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Review

Hepatitis B vaccine immunization strategies and antibody level protection: A review

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ABSTRACT

Hepatitis B is caused by the hepatitis B virus (HBV), which infects the liver and may lead to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B virus infection is highly prevalent around the globe and is a major public health problem in the world. Elimination of HBV transmission is an achievable public health goal, particularly in light of the proven effectiveness and safety of hepatitis B vaccine. In 1991, the World Health Organization (WHO) endorsed that all the countries should integrate HBV vaccination in their national immunization programs. Therefore, it appears fundamental to summarize already available information to improve the understanding of hepatitis B vaccine immunization strategy and level of protection. For this purpose, we aim to conduct an electronic search of MEDLINE *via* PubMed/ Medline, Google Scholar and Science Direct.

KEYWORDS: hepatitis B, vaccine, seroprotection, immunization.

INTRODUCTION

Hepatitis B is caused by the hepatitis B virus (HBV), which infects the liver and may lead to chronic liver disease, including cirrhosis and hepatocellular carcinoma [1]. HBV represents a worldwide public health problem, causing major morbidity and mortality. Most of the serious consequences of HBV infection (i.e. liver cancer and cirrhosis) occur among persons who are chronically infected and serve as the main reservoir for the transmission of new infections [2, 3]. The main objective of hepatitis B immunization strategy is to prevent chronic HBV infections [4]. Therefore, it appears necessary to summarize already available information for better comprehension of the HBV vaccine immune mechanism response, immunization strategy and duration of protection. For this purpose, we aim to conduct a systematic review to thoroughly summarize the available information towards answering the key questions.

1. Search strategy

An electronic search of MEDLINE was performed via PubMed/Medline, Google Scholar and Science Direct using combinations of search terms (*Hepatitis B vaccine*, *Immunization strategy*, *antibody response*, *immunogenicity*). A manual review of personal files and reference lists from published studies was conducted concurrently. Search was limited to study conducted in humans, and published either in English or in French.

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2. Hepatitis B virus worldwide global distribution and outcome

According to the World Health Organization, more than 240 million people are infected with the hepatitis B virus (HBV) worldwide, and the majority is living in the developing Countries [5]. Approximately 30% of the world's population, i.e. about 2 billion people, have serological evidence of infection with HBV [6]. Approximately 45% of the world population (Figure 1) live in areas where chronic HBV infection is highly endemic (> 8% of the population are HBsAg-positive), 43% live in areas of intermediate endemicity (2-7% HBsAg-positive) and 12% live in areas of low endemicity (<2% HBsAg-positive) [4]. In Africa, the virus is highly endemic and prevalence is highest in the World Health Organization African region [7, 8]. HBV is spread by contact with the blood or bodily fluids (vaginal secretions, semen, saliva, etc.) of an infected person, as well as from mother to child during childbirth. For many people, hepatitis B is a short-term illness as clinical signs and symptoms of acute hepatitis B usually resolve within 1 to 3 months. Fulminant liver failure occurs in approximately 0.5% to 1.0% of adults with reported acute hepatitis B. In a subset of persons, the HBV can also cause a chronic liver infection that can later develop into cirrhosis or hepatocellular carcinoma (HCC) [9)]. The probability that an infection with this virus will become chronic depends upon the age at which infection occurs (90% transition to chronicity in infants versus 10% in adults) [10]. The age at which a person becomes infected with HBV is the main factor determining the outcome (Figure 2). Among children under 5 years of age who become infected, fewer than 10% are symptomatic, whereas 80-90% of infants infected during the first year of life and 30-50% of children infected between 1 and 4 years of age develop the chronic condition. However, 30-50% of adults are symptomatic when first infected but only 2-5% become chronically infected [11].

