[5] Pozzato G, Mazzaro C, Crovatto M, Modolo ML, Ceselli S, Mazzi G, et al. Low-grade malignant lymphoma, hepatitis C virus infection, and mixed cryoglobulinemia. Blood 1994;84:3047–3053.
[6] Peveling-Oberhag J, Crisman G, Schmidt A, Doring C, Lucioni M, Arcaini L, et al. Dysregulation of global microRNA expression in splenic marginal zone lymphoma and influence of chronic hepatitis C virus infection. Leukemia 2012;26:1654–1662.
[7] Fognani E, Giannini C, Piluso A, Gragnani L, Monti M, Caini P, et al. Role of microRNA profile modifications in hepatitis C virus-related mixed cryoglobulinemia. PLoS One 2013;8:e62965.
[8] Zhang Z, Florez S, Gutierrez-Hartmann A, Martin JF, Amendt BA. MicroRNAs regulate pituitary development, and microRNA 26b specifically targets lymphoid enhancer factor 1 (Lef-1), which modulates pituitary transcription factor 1 (Pit-1) expression. J Biol Chem 2010;285:34718–34728.
[9] Gutierrez Jr A, Tschumper RC, Wu X, Shanafelt TD, Eckel-Passow J, Huddleston 3rd PM, et al. LEF-1 is a prosurvival factor in chronic lymphocytic leukemia and is expressed in the preleukemic state of monoclonal B-cell lymphocytosis. Blood 2010;116:2975–2983.
[10] Cubedo E, Gentles AJ, Huang C, Natkunam Y, Bhatt S, Lu X, et al. Identification of LMO2 transcriptome and interactome in diffuse large B-cell lymphoma. Blood 2012;119:5478–5491.

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Long-term protection of neonatal hepatitis B vaccination in a 30-year cohort in Hong Kong

To the Editor:

Universal neonatal hepatitis B (HB) vaccination programme is effective in the control of hepatitis B virus (HBV) infection in countries with different endemicity [1,2]. However, the long-term protective effect of neonatal hepatitis B vaccination into adulthood, especially in endemic areas and to subjects with high risk of infection, remains uncertain [3]. Universal neonatal HB vaccination programme has been introduced in Hong Kong, a region of moderate to high endemicity of hepatitis B, since 1988. To study the long-term effect of neonatal HB vaccination in those with high risk of HBV infection in Hong Kong, we evaluated the serial changes of HBV serological markers over a 30-year period in a cohort born to hepatitis B carrier mothers and who received neonatal hepatitis B vaccination.

In 1983, 1112 neonates, born to hepatitis B carrier mothers in a public hospital in Hong Kong, were recruited for a study to evaluate the response of passive–active hepatitis B vaccination with hepatitis B immunoglobulin and three-dose regimen of hepatitis B vaccines of three different schedules: conventional (0, 1, and 6 months), delayed (2, 3, and 8 months), and accelerated (0, 1, and 2 months) [4]. HBV serological markers, including HBsAg, antibody to surface antigen (anti-HBs) and antibody to core-antigen (anti-HBc), were determined upon completion of vaccination and at subsequent intervals up to 30 years of follow-up. Anti-HBs positivity was defined as anti-HBs level higher or equal than 10 IU/L. Anti-HBc seroconversion was defined as anti-HBc positivity for two consecutive readings measured at or after the 2nd year. Upon completion of the three-dose vaccination, 1006 (92.6%) out of 1086 subjects developed anti-HBs positivity. Thirty-nine subjects failed the vaccination and developed chronic HBV infection, giving the HBsAg positivity rate of 3.5%. Thirty-five (89.7%) of them were born to mothers who were also hepatitis B e-antigen (HBeAg) positive. All of these 39 subjects were tested HBsAg positive before the age of two, with no new infection found at subsequent follow-up time points of years 3, 5, 7, 10, 13, 16, 21, 25, and 30 post-vaccination (Table 1). At the 30th year of follow-up, the anti-HBs positivity rate fell to 37.4%. There were no differences in the development of HBsAg and anti-HBs positivity between subjects receiving three different vaccination schedules (p >0.05). Ninety-seven subjects developed anti-HBc seroconversion over the 30-year period, giving a rate of 9% (39 subjects tested for HBsAg positive were excluded), with no statistically significant difference in anti-HBs positive and negative subjects (9.3% *vs.* 5%, p >0.05).

