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Case report

Acute hepatitis B in a healthcare worker: A case report of genuine vaccination failure☆

Hein J. Boot[1,*], Laurens A. van der Waaij[2], Jurjen Schirm[3], Cees G.M. Kallenberg[4], Jim van Steenbergen[1], Bert Wolters[5]

[1]*Centre for Infectious Disease Control, National institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands*
[2]*Department of Gastroenterology, Martini Hospital, Groningen, The Netherlands*
[3]*Laboratory for Infectious Diseases, Groningen, The Netherlands*
[4]*Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, The Netherlands*
[5]*Municipal Health Service, Groningen, The Netherlands*

***Background*: Individuals who reach the antibody threshold level of 10 IU/l against the surface protein of the hepatitis B virus (HBV) after completion of a series of hepatitis B vaccination are considered to be long-term protected against a clinically manifest HBV infection.**

***Case report*: Here we describe an acute hepatitis B infection in a patient who received five hepatitis B vaccinations. Although his initial response to vaccination was moderate, he finally reached an excellent hepatitis B surface antibody level (anti-HBs) titres of more than 1000 IU/l in response to a booster vaccination with a recombinant DNA vaccine. Nevertheless, he developed full-blown acute hepatitis due to an HBV infection 14 years after this booster vaccination. A DNA analysis of the surface protein encoding region followed by phylogenetic analysis showed that our patient was infected with a normal HBV strain that is circulating among men who have sex with men. To our knowledge, this is the first report of a genuine hepatitis B vaccination failure in someone who acquired a high anti-HBs level in response to a recombinant DNA hepatitis B vaccine.**

***Conclusion*: Healthcare workers whose response to the initial hepatitis B vaccination is moderate might be vulnerable to hepatitis B virus infection.**

***Keywords*: Vaccination failure; Healthcare worker; Hepatitis B Virus; Hepatitis B surface antigen (HBsAg); HBV Genotype A; Waning immunity**

1. Introduction

After the identification of the hepatitis B virus (HBV) as the causative agent of serum hepatitis B, vaccines were rapidly developed. Both the plasma-derived and recombinant DNA hepatitis B (HB) vaccines are very effective at the population level [1,2]. For individuals, the internationally accepted guideline for long-term protection against HBV infection is a level of anti-HBs antibodies of at least 10 IU/l at 1–3 months post-vaccination [3–5]. However, a relatively large proportion of HB vaccine recipients – up to 10% of adult vaccinees – respond low (serum antibody level <10 IU/l) or not at all (<1 IU/l) [2]. Low and non-response depend on many factors such as age, genetic constitution, obesity, smoking, etc. [6–8].

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* Corresponding author.
E-mail address: Hein.Boot@RIVM.NL (H.J. Boot).

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Breakthrough infections – defined as seroconversion for antibodies to the HB core (HBc) antigen – have been reported both for children and adults with proven adequate HB vaccine responses. However, such breakthrough infections are considered clinically irrelevant, as they are without symptoms and do not result in chronic HBV infections [2].

Hepatitis B virus can establish sub-clinical chronic infection and is highly transmissible by blood–blood contacts in non-vaccinated individuals. These properties, in combination with vaccination failures, might lead to unnoticed transmission, especially in a healthcare setting [9]. In developed countries, low and non-responders are offered revaccination, which results in the seroconversion of most low responders [4], but about half of the non-responders do not develop HB surface (HBs) antibody levels even after repeated vaccinations [10]. Individuals who initially respond well to HB vaccination, but do not have detectable anti-HBs titres at the time of HBV exposure are considered to be protected due to an anamnestic immune response to exposure to HBV. Because HB vaccines have only been available since the early 1980s, data about long-term protection are limited. Here we report an acute HBV infection in a 50-year-old healthcare worker who received five HB-vaccinations in the last 22 years and, based on his post-vaccination anti-HBs titres, was considered to be adequately protected against a clinical HBV infection.