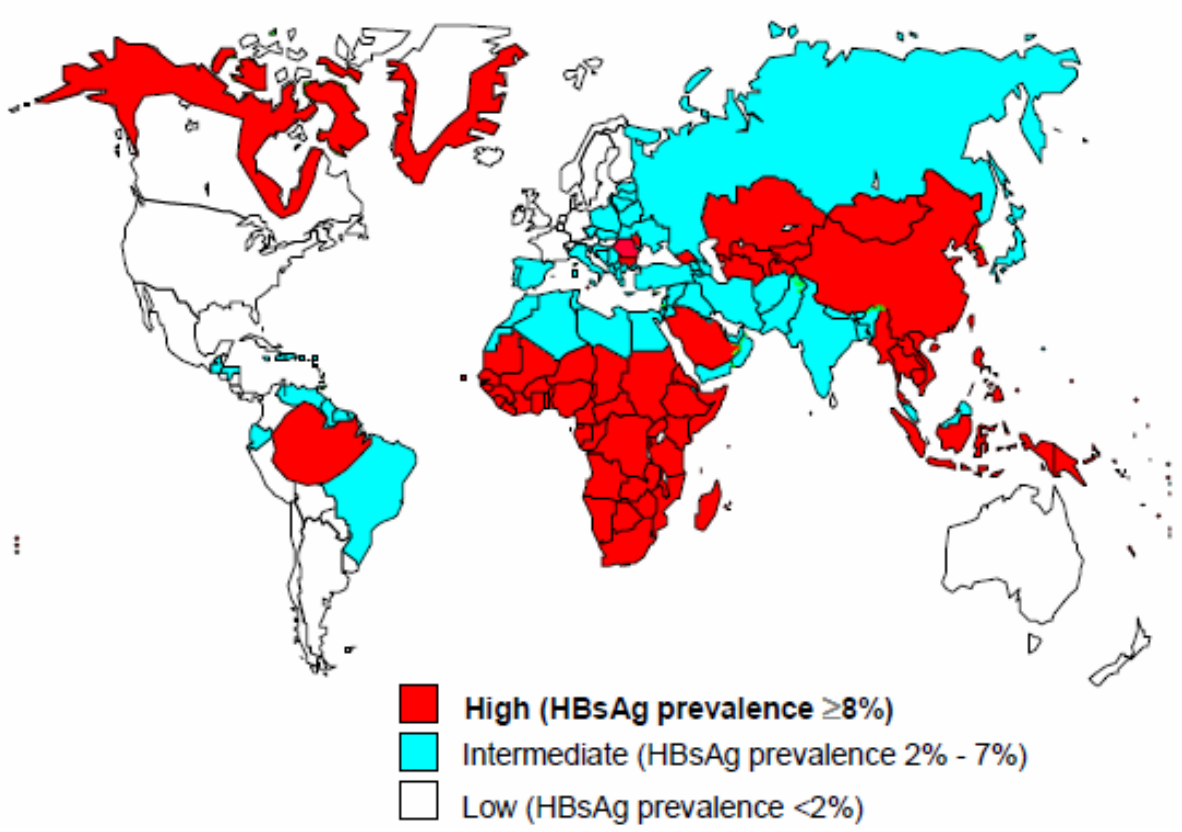

Figure 1. Geographical distribution of HBV endemicity, adapted from [4].

