HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 8, 2093–2097
https://doi.org/10.1080/21645515.2018.1462428

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COMMENTARY

From infancy and beyond… ensuring a lifetime of hepatitis B virus (HBV) vaccine-induced immunity

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ABSTRACT

Despite the long-term efficacy and immune persistence observed following HBV vaccination of infants, the need for a booster dose following infant immunization continues to be deliberated. Evidence from HBV booster dose response studies and long-term immunization program reviews are the basis for the recommendation that a vaccine booster is not necessary. However, further studies continue to emerge and highlight the need for standardization among observational studies in order to appropriately compare outcomes. There is an assumption that neonatal and infant (within 12 months of age) vaccine immune responses are equivalent; however, evidence exists for distinct vaccine responses within the first year of life. HBV vaccine programs have evolved over time, particularly regarding the type and dosage of vaccine used. Several universal neonatal immunization programs initially incorporated a 2.5 μg dosage (Recombivax-HB, Merck). This dosage has been shown in multiple long-term studies and meta-analyses to be associated with a lower primary response, decreased antibody persistence over time, and a reduced booster response 10 to 20 years following immunization. Ongoing surveillance of this and other HBV neonatally-vaccinated populations, particularly in low endemic regions, is necessary to understand the impact on long-term protection in order to ensure lifelong protection against hepatitis B infection.

ARTICLE HISTORY
Received 22 March 2018
Accepted 4 April 2018

KEYWORDS
hepatitis B virus; vaccine; neonatal; immune memory; seroprotection; infant immunity

Discussion and debate continues regarding the long-term persistence of immunity following universal infant hepatitis B virus (HBV) vaccination and the need for a subsequent booster dose in adolescence.[1-5] This is despite the fact that a three-dose schedule of HBV vaccine has been shown to provide decades-long protection against HBV infection in fully vaccinated, immunocompetent individuals,[6,7] although no eligible randomised clinical trials exist to actually prove that a booster dose is or is not required.[8] The lack of randomised controlled trials necessitates the comparison of observational studies from different countries or vaccination programs incorporating different features which often leads to difficulties in comparative interpretation. Features which may be difficult to reconcile or compare among studies include, 1) the type of vaccine used, 2) the length of time between each dose in a schedule, 3) the vaccine dosage used, 4) the number of primary immunization doses provided, and 5) the HBV status of the mother and whether the infant is resident within an endemic or non-endemic region (Table 1). Studies evaluating the anamnestic response to primary immunization years or decades previous also include variables that make study comparison complex, such as the booster dose quantity used or knowledge of the primary immune response in boosted participants. The lack of a concrete definition for the designation of "lasting" individual immunity further complicates interpretation; is it based only on ongoing seroprotection (anti-HBs $\geq$10 mIU/mL) or an adequate immune memory response? Although public health approaches to HBV immunization typically have the common goal to prevent and reduce infections, the most appropriate national interventions will depend on the population and circumstances of each country or region. This may in turn affect the magnitude of seroprotective and lasting immune responses that result from each intervention. For example, the World Health Organization (WHO) global health sector strategy on viral hepatitis commits to the goal of eliminating viral hepatitis as a major public health threat by 2030 through, in part, enhancing and expanding interventions including HBV vaccination.[9] Several of the core intervention targets identified include prevention of mother-to-child HBV transmission, expanded universal infant vaccination, and prevention of HBV infection in healthcare settings and in people who inject drugs. Thus, targeted vaccination of adults engaging in high risk activities may have somewhat different acceptable immunoprotective objectives compared to universal neonatal vaccination, particularly when taking into account the age association with risk of developing chronic hepatitis B infection. Ultimately, control of incident infection and a reduction in chronic carriage within a population validates the success of an HBV immunization program.

Immunization starting with a first dose within 24 hours of birth is recommended[10] due to the high risk (90%) of developing lifelong, chronic HBV infection in neonates, with the risk

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Table 1. Features to consider when assessing and comparing HBV vaccine immune persistence studies.

1. Type of vaccine used
   a. Plasma-derived
   b. Recombinant
      i. Multiple manufacturers and formulations
         1. monovalent
         2. multivalent
2. Length of time between doses
   a. 1 month
   b. 2 months
   c. 4 months
   d. 6 months
3. Vaccine dose (dependent on formulation and age)
   a. 2.5 μg
   b. 5.0 μg
   c. 10.0 μg
   d. 20.0 μg
4. Number of scheduled doses
   a. 2 doses (adolescent and older)
   b. 3 doses
   c. 4 doses
5. HBV status of the mother (for first dose at birth or in infancy)
   a. HBsAg positive, HBeAg negative
   b. HBsAg positive, HBeAg positive
   c. HBsAg negative
6. Age at first dose
   a. at birth: timely, within 24 hours; late, within 7 days of birth
   b. 2 to 6 months
   c. Childhood
   d. Adolescence
   e. Adult
7. HBV endemicity of region of birth
   a. Low endemicity (<2%)
   b. Intermediate endemicity (>2% to 7%)
   c. High endemicity (>8%)
8. Anamnestic response study
   a. Post-primary anti-HBs level
   b. Number of years after primary vaccination
   c. Booster dose used (formulation/dose)