2. Case report

A 50-year-old homosexual Caucasian man, who was born and raised in the Netherlands and who had worked in a hospital setting for more than 25 years, developed classical symptoms of acute hepatitis. At the time when his general practitioner referred him to the hospital, he had nausea for 10 days accompanied by anorexia and mild upper-abdominal pain. He had developed jaundice with yellow-brown faeces and dark urine 5 days before referral. He had no pruritis. His daily alcohol consumption had been moderate in the preceding years. He had used omeprazole and atenolol for more than 5 years. At physical examination, he was jaundiced and had a tender liver, but it was not enlarged, and no signs of chronic liver disease or encephalopathy were present. At admission, aminotransferase activities were 3510 U/l for alanine aminotransferase (ALAT; normal <40), 2243 U/l for aspartate aminotransferase (ASAT; normal <40), and a total bilirubin level of 128 μmol/l (normal <18). Six weeks later, the liver transaminases were normal and the patient was asymptomatic. No signs of liver failure developed during the course of the disease.

At admission, serologic testing was positive for HB surface antigen (HBsAg), HB e antigen (HBeAg) and anti-HBc (both IgM and IgG), while other serologic tests were negative (Table 1). Acute infection with HBV was subsequently diagnosed.

Table 1
History of hepatitis B vaccination, hepatitis B vaccine response and hepatitis-B-virus-related disease.

Year	Date	Vaccine	Anti-HBs[1]	Relevant status[3]
1985	24-07-85	HBVax (plasma)		
1985	20-08-85	HBVax (plasma)		
1986	25-02-86	HBVax (plasma)		
1986	06-08-86		Positive (SRU = 10)	
1987	20-05-87		Negative (SRU = 0)	
1987	26-05-87	HBVax (plasma)		
1987	26-06-87		Positive (SRU = 11)	
1993	17-08-93	HBVax (rec. DNA)		
1993	19-10-93		Positive (>1000 IU/l)	
1994	07-03-94		Positive (>1000 IU/l)	Negative: HBsAg, anti-HBe and anti-HBc
2004[2]	04-10-04		Negative (0 IU/l)	Negative: HBsAg, anti-HBc, anti-HIV
2007	19-03-07			Onset of clinical symptoms
2007	29-03-07		Negative (0 IU/l)	Positive: HBsAg (>250 IU/ml), HBeAg, anti-HBc (total and IgM), and HBV DNA Negative: HAV (IgM), EBV (IgM and IgG) and CMV (IgM and IgG) ALAT = 3510 IU/l; Bilirubin = 205 μmol/l
2007	04-06-07		Negative (0.4 IU/l)	Positive: HBsAg (58 IU/ml), HBeAg and anti-HBc (total and IgM)
2007	26-10-07		Positive (10.2 IU/l)	Positive: anti-HBe & anti-HBc (total and IgM) Negative: HBsAg, HBeAg and HBV DNA
2007	09-11-07		Positive (12.3 IU/l)	Negative: anti-HIV

[1] Anti-HBs values are given as sample ratio units (SRU) or International Units per litre (IU/l).
[2] Result of retrospective analysis of stored serum.
[3] HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; Anti-HBe, antibodies against hepatitis B e antigen; Anti-HBc, antibodies against the hepatitis B core antigen; Anti-HIV, antibodies against human immunodeficiency virus; IgM, immunoglobulin M; IgG, immunoglubulin G; HAV, hepatitis A virus; EBV, Epstein-Barr virus; CMV, Cytolomegavirus; ALAT, alanine aminotransferase.