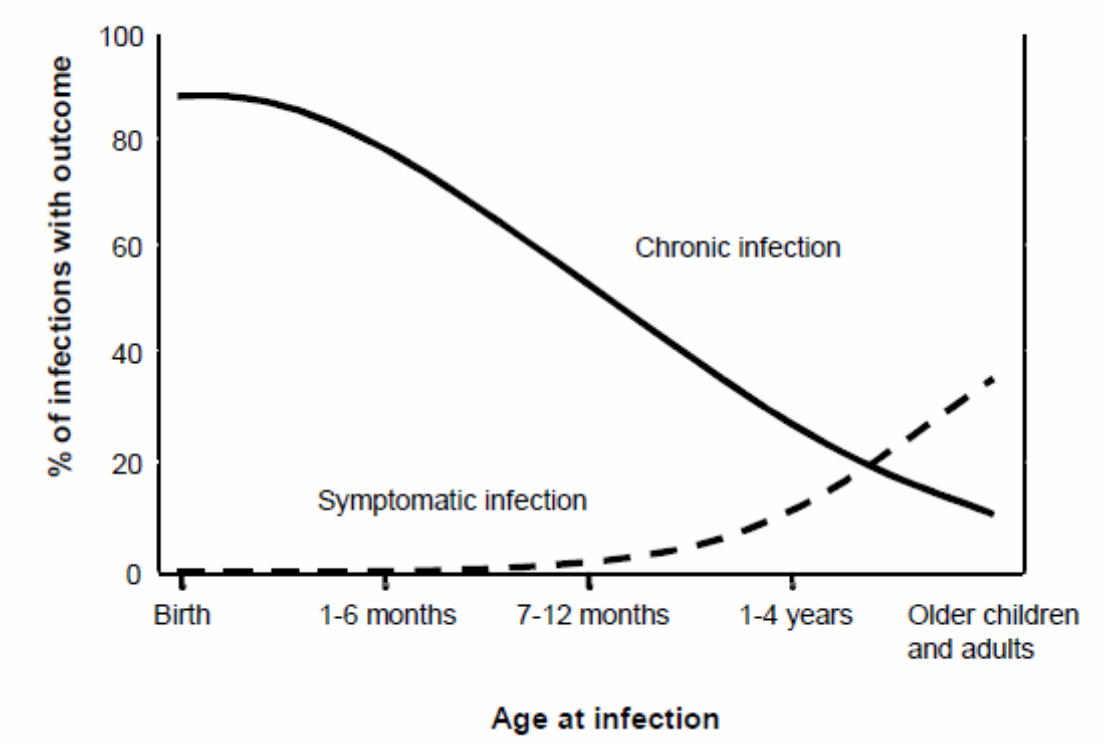

Figure 2. Outcome of hepatitis B virus infection by age at infection, adapted from [4].

3. History of the HBV vaccine and recommandation

The first HBV vaccine (a heat-treated form of HBV) was developed by Blumberg and Millman in 1969. The United States Food and Drug Administration approved a plasma derived HBV vaccine produced by Merck Pharmaceuticals in 1981 that involved inactivation of viral particles in the blood which had been collected from HBsAg-positive donors. In 1986, the subsequent generation of genetically engineered (or DNA recombinant) a highly purified HBV vaccine was synthetically prepared without containing any of the blood products. In the present time, all recombinant vaccines which contain HBsAg are expressed in yeast *Saccharomyces cerevisiae, Hansenula polymorpha*, *Pichia pastoris* or mammalian (Chinese hamster ovary) cells [12, 13]. WHO recommends that hepatitis B vaccine be included in routine immunization schedules for all children in all countries [14]. In 1991, the World Health Organization (WHO) endorsed that all the countries should integrate HBV vaccination in their national immunization programs [6]. In 2016, the WHO adopted a strategy to globally eliminate HBV infection as a public health threat by 2030, with a goal of reducing its incidence by 90% and its mortality by 65% [15]. It was then recognized that the only practical means to interrupt transmission of HBV was to vaccinate all individuals before their exposure, and this would best be accomplished in infancy. Also, there is a particular need to protect infants because of their predilection to develop chronic HBV infection.