decreasing to approximately 20% to 30% by 1 to 5 years of age.[11] Approximately 95% of immunocompetent infants vaccinated with 3 doses of HBV vaccine demonstrate seroprotective anti-HBs levels (≥10 mIU/mL), with levels >100 mIU/mL considered to provide an enduring response.[7] Following primary immunization, protective antibody levels may decrease to low or undetectable levels.[6,7] Evidence from numerous immunization program reviews and post-primary anamnestic response studies are the basis for the WHO recommendation that a HBV vaccine booster dose later in life is not necessary.[10] Many of these foundational studies included a first vaccine dose months following birth, or a schedule having greater than 3 doses, or include countries in which hepatitis B infection is endemic. As many countries have now instituted the 1992 WHO recommendation for universal infant HBV immunization starting with a dose at birth, more data is emerging from countries of varying endemicity, which confirm the efficacy of the HBV vaccine but also contribute to the ongoing discussion regarding immune persistence. The most recent WHO hepatitis B vaccine position paper posits that studies assessing life-long protection following HBV immunization are still needed, such that certain sub-populations may require a vaccine booster dose.[10]

One aspect that may be neglected in discussions or review literature is the lack of distinction regarding the age at immunization when discussing "infant vaccination". The WHO distinguishes between a timely birth dose (within 24 hours of birth) and a late birth dose (after 24 hours but within 7 days)[10]; but quite often the terms "infant or new-born vaccination" are generalized to encompass a first vaccine dose given anytime within the first year of life. Immunization within the first year of life at any age does not necessarily induce the same peak level of vaccine-induced antibody.[12] HBV vaccination at birth and the response to it is unique compared to other infant vaccinations. Most other vaccinations start at 2 months of age[13] in order to obtain an enhanced immune response[14] as the neonatal response to most vaccines is quite weak. It is understood that infant antibody responses mature throughout the first year of life and that proliferative T cell responses to vaccines are more robust when administered at 2 to 6 months of life rather than at birth.[14] However, HBV vaccine has been shown to produce a robust response in neonates, with induction of primary and memory antibody responses that are similar to the adult response.[12,15] This vigorous neonatal response may be sufficient to overcome maternal antibody interference with anti-HBs production, although this is still somewhat disputed.[16,17] Studies have described no association between the age at first dose and sufficient immunogenicity of the HBV vaccine;[8] however, the peak levels of vaccine-induced antibody have been shown to be higher among infants immunized between one and three months of age compared to within the first three to seven days of life.[13,18-21] Similarly, prematurity, as opposed to a specific birth weight, was a greater predictor of a reduced anti-HBs antibody response compared to full term infants,[22] resulting in the recommendation that premature infants receive a HBV vaccine birth dose followed by a complete HBV vaccine series corresponding to gestational age.[10]

The infant immune system has been characterized as immature, with a restricted immunoglobulin repertoire having low affinity antibody responses as well as an impaired T cell function with poor B and T cell interaction.[23] The Th2/regulatory T cell-type response and reduced B cell somatic hypermutation that predominates in early infancy results in immune tolerance and a diminished humoral response, which shifts to a Th1-type response and a progressive maturation of immunoglobulin class switching and responses through the first year of life.[11] Although pro-inflammatory responses are diminished in neonates, synergistic stimulation of specific Toll-like receptors (TLR) and C-type lectin receptors (CLR) offers immune activation that varies with age, being greatest in newborns.[11,14] This neonatal characteristic immune profile is now being increasingly thought of as highly specialized and uniquely adapted to contend with the various forces the newborn immune system is subjected to.[24] Indeed, the increasing innate response in the first days following birth, including production of IL-6 and stimulation of TLR and CLR, may help to heal tissues injured during birth and to resist infectious pathogens.[25] As well, although neonatal adaptive immune responses are inclined towards tolerance to prevent maternal alloimmune responses, evidence of non-specific innate immunological memory or "trained immunity" is observed with newborn infant immune cells exposed *in vitro* to unrelated pathogens following vaccination.[11]

These differences in immune function and vaccine-induced peak responses throughout the first year of life suggest a finer

distinction may help interpretation of long-term immune persistence studies following "infant" HBV immunization. The age-dependent peak antibody response following primary vaccination will affect future antibody persistence and immune memory. Lower peak anti-HBs concentrations result in a more rapid decline in protective antibody levels[26-28] and a weaker anamnestic response to booster challenge[13,21,29,30] 5 to 15 years following primary vaccination. This reduced anamnestic response suggests that the memory B cells triggered preferentially in response to primary vaccination may not persist.[12] Meta-analyses have described no significant difference in the proportion of individuals having protective anti-HBs levels 5 to 20 years following primary vaccination either at birth or in infancy (approx. 3 months of age)[6] based primarily on infant vaccination studies from a single country (Italy) and in agreement with a birth dose study involving infants born to HBsAg-positive mothers.[31] More recent investigations, which include other regions or populations, describe the age at primary vaccination as being significantly associated with anti-HBs levels ≥10mIU/mL decades later.[21,32,33] There is agreement that a better understanding of seroprotective persistence following neonatal vaccination in low or intermediate endemic regions is needed, where the influence of environmental or "natural" boosting is not a factor.[10,34] Many low endemic countries are observing gradual increases in HBV prevalence or a flattening incidence rate despite successful universal vaccination programs. This is most likely due to increasing immigration of chronically infected individuals from highly endemic countries.[7,35,36] This is a further consideration when assuring the ongoing protection from hepatitis B infection for universal neonatal vaccinees.

