receptive anal intercourse by 10.9% and current injection drug use or a history of such use by 1.9%. *Chlamydia trachomatis* infection, proven by culture, and clinically diagnosed genital warts were present in 16.7% and 11.8% respectively at the time of the first visit. Within 6 weeks after the first dose of vaccine, 120 (46.9%) of the 256 subjects had returned for the second dose.

Effect of compliance enhancement method

The 136 subjects who did not return within 6 weeks after the first dose were randomly assigned to the 2 intervention groups. The groups were comparable with regard to key attributes that could affect the probability of compliance with the second dose (Table 1).

The groups did not differ significantly with regard to the hypothesized risk factors of sex, postsecondary educa-

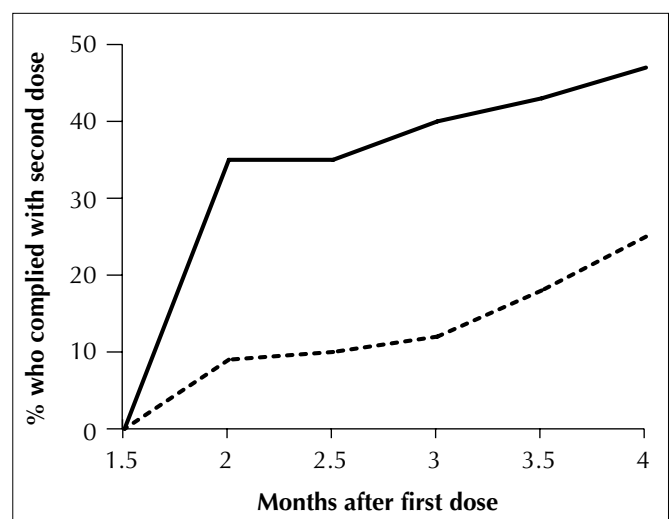


Fig. 1: Compliance with second dose of hepatitis B vaccine over 4 months among subjects at an STD clinic who did not return within 6 weeks after the first dose. Solid line represents those randomly assigned to receive enhanced intervention (telephone and mail reminders) to encourage compliance; broken line represents those randomly assigned to receive regular intervention (mail reminder only).

tion, number who had more than 1 sexual partner in the past year, use of a condom during the last time of vaginal intercourse (data not shown) and presence of genital warts at the time of the first visit.

Of the 67 subjects in the enhanced intervention group, 32 (48%) returned within 4 months for the second dose. This number was significantly higher ($p = 0.008$) than that in the regular intervention group, in which 17 (25%) of the 69 subjects returned within 4 months (Fig. 1). The profile of the randomized trial and the outcomes after 4 months are shown in Fig. 2.

In the enhanced intervention group 27 subjects were contacted by telephone and 17 (63%) of them returned for the second dose; the receptionist was able to reach 14 (82%) of the 17. Four clients in the enhanced intervention group and 6 in the regular intervention group returned after receiving the mailed reminder. Eleven clients in each group returned before receiving a telephone call or mailed reminder.

The overall compliance rate at 4 months for each intervention group was calculated by adding 60 (half of the subjects who returned within 6 weeks after the first dose) to the number who returned in each group. The estimated compliance rate was significantly higher ($p = 0.021$) in the enhanced than in the regular intervention group (72% [92/127] v. 60% [77/129]).

Predictors of noncompliance

In order to find any associations with risk factors for noncompliance, we compared compliers with noncompliers in a cohort comprising subjects who either returned for the second dose before initiation of the randomized trial or were assigned to the regular intervention group (Table 2). We found a linear association between noncompliant behaviour and lower education levels ($p = 0.004$), previous gonorrhoea ($p = 0.05$) and concurrent chlamydial infection ($p = 0.05$). Logistic regression analysis of these 3 variables showed that no postsecondary education ($p = 0.0001$) was the only independent predictor of noncompliant behaviour. The risk of noncompliance was 50% (6/12) among those with less than a grade 10 education, 34% (31/92) among those with a grade 10–13 education, 15% (5/33) among those with some college education and 9% (3/34) among those with some university education ($p = 0.004$, Mantel–Haenszel test for linear association).