4. Hepatitis B Virus and the HBsAg *a* determinant

HBV is an oncogenic DNA virus that belongs to the Hepadnaviridae family. Briefly, HBV virus, initially called the Dane particle, is a 42-nm virus. HBV is composed of a nucleocapsid core, surrounded by an outer lipoprotein coat (also called envelope). The virus contains 3 primary structural antigens: surface (HBsAg), core (HBcAg), and e (HBeAg) (Figure 3) [16]. HBsAg is produced in excess amounts and found in the blood of infected individuals in the form of spherical and tubular particles (approximately 22 nm). These immunogenic, but noninfectious, subviral particles lack genomic DNA and paved the way to develop hepatitis B

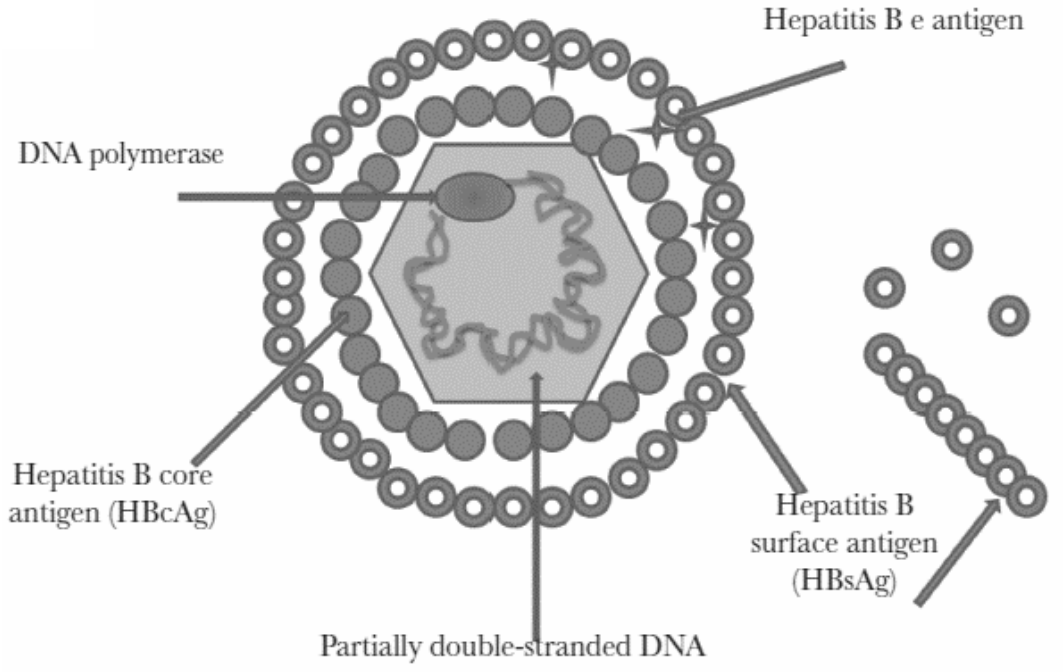

Figure 3. A simplified figure of the HBV particle and surface antigens, adapted from [1].

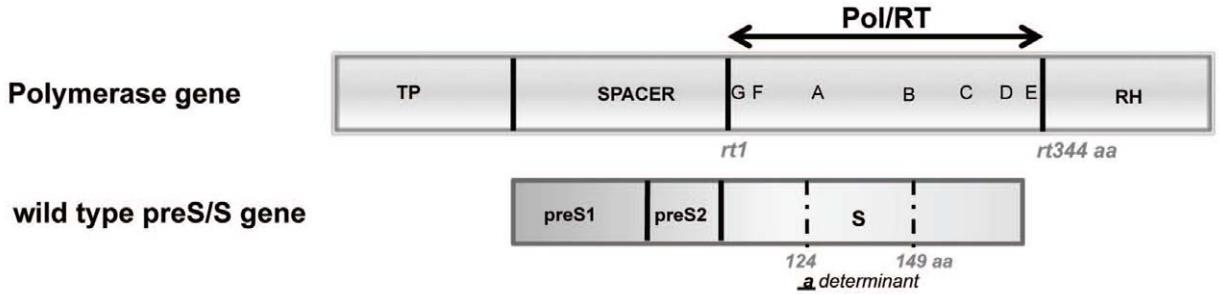

Figure 4. Schematic representation of the overlap between the HBV polymerase and envelope open reading frames. The numbers indicate amino acid (aa) sites. Numbering is according to genotype D. The *a* determinant of HBsAg that is located between aa 124 and 149, and which includes the major antibody neutralization domain of HBV, is indicated, adapted from [21].

