HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 13, NO. 4, 918–920
http://dx.doi.org/10.1080/21645515.2016.1267084

Taylor & Francis
Taylor & Francis Group

REPLY LETTER

Long-term persistence of immunity after hepatitis B vaccination: Is this substantiated by the literature?

Terence T. Lao

Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

ABSTRACT

Hepatitis B vaccination is held to provide life-long protection against hepatitis B virus (HBV) infection, but evidence for this notion remains wanting, since no studies have assessed the vaccinees in their fourth decade of life. Indeed, there are several reports indicating that despite vaccination in infancy, the prevalence of HBV infection still increased with age in the vaccinees, and that both anti-HBs titer and anamnestic response declined with age. Clearly it is time to clarify the long-term protection conferred by vaccination in infancy, and to implement remedial measures such as booster doses of vaccine in subjects without immunoprotection.

ARTICLE HISTORY
Received 11 November 2016
Accepted 24 November 2016

KEYWORDS
age; anamnestic response; hepatitis B virus; immune persistence; vaccination in infancy

Sir,

The report by Trevisan[1] and his comments on my earlier review[2] reflected precisely the current confusion about the longevity and protection of the hepatitis B vaccination program. First, Trevisan used data from Italy, where the prevalence of hepatitis B virus (HBV) infection is low relative to places such as Asia, so that the likelihood of exposure to HBV and horizontal transmission after infancy in vaccinated children would be comparatively lower. Second, the Italian mandatory vaccination against HBV introduced in 1991[3] was applied to adolescents as stated by Trevisan.[1] If this was the same program that was applied to the 6945 medical school students and health professionals aged between 18 and 68 y in Trevisan's report,[1] the interval between the age of vaccination and the age of testing for immunity or infection, which was not revealed, must have been quite short and probably within a decade for the majority of the study subjects. As the duration of protection cannot be estimated, any claim of longevity or persistence of immune protection conferred by vaccination in infancy cannot be substantiated. Third, the data provided by Trevisan included only subjects with serological evidence of past HBV infection, but no data on anti-HBs titer or anamnestic response on the rest of the cohort was provided, so that the report still did not constitute proof that the HBV vaccination in infancy confers protection up to adulthood. Finally, the message of my review[2] was not an allegation of lack of efficacy of the hepatitis B vaccine, but rather that we should establish the duration of immunoprotection induced by the HBV vaccine, and to provide remedial actions such as booster doses if longevity of protection cannot be ensured.

Indeed, a careful review of the literature does not provide a reassuring picture. In completed vaccinees, anti-HBc seroconversion has been found in 1.5% from 3–15 y of age[4] and in 8% 15 y later,[5] even though none of the subjects in these reports became chronic carriers at the time of the study. In Taiwan, 1.3% and 4.5% of complete and incomplete vaccinees respectively were HBsAg positive at age 2–6 y,[6] and 1.3% to 3.5% of immunized infants became HBsAg carriers 15 y later.[7] In rural Gambia, vaccination reduced the HBV carriage rate to 0% (0/472) at the age of 1–4 years, but it became 2.1% (4/192) at age 20–24 y.[8] Among Aboriginal adolescents, active and past HBV infection was found in 11% and 19% respectively despite complete vaccination in infancy.[9] In Hong Kong, the prevalence increased significantly from 0.9%, 2.3%, 4.3%, to 5.5% among first-year university students born after the introduction of vaccination, who were aged $\leq 18, 19, 20$, and ≥ 21 y respectively.[10] In Pakistan, HBV infection increased from 13.39% among subjects aged 11–20 y to 34.93% among subjects aged 21–30 y.[11] In Korea, the weighted age-specific prevalence increased from 1.9% in adolescents to 4.9% in those in their 20s.[12] Therefore low prevalence in children and adolescents is not synonymous with similarly low prevalence in adults in the same population residing in endemic areas.

It is important to realize that unless routine postvaccination serological testing (PVST) is performed, it remains unclear what proportion of the complete vaccinees is actually protected, as one earlier study found that 22.9% of vaccinated children had undetected antibody levels.[13] Routine PVST in the US demonstrated that 5.3% of 8654 HBsAg-negative infants born to HBsAg positive mothers failed to respond to a primary series, the incidence increased from 2% to 21.6% with PVST at 1–2 months and 15–16 months respectively.[14] Experience in Hong Kong similarly demonstrated in 160 children born to HBsAg positive mothers that 22.5% had anti-HBs at <10 IU/mL, and one of these children (0.6%) became HBsAg positive, when tested at the age of 18–24 months.[15] There is no dispute that following vaccination, antibody titer also falls with age, as shown in a study on 640 children with complete vaccination and born