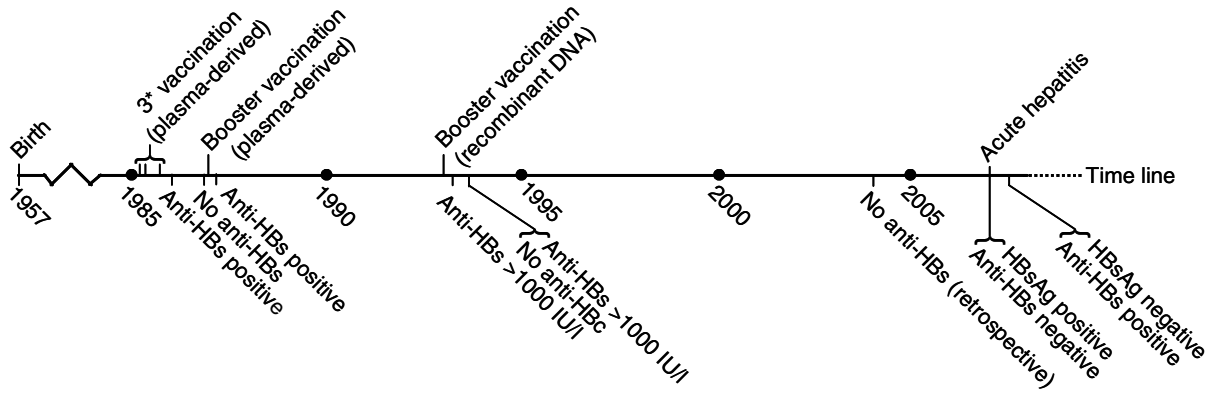

Fig. 1. History of hepatitis B vaccination and relevant serologic analysis prior to the onset of acute hepatitis B in 2007.

The patient received his initial HB-vaccinations (2 primary and 1 booster) with plasma-derived vaccine in 1985–1986 (see Fig. 1 for a chronologic overview and Table 1 for details). A moderate immunization response was recorded 5 months after the booster of the initial vaccination series. However, 10 months later serologic evaluation showed a complete lack of anti-HBs. A subsequent booster was given, again resulting in a moderate immunization response. Six years later, he received a single booster vaccination with a recombinant HB vaccine, resulting in a high level of anti-HBs (>1000 IU/l). Six months later he still had a very high level of anti-HBs (>1000 IU/l). Other HB serologic markers were determined in the 1994 serum sample, which show that he was not a chronically HB-infected patient (HBsAg and HBeAg were negative) and that he had not been infected with HBV before (anti-HBc and anti-HBe negative). Following the diagnosis of acute HBV infection in 2007, we analysed a stored serum sample from 2004. No anti-HBsAg or anti-HBc antibodies were present in this serum. To assess whether our patient was infected with an aberrant HBV strain, we determined the sequence of the surface protein encoding gene (S gene), as previously described [11]. It turned out that he was infected with a normal genotype A strain, which is the most prevalent acute HBV strain in the Netherlands (Fig. 2). Immunologic testing after the acute phase of the disease showed a normal number of lymphocytes ($2.34^{*}10^{9}$/l). However, the patient had a reverse CD4:CD8 ratio with decreased T-cell responsiveness against mitogens (data not shown), The patient did not use immunosuppressive drugs at the time of HB vaccination or HBV infection, was not infected with HIV, and had no apparent inherited immunodeficiencies.

3. Discussion

To our knowledge, this report of an acute HBV infection in a male nurse working in a hospital is the first report of genuine HB vaccination failure [12,13] Despite five hepatitis B vaccinations our patient developed full-blown acute HB within 15 years after receiving his last vaccine. There are three plausible explanations for his HB vaccination failure: (1) infection due to non-response to the HB vaccine, (2) infection due to a variant HBV despite adequate immunity, and (3) infection due to waning immunity:

1. Non-response or low response to HB vaccination is a well-known phenomenon [2]. Our patient had responded only marginally to his primary HB vaccination series with plasma-derived vaccines. However, after boosting with a recombinant DNA-based vaccine, he reached excellent anti-HBs titres (>1000 IU/l; 2 independent samples). Thus, non-response to HB vaccination can be excluded as a reason for vaccination failure.
2. HBV-immune-escape variants have been suggested as a reason for HB vaccination failure when they were first discovered [14]. Later, it turned out that these variants were mainly found in the context of passive immunity (HB immunoglobulin) such as liver transplant patients [15] and children born to HBV-infected mothers [16]. Sporadically antigenic variants are also found among chronically infected people [17] and blood donors [18]. Genetic analysis of the HBV isolate revealed that our patient was infected with a normal genotype A strain, which is the most prevalent strain among men who have sex with men (MSM) in the Netherlands [11] and elsewhere [19,20]. Our patient belongs to this HB-infection risk group; he reported that he had (unsafe) sex with at least five different male partners in the 6 months prior to the acute HBV infection. On the basis of the DNA analysis, we can exclude vaccination failure due to an HBV strain with an aberrant S protein.
3. Serum analysis after his last booster vaccination showed an excellent antibody response (>1000 IU/l anti-HBs). However, in a retrospective analysis of a 2004 serum sample, 11 years after his last HB vaccination, no anti-HBs was detectable. It is known that