vaccines [17, 18, 19]. The super compact HBV genome contains four overlapping genes (Figure 4). The preS/S gene has 3 ORFs that encode 3 forms of HBsAg: the large (pre-S1), medium (pre-S2) and small (S) structural proteins of the viral envelope. The C gene has two ORFs (C and pre-C) encoding the HBcAg (hepatitis B core antigen) and the e protein, which is processed to produce soluble HBeAg hepatitis e antigen. The X gene encodes a small protein with transactivator activity, while Pol (polymerase) gene encodes a large polymerase protein [20]. All HBV genotypes and serotypes share the common determinant a which spans aa 124–149 within the major hydrophilic region (MHR) and is in a form of two major and one minor loops with cysteine-disulphide bonds, protruding from the outersurface of the virus; the second hydrophilic loop (aa 139 to 147 or 149) is the major target for neutralizing anti-HBs produced following natural infection or vaccination. Neutralizing (protective) antibodies induced by vaccination are targeted largely towards the conformational epitope of the *a* determinant. This provides protection against all HBV genotypes

and subtypes and is responsible for the broad immunity afforded by HBV vaccination. Thus, alterations of residues within this region of the surface antigen can determine conformational changes that can allow replication of mutated viruses in vaccinated people (vaccine escape mutants or VEMs). In addition, such mutated viruses can be undetectable by the current diagnostic, posing a potential threat to the safety of blood supply [17, 18].

5. HBV immune response mechanism

The injected HBV vaccine containing HBsAg proteins are engulfed and processed by the antigen-presenting cells. The antigen-presenting cells process the antigen and attach the same to the surface of the antigen-presenting cells. The antigen-presenting cells present the antigen to the T helper cells, leading to clonal expansion of the T cells as well as production of memory T cells. The antigen can be recognized directly by B cells, producing a weak immune response, with binding of the antigen to the Fab region on the B cell receptor and secondary signaling from cytokines released by T-helper cells; B cells begin somatic hypermutation at the Fab region, which further increases the corresponding fit between the Fab region and the antigen. The B cells mature to plasma cells to produce neutralizing antibodies. They also undergo clonal expansion and memory cell formation for future defense (Figure 5). The protective efficacy of hepatitis B vaccination is related to the induction of anti-HBs antibodies, but it also involves the induction of memory B and T cells [22].

6. Vaccine type and seroprotection efficacy

The hepatitis B vaccine is a medication used in the prevention of hepatitis B infection. The vaccine is a non-infectious subunit of the virus, which leads to an active immunity [21]. A safe and effective vaccine against hepatitis B has been available since 1982. Two types of hepatitis B vaccine are available. Recombinant or genetically engineered vaccines are made using HBsAg synthesized in yeast or mammalian cells into which the HBsAg gene has been inserted. Plasma-derived vaccines are prepared from purified HBsAg from the plasma of persons with chronic HBV infection. The two types are similar with respect to safety, immunogenicity and efficacy [23]. Therefore, the recombinant HBsAg particles differ from natural viral particles in lacking the preS domain of HBsAg and lacking glycosylation due to their production in yeast. Mammalian cell-derived vaccines contain glycosylated pre-S1 and pre-S2 proteins, in addition to the major HBsAg protein. By covering not only the HBsAg S epitope, these vaccines, as well as some new vaccine adjuvants formulations that have been and are being developed, have been shown to be more immunogenic compared to the second-generation vaccines. These vaccines are showing improved immune response in immunocompromised populations and older adults and, in addition, these new vaccines can offer the possibility of simplified schedules, which might be very promising for the future [24].