CONTACT Terence T. Lao, MD lao-tt@cuhk.edu.hk Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong.

to HBsAg positive mothers that protective anti-HBs dropped from the initial 93% to 70%, 40% and finally 25% when tested at 5, 10, and 15 y of age respectively.[4] Another study also found that the percentage of protected individuals decreased with time with significant reduction of anti-HBs GMT after 5 y to reach 10 mIU/mL in about 15 years' time.[16] The worst scenario was in Micronesians, as only 7.3% of uninfected individuals vaccinated at birth had antibody protection.[5] But more importantly, decreased seroprotection can be associated simultaneously with decreased HBsAg carriage. In Taiwan, among new university entrants studied in 2005 and analyzed by birth before July 1984, July 1984-June 1986, and from July 1986 respectively, the positive rates for HBsAg were 8.7%, 3.2%, 1.7%, and that for anti-HBs were 61.2%, 72.6%, 46.5%, while non-protective level of anti-HBs increased from 11.9% for birth-year 1984 to 48.2% for birth-year 1987 students.[17] Another survey on first year nursing students found that while HBsAg positivity decreased from 4.9% in 2000 to 2.1% in 2006, anti-HBs also decreased from 77.1% to 39.7%, but both tests being negative increased from 18.0% to 58.2%.[18] In Hong Kong, 80.2% of 212 university entrants aged 17–23 y who had received neonatal vaccination were both HBsAg and anti-HBs negative, and although HBsAg was found in only 0.9%, a weak or absent anamnestic response was found in 43%.[19]

The critical issue about universal HBV vaccination is not whether it is effective in protecting children from HBV infection, but whether its protection can endure into adulthood, even if not lifelong. As natural pregnancy is only achieved with unprotected intercourse, prevalence of HBV infection in the obstetric population would serve as a reliable indicator of the extent of vaccine protection. Therefore our finding that HBV infection increased from 2.3% at age $\leq$ 16 y to peak at 8.4% at age 25 y among young mothers born in Hong Kong following the implementation of hepatitis B vaccination in infancy[20] raises the concern about the persistence of protection induced by vaccination in infancy. Instead of arguing about whether vaccination induces long-term protection, it is more important to ensure that vaccination *does* provide long-term protection. As universal hepatitis B vaccination was introduced around 3 decades ago in many countries, it is time to study the immunoprotection among the vaccinees so as to provide the evidence or otherwise of persistent vaccine protection. While still waiting for the answer, we should not be complacent but to consider booster doses especially in adolescents and young adults who are deemed to be at increased risk of horizontal transmission of HBV infection.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Trevisan A. Long-term persistence of immunity after hepatitis B vaccination: a fact not a fancy. Hum Vaccin Immunother 2016; [Epub ahead of print]; PMID:27905837; http://dx.doi.org/10.1080/21645515.2016.1257451

[2] Lao TT. Immune persistence after hepatitis B vaccination in infancy - Fact or fancy? Hum Vaccin Immunother 2016; 12(5):1172-6; PMID:26810256; http://dx.doi.org/10.1080/21645515.2015.1130195

[3] Stroffolini T, Mele A, Tosti ME, Gallo G, Balocchini E, Ragni P, Santonastasi F, Marzolini A, Ciccozzi M, Moiraghi A. The impact of the hepatitis B mass immunisation campaign on the incidence and risk factors of acute hepatitis B in Italy. J Hepatol 2000; 33(6):980-5; PMID:11131462; http://dx.doi.org/10.1016/S0168-8278(00)80132-4

[4] Roznovsky L, Orsagova I, Kloudova A, Tvrdik J, Kabieszova L, Lochman I, Mrazek J, Hozakova L, Zjevikova A, Pliskova L. Long-term protection against hepatitis B after newborn vaccination: 20-year follow-up. Infection 2010; 38(5):395-400; PMID:20589522; http://dx.doi.org/10.1007/s15010-010-0039-7

[5] Bialek SR, Bower WA, Novak R, Helgenberger L, Auerbach SB, Williams IT, Bell BP. Persistence of protection against hepatitis B virus infection among adolescents vaccinated with recombinant hepatitis B vaccine beginning at birth. A 15-year follow-up study. Pediatr Infect Dis J 2008; 27(10):881-5; http://dx.doi.org/10.1097/INF.0b013e31817702ba

[6] Lin DB, Wang HM, Lee YL, Ling UP, Changlai SP, Chen CJ. Immune status in preschool children born after mass hepatitis B vaccination program in Taiwan. Vaccine 1998; 16(17):1683-7; PMID:9713947; http://dx.doi.org/10.1016/S0264-410X(98)00050-4