A second important aspect to consider regarding the duration of immune protection in persons vaccinated at birth is the primary HBV vaccine dosage. Dosage differences among studies likely also confound comparisons and the association between age at primary vaccination and a more pronounced loss of protective immunity.[21] As proposed by Zhao and Zhou,[37] the observation in some studies of breakthrough HBV infection or an increase in HBsAg prevalence among young adults immunized at birth may be due more so to the lack of compliance during the first few years of program initiation 20 to 30 years earlier. In a similar fashion, recombinant vaccine dosages were often adjusted following program initiation in several countries. The pediatric Recombivax vaccine (Merck & Co.) dose of 2.5 μg/0.5 mL was widely used at the outset of universal vaccine programs in North America. Merck discontinued production and distribution of the 2.5μg dose in 1998, switching to a 5.0μg/0.5 mL dose for vaccinees at birth up to 19 years of age regardless of the mother's HBsAg status.[38] The explanation for the change was to simplify and synchronize the dosages given to neonates in universal and targeted (born to HBsAg positive mothers) programs, but it also became evident that higher seroconversion and response rates were elicited by the higher dose.[20] Although recombinant vaccine dosage differences do not appear to alter primary immunogenicity and the development of anti-HBs ≥10 mIU/mL,[39] multiple long-term studies and meta-analyses have shown an association of the 2.5μg dose with a lower primary response,[13,29,40] a more rapid antibody decline and decreased persistence over time,[6,34,39,41] and a reduced booster response years following primary immunization.[6,21,26,30,42] In older children and adults, higher primary vaccine dosages also elicit greater antibody response and persistence.[43] A higher dosage at primary vaccination has also been suggested to improve the prevention of mother-to-child transmission in infancy.[44] The United States and specific regions of Canada provided the pediatric 2.5μg dose (Recombivax-HB, Merck) through universal neonatal vaccination programs for children born to HBsAg negative mothers until 1998 and 2017, respectively.[38,45] Therefore, infants immunized over a period of time spanning approximately 7 to 22 years, equivalent to nearly an entire generation, have been vaccinated with the lower dose. Fortunately, Canadian follow-up studies of vaccine programs in which the 2.5μg dose was provided to infants and adolescents have shown ongoing immune protection against infection into adolescence or young adulthood, respectively,[34,46] further contributing to the reduction in overall HBV incidence and prevalence in the population.[47,48] However, due to the consistent observation of a lower than expected proportion of seroprotection (anti-HBs ≥10 mIU/mL), vigilant and ongoing surveillance will be necessary to understand the impact on long-term protection against hepatitis B infection in these populations, particularly those immunized starting at birth.

Despite these considerations, it is reassuring that vaccine-based cellular immunity appears to persist even with the loss of detectable antibody or a humoral memory response,[21,49] thus providing ongoing protection against infection resulting in chronic carriage. Transient infection resulting in anti-HBc positivity or cellular immune responses to core or polymerase proteins have been described in fully vaccinated individuals.[49,50] This suggests exposure resulting in sub-clinical or inapparent infection likely due to vaccine-induced protective, but non-sterilizing, immune responses. The long incubation period following HBV transmission is an advantage in this scenario as immune memory and ensuing responses have time to progress to prevent clinically apparent infection. The infrequency of reported HBV breakthrough infection years following immunization is also likely facilitated by herd immunity in the universally vaccinated population as well as the lower risk of developing chronic HBV infection with increasing age. However, loss of HBsAg-specific T cell memory also occurs with time[7] and so adequate protection against clinically apparent breakthrough infection may lapse, a particular concern in low endemic regions facing pressures with an ongoing introduction of individuals from endemic populations.

In conclusion, universal HBV vaccination has resulted in a remarkable decline of HBV incidence throughout the world contributing to a declining chronic prevalence rate overall.[36] Although concerns still linger regarding the extent of ongoing protection against infection afforded by primary vaccination starting at birth, it has been shown that individuals responding to primary vaccination with seroprotective antibody levels rarely have evidence of transient or overt infection,[28] and that immune memory can persist for decades. However, the challenge of determining the extent of protection over a lifetime when vaccination starts at birth continues, particularly in certain populations such as those born in low endemic regions or vaccinated with lower doses of vaccine.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgments

The author thanks Dr. Jingxin Cao and Dr. Oliver Baclic for careful reading of the manuscript, helpful comments and excellent suggestions.

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