7. Immunization strategies

Hepatitis B immunization strategies include, routine infant vaccination, prevention of perinatal HBV transmission, catch-up vaccination of older age groups and monitoring progress and assessing the impact of immunization. The routine vaccination of all infants as an integral part of national immunization schedules should be given high priority. Generally, the recommended number of doses of hepatitis B vaccine required to induce protective immunity varies by product and with the age of the recipient. Historically, the standard 3-dose hepatitis B vaccine series has consisted of 2 priming doses administered 1 month apart and a third dose administered 6 months after the first dose. Today, the WHO recommends multiple options for adding hepatitis B vaccine to existing infant immunization schedules. Several options are considered to be appropriate for infants:1 (monovalent) birth dose followed by either 2 doses of monovalent or hepatitis B-containing combination vaccine at 1 and 6 months of age; or at 2, 4, and 6 months of age; or at 3, 5, and 11 months of age; or at 8, 12, 16 weeks and 12 or 15 months; or at 6, 10, and 14 weeks of age, according to the WHO's Expanded Programme on Immunization schedule. Currently, a variety of hepatitis B vaccine schedules have been used successfully worldwide. In general, preference is given to effective options that require minimal additional visits for immunization, to increase

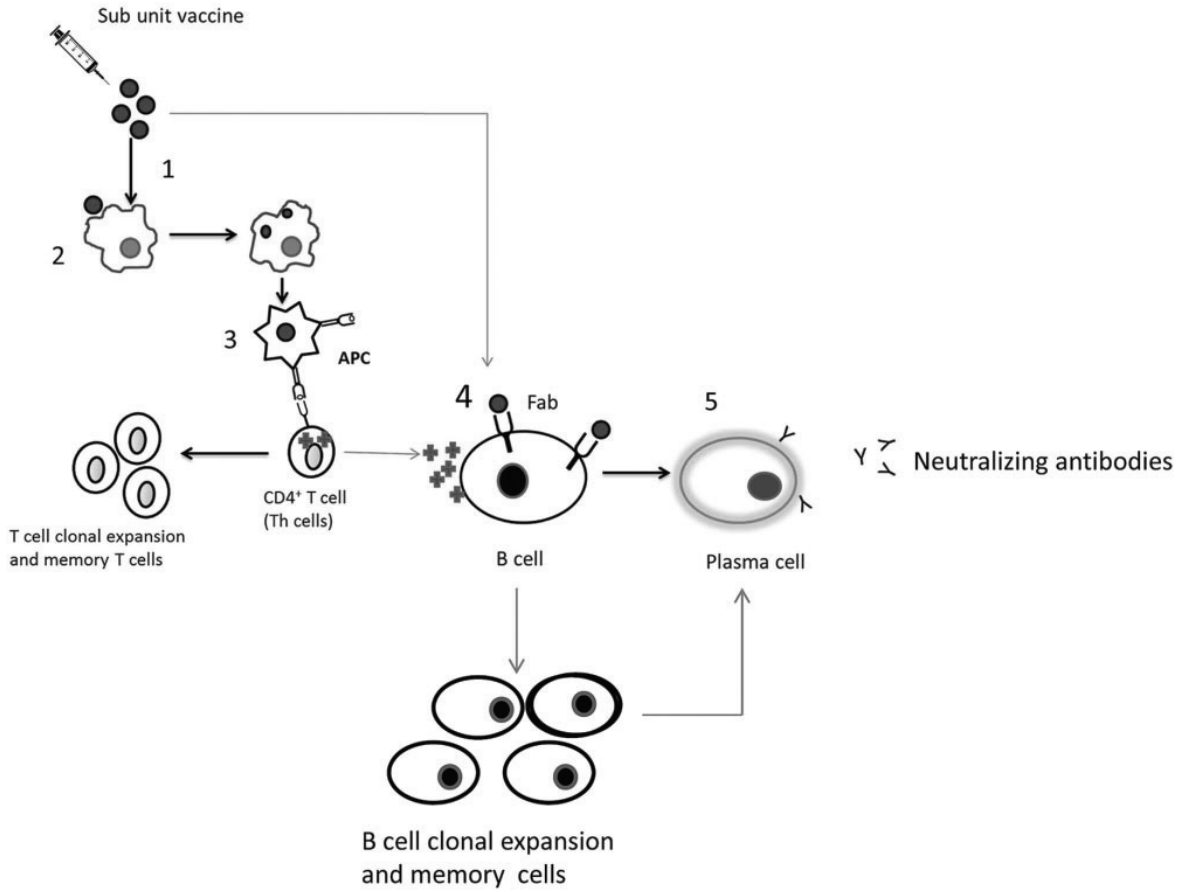

Figure 5. Schematic representation of the mechanism of action of HBV vaccine, adapted from [22].

compliance and to reduce the logistics burden. A course of three doses of hepatitis B vaccine induces protective levels of antibody to HBsAg (anti-HBs) in over 95% of healthy infants and children when given in a variety of schedules [25-29]. In countries of intermediate and high endemicity of HBV infection, routine infant hepatitis B vaccination is a high priority because the majority of chronic infections are acquired during early childhood. The routine vaccination of infants is also a high priority in countries of low endemicity because this is the only strategy that can prevent HBV infections acquired in all age groups (children, adolescents and adults). In these countries the majority of chronic infections are acquired among adolescents and adults but early childhood infections are important in maintaining the burden of chronic infection. Furthermore, many children who are infected have mothers who are not infected with HBV. These infections would not be prevented by identifying infants born to HBsAg-positive women and giving them a birth dose of hepatitis B vaccine that screen pregnant women for HBsAg [30-33]. Routine childhood immunization is also required in order to achieve optimal prevention of HBV infections acquired by adolescents and adults, because strategies targeting adolescent and adult risk groups have failed to control