Education level and response to intervention

Those without postsecondary education were not only the most likely to be noncompliant but were also more likely to respond to the enhanced intervention than to the

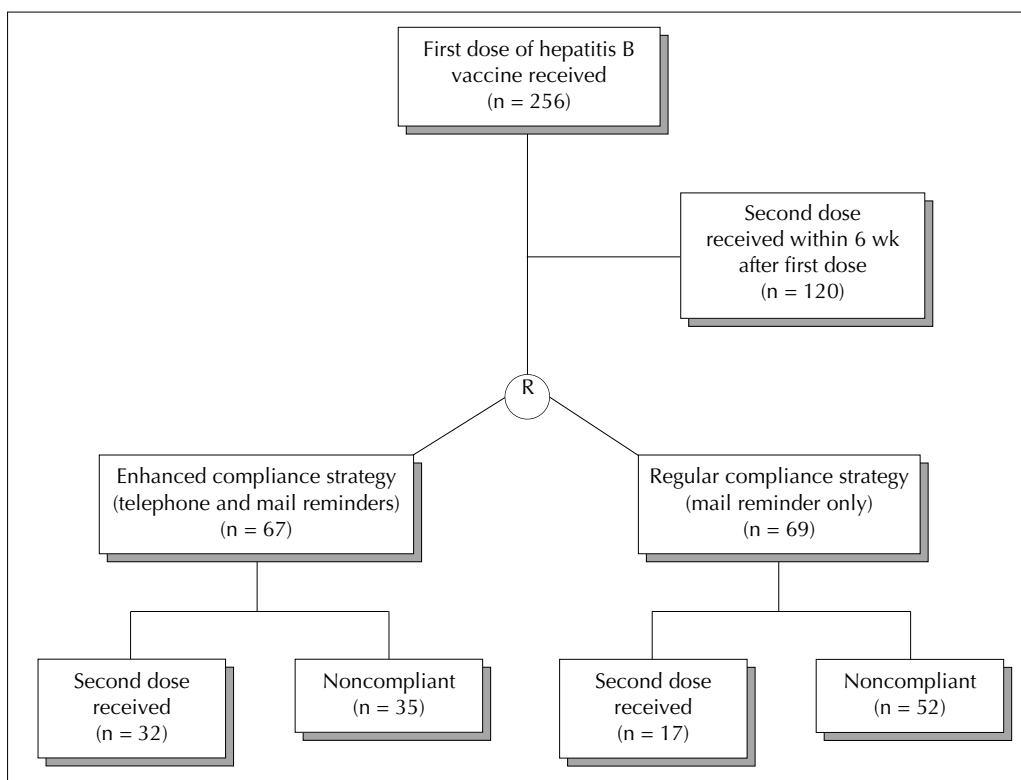


Fig. 2: Profile of randomized controlled trial of strategy to enhance compliance with second dose of hepatitis B vaccine and outcomes after 4 months. R = randomization.



regular intervention (compliance rate 44% and 22% respectively; relative risk [RR] 2.1; 95% confidence interval [CI] 1.1–4.1; $p = 0.02$). The corresponding figures among those with higher levels of education were 54% and 53% respectively (RR 1.0; 95% CI 0.5–2.1; $p = 1.0$).

Discussion

Many important and difficult problems, including our poor understanding of noncompliant behaviour, need to be solved before the World Health Organization's strategy for the global elimination of hepatitis B infection² can succeed. The results of our randomized controlled trial to explore the risk factors for noncompliance with the second dose of hepatitis B vaccine help to give some answers. We found that the risk was strongly associated with level of education, varying from 50% among those with less than a grade 10 education to 9% among those with some university education. However, White and Lines⁶ showed an inverse correlation between education and parents' compliance with neonatal hepatitis B vaccination in Australian maternity hospitals. In comparison with Australian-born parents, those from Southeast Asia had less knowledge of hepatitis B and less formal education but were more compliant with the vaccination (18.7% v. 81.3%, $p < 0.05$). A large proportion of compliers (68.1%) and noncompliers (70.6%) thought that vaccination could harm their babies, which suggests that, in this setting, ed-

ucation is needed about the safety of vaccination. People attending our STD clinic were informed about the safety of the vaccine by the clinic personnel before vaccination.

Among the subjects in our study who were entered into the randomized trial, the enhanced intervention (telephone and mailed reminders) was almost twice as effective as the regular method (mailed reminder alone) in encouraging them to return for the second dose (48% v. 25%). Several studies have examined methods of improving compliance in vaccination programs and have shown that an enhanced method significantly increases compliance rates. Among injection drug users, Mezzelani and associates⁷ reported that 85% of those who were seronegative for hepatitis B and were recruited into the vaccination program received all 3 doses. The method they used to enhance compliance was one-to-one, long-term counselling by staff at the centre before recruitment. Kollar and collaborators⁸ reported that a high success rate of a vaccination program in a primary care adolescent clinic was related to the commitment of health care providers in encouraging hepatitis B vaccination and discussing its importance during parent-adolescent counselling. In that study, 85% of the adolescents received all 3 doses. In our study, all of the subjects were counselled individually by a public health nurse before vaccination.