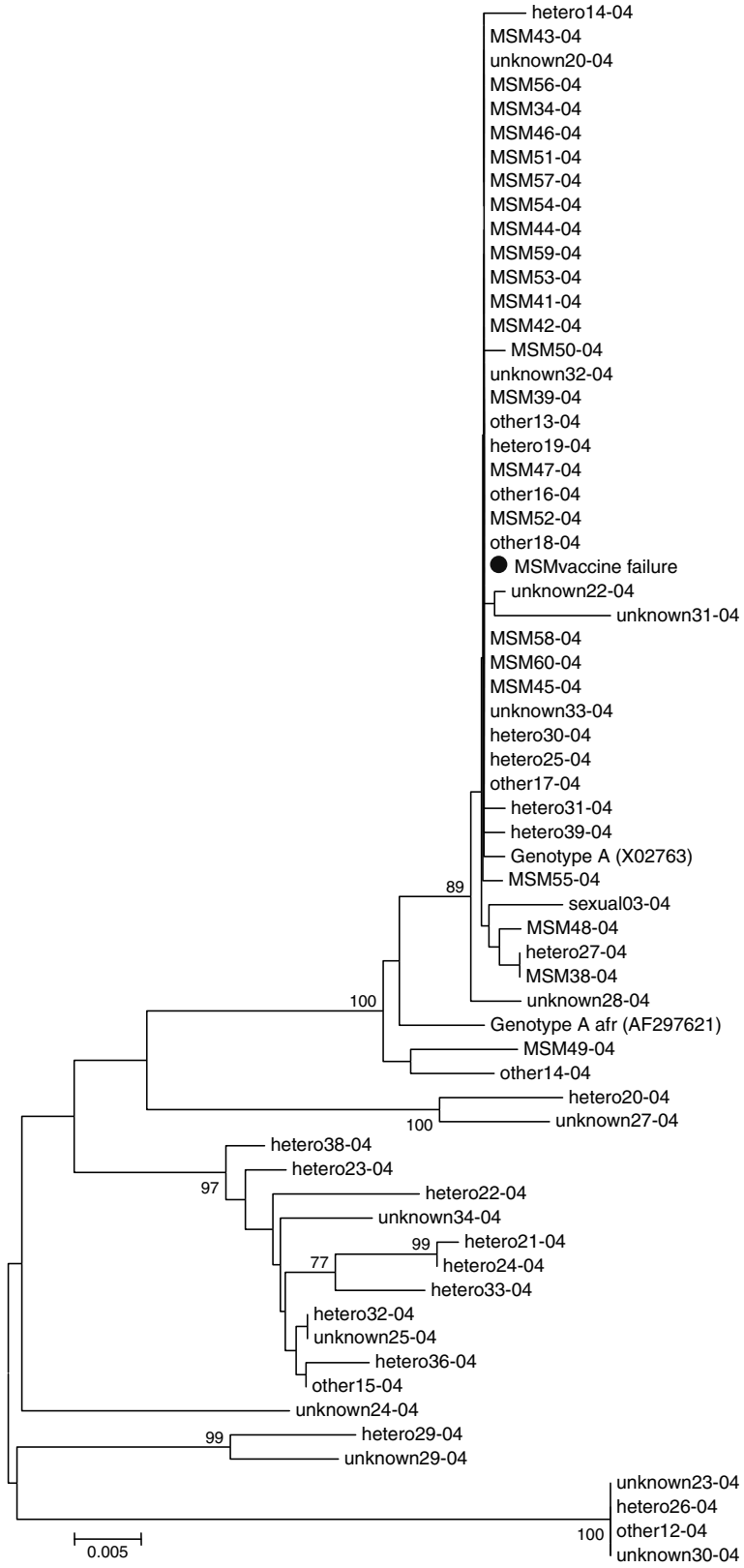

Fig. 2. Phylogenetic tree (neighbour-joining algorithm, 250 bootstraps) of acute hepatitis B virus (HBV) isolates from the Netherlands. All available sequences of acute HBV strains of the last 6 months of 2004 as well as the HBV isolate of our patient (MSM vaccine failure) were analysed. The most likely source of transmission is indicated for each strain (MSM = men who have sex with men; hetero = heterosexual contact; other = multiple routes, e.g. dentist, hairdresser, etc.; unknown = no transmission data available). Prototype genotype A strains are indicated by their genbank accession number.

vaccine-induced anti-HBs levels decline rapidly [21]. However, decline of anti-HBs to low or undetectable levels is not seen as a risk factor, as long as initial post-vaccination levels of anti-HBs are greater than 10 IU/l. Our patient clearly fulfilled this criterion. The anti-HBs titres of our patient not only declined rapidly after HB vaccination, but seem also to have declined rapidly after his HBV infection. Seven months after the onset of clinical symptoms, his anti-HBs titre was only 10.2 IU/l. Despite the rapid decline in vaccine-induced anti-HBs antibodies, our patient was able to mount an adequate immune response as he cleared his HBV infection in the normal time. The waning of vaccine induced immunity is apparently responsible for the inadequate protection against HBV exposure.

Sub-clinical, transient HBV infections (isolated anti-HBc positive only) in vaccinated children [22–25] and adults [26–28] have been described, and they are most frequently associated with no or little response to HB vaccination. Also, one clinically relevant HBV infection has been reported in a long-term follow-up study of a plasma-derived vaccine trial involving homosexual men [29]. Hepatitis B vaccination failure may be more common than previously thought, since other cases may not have been recognized or may not have been published due to incomplete data on vaccination of infected individuals. Furthermore, due to the relatively high frequency of primary vaccination failure among adults, acute HBV after HB vaccination cannot be classified as a genuine vaccine failure if the post-vaccination anti-HBs level is unknown.