hepatitis B adequately. These immunization strategies for high-risk groups have not been very successful because of the difficulty of immunizing persons in many risk groups before they initiate high-risk behaviours and because of infections occurring among persons with no identified risk factor. To prevent mother-to-child transmission (MTCT), the WHO recommends that all neonates, regardless of maternal HBV infection, receive their first dose of the hepatitis B vaccine as soon as possible after birth, preferably within 24 h, as a monovalent formulation. This hepatitis B birth dose vaccine

(HepB-BD) should be followed by at least two additional doses that can be given as a monovalent or as part of a combined vaccine. An alternative strategy is to screen all pregnant women for HBsAg and to provide immunization at birth to infants of HBV-infected mothers [34]. Post-exposure immunization, beginning at birth with either hepatitis B vaccine alone or with hepatitis B vaccine and hepatitis B immune globulin (HBIG), can prevent the spread of more than 90% of HBV infections from mother to baby. The efficacy of giving recombinant hepatitis B vaccines alone is similar to that of giving hepatitis B vaccine with HBIG. Thus the use of HBIG is not necessary, particularly in countries where pregnant women are not screened for HBsAg [35]. When hepatitis B vaccine is incorporated into routine childhood vaccination schedules the need for catch-up vaccination in age groups older than one year should be assessed. In particular it should be noted that health care workers exposed to blood are likely to be at high risk of becoming infected with HBV. The need for catch-up vaccination of older persons in other groups varies, depending on the endemicity of HBV infection in particular countries. The establishment of surveillance for acute hepatitis B and the performance of seroprevalence studies on HBV infection can assist in determining the groups at highest risk of acquiring HBV infection, e.g. clients and staff of institutions for the developmentally disabled, injecting drug users, men who have sex with men, and persons with multiple sex partners. Vaccination and other prevention efforts may be targeted at these groups. The relevant question is do subjects with anti-HBs levels below 10 IU/L, who are exposed to biological risk, need a booster dose. These subjects should not be considered as nonresponders. According to the definition from the Centers for Disease and Control and Prevention, a nonresponder is “a person who does not develop protective surface antibodies after completing two full series of the HBV vaccine and for whom an acute or chronic HBV infection has been ruled out” [36]. For many years, booster immunizations were advocated for individuals having increased risk of HBV infection (mostly occupational), when the anti-HBs titer reaches the minimal protective titer 10 IU/L (in most countries) or 100 IU/L (in the UK) [37].