Although in our study the subjects with no postsecondary education were more likely to be noncompliant, it is encouraging that they were highly responsive to the en-

Table 2: Variables examined for association with noncompliance with second dose of hepatitis B vaccine

Variable	Second dose		Relative risk (and 95% CI*)	<i>p</i> value
	No. who returned	No. who did not return		
Male sex	83/128	33/45	0.9 (0.8–1.1)	0.3
Age ≤ 25 yr	80/133	28/50	1.0 (0.9–1.3)	0.61
Education level			–	0.004†
< Grade 10	6/126	6/45		
Grade 10–13	61/126	31/45		
Some college	28/126	5/45		
Some university	31/126	3/45		
Birth outside Canada	16/126	9/45	0.8 (0.6–1.1)	0.35
Previous chlamydial infection	17/127	6/43	1.0 (0.7–1.3)	0.93
Previous gonorrhoea	8/126	7/43	0.7 (0.4–1.0)	0.05
Previous genital herpes	3/128	3/43	0.7 (0.2–1.2)	0.17
Previous genital warts	16/127	3/42	1.1 (0.8–1.3)	0.41
Previous syphilis	1/128	1/43	0.7 (0.02–1.3)	0.44
Current chlamydial infection	7/127	11/42	0.5 (0.2–0.8)	0.05
Current gonorrhoea	3/126	1/42	1.0 (0.3–1.3)	0.22
Current genital herpes	2/126	2/42	0.7 (0.1–1.3)	0.26
Current genital warts	22/126	3/42	1.2 (0.9–1.4)	0.1
Current syphilis	0/126	0/42	–	–
Homosexual or bisexual male	7/128	2/45	1.1 (0.5–1.3)	0.5
Condom use (always or sometimes)	109/123	38/44	1.1 (0.8–1.6)	0.69
New sex partner in past year	93/128	35/45	0.9 (0.8–1.2)	0.5

*CI = confidence interval.

†Mantel-Haenszel test for linear association.



hanced strategy of telephone reminders, in most cases initiated by the receptionist. Considering that a third and final dose of hepatitis B vaccine is necessary at a later date, we acknowledge that factors associated with noncompliance and the effectiveness of a method to enhance compliance with the third dose may differ from those associated with the second dose.

Ten of the 19 national health objectives for the year 2000 that target vaccination in the US are related to the vaccination of adults who remain susceptible to diseases because they are inadequately immunized. Objectives include increasing hepatitis B vaccination rates in high-risk populations to at least 90%.⁹ The use of telephone and mailed reminders as well as knowledge about non-compliance predictors such as education level could help to reach this goal. Although we have shown that the strategy of telephone and mailed reminders was more effective than mailed reminders alone, especially among less educated clients, it remains to be determined whether this strategy is cost-effective.

Qualitative research to understand better why vaccine recipients do not return for subsequent doses in multi-dose regimens would be useful for developing more effective vaccination programs.

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References

1. Successful strategies in adult immunization. *MMWR* 1991;40:700-9.
2. Ghendon Y. WHO strategy for the global elimination of new cases of hepatitis B. *Vaccine* 1990;4:795-800.
3. Committee on Infectious Diseases. Universal hepatitis B immunization. *Pediatrics* 1992;4:795-800.
4. Delage G, Carter AO. Hepatitis B infection in Canada. Epidemiology and implications for control. *Can Fam Physician* 1992;38:2656-66.
5. National Advisory Committee on Immunization. *Canadian immunization guide*. 4th ed. Ottawa: Department of National Health and Welfare; 1993. Cat no H49-8/1993E.
6. White C, Lines D. Compliance with neonatal hepatitis B vaccination [letter]. *Med J Aust* 1995;162:613.
7. Mezzelani P, Venturini L, Turrina G, Lugoboni F, Des Jarlais DC. High compliance with hepatitis B virus vaccination program among intravenous drug users [letter]. *J Infect Dis* 1991;163:923.
8. Kollar LM, Rosenthal SL, Biro F. Hepatitis B vaccine series compliance in adolescents. *Pediatr Infect Dis J* 1994;13:1006-8.
9. Public Health Service. *Healthy people 2000: national health promotion and disease prevention objectives*. Washington: US Department of Health and Human Services, Public Health Service; 1991:121-3.

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