On the basis of this case report, we conclude that the generally accepted correlation of long-term immunity after an adequate vaccine response does not hold true for every individual. Because HB vaccination started in the 1980s, it has been more than 10 years since many healthcare workers have received their last HB vaccination. If more cases of genuine HB vaccination failure surface, revaccination of healthcare workers with poor initial HB vaccination responses at long intervals (e.g. 10 years) might be considered to secure the prevention of HBV transmission in the healthcare setting.

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References

[1] Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev 2006;28:126–135.

[2] Mast E, Mahoney FJ, Kane M, Margolis H. Hepatitis B vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines. Philadelphia: W.B. Saunders Company; 2004. p. 299–337.

[3] European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? Lancet 2000;355:561–565.

[4] Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep 2006;55:1–33.

[5] WHO. Hepatitis B vaccines. Wkly Epidemiol Rec 2004;79:255–263.

[6] Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. Clin Infect Dis 2002;35:1368–1375.

[7] De Silvestri A, Pasi A, Martinetti M, Belloni C, Tinelli C, Rondini G, et al. Family study of non-responsiveness to hepatitis B vaccine confirms the importance of HLA class III C4A locus. Genes Immun 2001;2:367–372.

[8] Zuckerman JN. Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. J Med Virol 2006;78:169–177.

[9] Spijkerman IJ, van Doorn LJ, Janssen MH, Wijkmans CJ, Bilkert-Mooiman MA, Coutinho RA, et al. Transmission of hepatitis B virus from a surgeon to his patients during high-risk and low-risk surgical procedures during 4 years. Infect Control Hosp Epidemiol 2002;23:306–312.

[10] Craven DE, Awdeh ZL, Kunches LM, Yunis EJ, Dienstag JL, Werner BG, et al. Nonresponsiveness to hepatitis B vaccine in health care workers. Results of revaccination and genetic typings. Ann Intern Med 1986;105:356–360.