8. Seroprotection level and duration

Protection against infection is associated with presence of antibody, which is directly related to the peak concentration of anti-HBs after primary vaccination. Neutralizing (protective) antibodies (anti-HBs) induced by vaccination are targeted largely towards the amino acid hydrophilic region, referred to as the common *a* determinant which is present on the outer protein coat or surface antigen (HBsAg), spanning amino acids 124–149. This provides protection against all HBV genotypes (from A to H) and is responsible for the broad immunity afforded by hepatitis B vaccination [21]. IgG antibodies to HBsAg after completion of vaccination are used as a marker of immunity to HBV. An anti-HB antibody concentration of 10 mIU/mL or more measured 1-3 months after the administration of the last dose of the primary vaccination series is considered a reliable marker of protection against HBV infection [23]. However, 5 to 10% of subjects are non-responders (no antibody response after vaccination or less than 10 mIU/mL) or small responders (moderate response that rapidly disappears) according to WHO. In addition to this provision, a special recommendation of antibody titer is made for groups at risk with regard to their socio-professional activities. These include health workers, newborns of HBSAg-positive mothers, parenteral drug users, sex workers, etc. The recommendation proposes that these individuals have an anti-HBs antibodies titer of at least 100 mIU/mL to be considered protected [38]. The duration of protection after hepatitis B vaccination is not exactly known yet. A primary 3-dose series induces protective antibody concentrations in >95% of healthy infants, children and young adults [34]. Among children who respond to a primary 3-dose vaccination series with anti-HBs concentrations of 10 mIU/mL or greater, 15% to 50% have low or undetectable concentrations of anti-HBs 5 to 15 years after vaccination. Among adult vaccines, anti-HB concentrations decline to <10 mIU/mL in 7%–50% within 5 years after vaccination and in 30%-60% within 9-11 years [16]. However, protection has been shown to outlast the presence of vaccine-induced antibodies, conferring effective long-term protection against acute disease and development of HBsAg carriage for up to 20 to 30 years now. Initial anti-HB level and

age at vaccination seemed to play an important role in the persistence of antibodies [39]. Between 8-42% of the people with protective antibody following vaccination lost it within 5 years. However, the time taken for the disappearance of antibody shows wide variation. Although the possibility of developing HBsAg among subjects who respond to an HBV vaccine is almost nil, risks may persist for developing anti-core HBV antigen (anti-HBcAg) conversion with the decline of anti-HBsAg titer. However, it was demonstrated that after a usual three-dose HBV vaccination, approximately 90% (range: 74–100%) of the subjects who received the vaccine remained protected for 30 years and over regardless of the anti-HBs antibody titer [40].

CONCLUSION

Immunization against HBV is safe and has been accepted worldwide as a part of the routine immunization program. High levels of protection from recombinant hepatitis B vaccine are achieved in term infants vaccinated at birth, effectively preventing transmission of HBV and resultant morbidity and mortality. There are numerous factors which determine the nature and duration of protection for the HBV vaccination. Research need to be improved for therapeutic vaccination in oder to activate humoral immunity and induce a multifunctional and multi-specific T cell response, to counter the major HBV antigens for effective viral control.

AUTHOR CONTRIBUTIONS

Study concept, design, definition of intellectual content and literature search: DK and HYE. Manuscript preparation: DK, HYE and DPI. Manuscript review: DK, HYE, DPI, HS, HSR, GS, MK, ARN and YT.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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