We described the first study showing long-term protective effect of neonatal HB vaccination into a cohort up to 30 years of follow-up. While most studies reported in the literature measured immune-protection by detectable levels of antibodies to HBV [5,6], this study provided direct evidence of effective protection in subjects with high risk of infection, both via perinatal route or close interpersonal contact with their infected mothers and possibly other infected household members at childhood. Among 97 subjects who developed anti-HBc seroconversion, a majority (43%) of these seroconversions occurred at or before year two. On the other hand, with such a long follow-up period up to 30 years, this study also demonstrated the protective effect of vaccine into adulthood, when the subjects might be exposed to horizontal transmission of HBV, notably from sexual contact. Despite the dropping rate of anti-HBs and new occurrence of anti-HBc seroconversion over the years, there was no new development of HBsAg positivity after the first two years in the entire follow-up period.

Our findings were in line with other studies which suggested long-term protection of HB vaccine albeit with shorter follow-up durations. Persistence of serum protective antibody level was shown in older children or adolescents who received vaccination at infancy [6–8]. Moreover, anamnestic response was demonstrated in those who had lost protective antibody level, years after vaccination [9]. A recent study further suggested that, apart from a protective serum antibody level, cellular immune response might also play a role for protection against HBV after vaccination [10].

There were two limitations in this study. First, subjects who were not followed-up might have affected the overall representativeness of the data. At the 30th year of follow-up, 246 (22.1%) subjects returned for serological tests. 372 (33.5%) subjects defaulted follow-up, and 492 (44.2%) subjects were lost to fol-

Table 1. Temporal change of hepatitis B virus serological markers in the study cohort over 30 years.

Follow-up time	Baseline[#]	Year 1	Year 2	Year 3	Year 5	Year 7	Year 10	Year 13	Year 16	Year 21	Year 25	Year 30
Total No. of subjects	1086	1075	1069	1044	953	795	792	714	610	358	278	246
Anti-HBs seroconversion	1006 (92.6%)	980 (91.2%)	872 (81.6%)	766 (73.4%)	612 (64.2%)	477 (60%)	355 (44.8%)	253 (35.4%)	203 (33.3%)	130 (36.3%)	103 (37.1%)	92 (37.4%)
HBsAg positivity	23	12	4	0	0	0	0	0	0	0	0	0
Anti-HBc seroconversion*	-	-	42	14	13	12	7	4	2	2	1	0**

[#]Upon completion of a 3-dose vaccination.
*Excluded 39 subjects who developed HBsAg positivity.
**Based on one anti-HBc result.

low-up. Two subjects died in the study period but neither of them was known to be HB carrier. Second, the cohort received three different vaccination schedules that different response to three vaccination schedules could not be totally excluded.

In conclusion, this study demonstrated direct long-term efficacy of neonatal HB vaccination in a high-risk cohort, up to 30 years in an endemic region. The implementation of universal neonatal HB vaccination in Hong Kong since 1988 is likely to remain effective for long-term prevention of HBV infection in the territory in the absence of a policy of booster in the adolescent or early adult population.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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References

[1] Ni YH, Chang MH, Wu JF, Hsu HY, Chen HL, Chen DS. Minimization of hepatitis B infection by a 25-year universal vaccination programme. J Hepatol 2012;57:730–735.
[2] Boccalini S, Taddei C, Ceccherini V, Bechini A, Levi M, Bartolozzi D, et al. Economic analysis of the first 20 y of universal hepatitis B vaccination program in Italy: an a posteriori evaluation and forecast of future benefits. Hum Vaccin Immunother 2013;9.
[3] Wu TW, Lin HH, Wang LY. Chronic hepatitis B infection in adolescents who received primary infantile vaccination. Hepatology 2013;57:37–45.
[4] 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.
[5] Gabbuti A, Romano L, Blanc P, Meacci F, Amendola A, Mele A, et al. Long-term immunogenicity of hepatitis B vaccination in a cohort of Italian health adolescents. Vaccine 2007;25:3129–3132.
[6] Alfaleh F, Alshehri S, Alansari S, Aljeffri M, Almazrou Y, Shaffi A, et al. Long-term protection of hepatitis B vaccine 18 years after vaccination. J Infect 2008;57:404–409.
[7] Aypak C, Yüce A, Yıkılkan H, Görpelioğlu S. Persistence of protection of hepatitis B vaccine and response to booster immunization in 2- to 12-year-old children. Eur J Pediatr 2012;171:1761–1766.
[8] 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.
[9] Chaves SS, Fischer G, Groeger J, Patel PR, Thompson ND, Teshale EH, et al. Persistence of long-term immunity to hepatitis B among adolescents immunized at birth. Vaccine 2012;30:1644–1649.
[10] Carollo M, Palazzo R, Bianco M, Pandolfi E, Chionne P, Fedele G, et al. Hepatitis B specific T cell immunity induced by primary vaccination persists independently of the protective serum antibody level. Vaccine 2013;31:506–513.

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