[11] van Houdt R, Bruisten SM, Koedijk FD, Dukers NH, Op de Coul EL, Mostert MC, et al. Molecular epidemiology of acute hepatitis B in the Netherlands in 2004: nationwide survey. J Med Virol 2007;79:895–901.

[12] Banatvala JE, Van Damme P. Hepatitis B vaccine – do we need boosters? J Viral Hepat 2003;10:1–6.

[13] Boddicker JD, Rota PA, Kreman T, Wangeman A, Lowe L, Hummel KB, et al. Real-time reverse transcription-PCR assay for detection of mumps virus RNA in clinical specimens. J Clin Microbiol 2007;45:2902–2908.

[14] Carman WF, Zanetti AR, Karayiannis P, Waters J, Manzillo G, Tanzi E, et al. Vaccine-induced escape mutant of hepatitis B virus. Lancet 1990;336:325–329.

[15] Protzer-Knolle U, Naumann U, Bartenschlager R, Berg T, Hopf U, Meyer zum Buschenfelde KH, et al. Hepatitis B virus with antigenically altered hepatitis B surface antigen is selected by high-dose hepatitis B immune globulin after liver transplantation. Hepatology 1998;27:254–263.

[16] Tabor E. Infections by hepatitis B surface antigen gene mutants in Europe and North America. J Med Virol 2006;78 (Suppl.1):S43–S47.

[17] Yamamoto K, Horikita M, Tsuda F, Itoh K, Akahane Y, Yotsumoto S, et al. Naturally occurring escape mutants of hepatitis B virus with various mutations in the S gene in carriers seropositive for antibody to hepatitis B surface antigen. J Virol 1994;68:2671–2676.

[18] Levicnik-Stezinar S. Hepatitis B surface antigen escape mutant in a first time blood donor potentially missed by a routine screening assay. Clin Lab 2004;50:49–51.

[19] Perez-Olmeda M, Nunez M, Garcia-Samaniego J, Rios P, Gonzalez-Lahoz J, Soriano V. Distribution of hepatitis B virus genotypes in HIV-infected patients with chronic hepatitis B: therapeutic implications. AIDS Res Hum Retroviruses 2003;19:657–659.

[20] Koibuchi T, Hitani A, Nakamura T, Nojiri N, Nakajima K, Jyuji T, et al. Predominance of genotype A HBV in an HBV-HIV-1 dually positive population compared with an HIV-1-negative counterpart in Japan. J Med Virol 2001;64:435–440.
[21] Jilg W, Schmidt M, Deinhardt F, Zachoval R. Hepatitis B vaccination: how long does protection last? Lancet 1984;2:458.
[22] Young BW, Lee SS, Lim WL, Yeoh EK. The long-term efficacy of plasma-derived hepatitis B vaccine in babies born to carrier mothers. J Viral Hepat 2003;10:23–30.
[23] Wainwright RB, Bulkow LR, Parkinson AJ, Zanis C, McMahon BJ. Protection provided by hepatitis B vaccine in a Yupik Eskimo population–results of a 10-year study. J Infect Dis 1997;175:674–677.
[24] Lin YC, Chang MH, Ni YH, Hsu HY, Chen DS. Long-term immunogenicity and efficacy of universal hepatitis B virus vaccination in Taiwan. J Infect Dis 2003;187:134–138.
[25] Lee PI, Lee CY, Huang LM, Chang MH. Long-term efficacy of recombinant hepatitis B vaccine and risk of natural infection in infants born to mothers with hepatitis B e antigen. J Pediatr 1995;126:716–721.
[26] Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980;303: 833–841.
[27] Ayerbe MC, Perez-Rivilla A. Assessment of long-term efficacy of hepatitis B vaccine. Eur J Epidemiol 2001;17:150–156.
[28] McMahon BJ, Bruden DL, Petersen KM, Bulkow LR, Parkinson AJ, Nainan O, et al. Antibody levels and protection after hepatitis B vaccination: results of a 15-year follow-up. Ann Intern Med 2005;142:333–341.
[29] Hadler SC, Francis DP, Maynard JE, Thompson SE, Judson FN, Echenberg DF, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986;315:209–214.