[7] Lu CY, Chiang BL, Chi WK, Chang MH, Ni YH, Hsu HM, Twu SJ, Su IJ, Huang LM, Lee CY. Waning immunity to plasma-derived hepatitis B vaccine and the need for boosters 15 years after neonatal vaccination. Hepatology 2004; 40(6):1415-20; PMID:15565627; http://dx.doi.org/10.1002/hep.20490

[8] Van der Sande MAB, Waight P, Mendy M, Rayco-Solon P, Hutt P, Fulford T, Doherty C, McConkey SJ, Jeffries D, Hall AJ, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. J Infect Dis 2006; 193(11):1528-35; PMID:16652281; http://dx.doi.org/10.1086/503433

[9] Dent E, Selvey CE, Bell A, Davis J, McDonald MI. Incomplete protection against hepatitis B among remote Aboriginal adolescents despite full vaccination in infancy. Commun Dis Intell Q Rep 2010; 34(4):435-9; PMID:21413528

[10] Suen SSH, Lao TT, Chan OK, Lau TK, Leung TY, Chan PK. Relationship between age and prevalence of hepatitis B infection in first-year university students in Hong Kong. Infection 2013; 41(2):529-35; PMID:23233215; http://dx.doi.org/10.1007/s15010-012-0379-6

[11] Khan F, Shams S, Qureshi ID, Israr M, Khan H, Sarwar MT, Ilyas M. Hepatitis B virus infection among different sex and age groups in Pakistani Punjab. Virol J 2011; 8:225-9; PMID:21569532; http://dx.doi.org/10.1186/1743-422X-8-225

[12] Jeong SH, Yim HW, Yoon SH, Jee YM, Bae SH, Lee WC. Changes in the intrafamilial transmission of hepatitis B virus after introduction of a hepatitis B vaccination programme in Korea. Epidemiol Infect 2010; 138(8):1090-5; PMID:19951454; http://dx.doi.org/10.1017/S0950268809991324

[13] Gold Y, Somech R, Mandel D, Peled Y, Reif S. Decreased immune response to hepatitis B 8 years after routine vaccination in Israel. Acta Paediatr 2003; 92(10):1158-62; PMID:14632331; http://dx.doi.org/10.1111/j.1651-2227.2003.tb02477.x

[14] Ko SC, Schillie SF, Walker T, Veselsky SL, Nelson NP, Lazaroff J, Crowley S, Dusek C, Loggins K, Onye K, et al. Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. Vaccine 2014; 32(18):2127-33; PMID:24560676; http://dx.doi.org/10.1016/j.vaccine.2014.01.099

[15] Lao TT, Cheung KL, Wong V. Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. Vaccine 2015; 33(1):15-6; PMID:25017181; http://dx.doi.org/10.1016/j.vaccine.2014.05.036

[16] Bracciale L, Fabbiani M, Sansoni A, Luzzi L, Bernini L, Zanelli G. Impact of hepatitis B vaccination in children born to HBsAg-positive mothers: a 20-year retrospective study. Infection 2009; 37(4):340-3; PMID:19629385; http://dx.doi.org/10.1007/s15010-008-8252-3

[17] Su FH, Chen JD, Cheng SH, Sung KY, Jeng JJ, Chu FY. Waning-off effect of serum hepatitis B surface antibody amongst Taiwanese university students: 18 years post-implementation of Taiwan's national

hepatitis B vaccination programme. J Viral Hepat 2008; 15(1):14-9; PMID:18088240

[18] Lin CC, Chang CK, Huang YL, Tseng HF. Low seroprevalence of hepatitis B surface antibody among nursing students in Taiwan: an implication for boosting. Vaccine 2007; 25(51):8508-11; PMID:18006122; http://dx.doi.org/10.1016/j.vaccine.2007.10.018

[19] Chan PKS, Ngai KLK, Lao TT, Wong MC, Cheung T, Yeung ACM, Chan MC, Luk SW. Response to booster doses of hepatitis B vaccine among young adults who had received neonatal vaccination. PLoS One 2014; 9(9):e107163; PMID:25198289; http://dx.doi.org/10.1371/journal.pone.0107163

[20] Lao TT, Sahota DS, Law LW, Cheng YK, Leung TY. Age-specific prevalence of hepatitis B virus infection in young pregnant women, Hong Kong special administration region of China. Bull World Health Organ 2014; 92(11):782-9; PMID:25378739; http://dx.doi.org/10.2471/BLT.13.133413