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Editorial

A hepatitis B vaccine booster shot at age 10 could be cost-saving in China: But is it too soon to tell?

Worldwide, over 240 million people are living with chronic hepatitis B virus (HBV) infection (Ott et al., 2012), and 786,000 individuals die from HBV related deaths, including cirrhosis and liver cancer, each year (MacLachlan et al., 2015; Lozano et al., 2012). The HBV vaccine has been shown to be highly effective, and over one billion doses have been delivered worldwide (World Health Organisation, 2018). The burden of hepatitis B in China is one of the highest in the world, with almost one-third of the world's hepatitis B cases diagnosed in China. The initial HBV vaccines were licensed in China in 1985 and from 1992 the government actively recommended vaccination of infants, including the first dose being administered within the first 24 hours of birth (Centers for Disease Control and Prevention, 2007; Wang et al., 2016). Since 2002, infant HBV vaccination has been government funded (Cui et al., 2017a). The program has achieved high coverage in infants, with 93.4% receiving three-doses for the 2005 birth cohort; 82.6% received the first dose within the first 24 h of birth (Centers for Disease Control and Prevention, 2007). Survey results have shown declines in hepatitis B virus surface antigen (HBsAg) prevalence in children aged 0–14 years from 10% in 1992 to <1% in 2014 (Cui et al., 2017a), and modelled analyses of HBV vaccination have consistently found that infant HBV vaccination, as well as catch-up vaccination for adolescents, is cost-saving for China (Hutton et al., 2010; Yin et al., 2015).

Findings from four continents over 30 years of primary HBV vaccination indicated that "*a full primary course of hepatitis B vaccine confers complete protection against acute clinical disease and chronic hepatitis B infection for long periods of time*," even though anti-HBs (a surface antigen that indicates immunity) wane and eventually become undetectable over time in some successfully vaccinated individuals (FitzSimons et al., 2013). Therefore, the WHO does not recommend booster vaccination in successfully immunised individuals, although some countries, including the USA, do recommend boosters for immunocompromised individuals (Centers for Disease Control and Prevention, 2018). In recent years, some studies have indicated that breakthrough infection could occur in endemic areas in China.

In 2017, Wang and colleagues identified a relationship between a mother's HBsAg status and HBV breakthrough infection in their children in late adolescence or early adulthood (Wang et al., 2017). This study involved 9,786 participants who received neonatal vaccination as infants in China, and were negative for HBsAg at age 10–11 years in 1996–2000. The authors found that 50 (0.51%) individuals developed chronic HBV infection between ages 23–28, and that the risk of developing chronic HBV infection was higher in children born to HBsAg-positive mothers (28/936; 2.99%), compared to that in children born to HBsAg-negative mothers (22/8,850; 0.25%), resulting in an adjusted odds ratio of 12.56 (95%CI: 7.14–22.08) for individuals born to HBsAg-positive mothers compared to HBsAg-negative mothers. Children born to HBsAg-positive mothers who received a booster had a lower rate of developing chronic HBV infection than those who did not receive the booster (3.09% versus 7.21%), but this was not statistically significant ($p = 0.074$). However, the study found that the booster vaccine appeared to offer little protection in children born to HBsAg-negative mothers. The study therefore concluded that adolescent booster vaccination could be appropriate for some individuals born to HBsAg-positive mothers when their serum anti-HBs fall below 10 mIU/ml.

Prompted by these findings, Wang/Shi et al. present modelling results on the cost-effectiveness of one-dose booster vaccination for children aged 10 years who were born to HBsAg-positive mothers in the current issue of the International Journal for Infectious Diseases [ref main article]. Two key strategies were considered for children aged 10 years who were born to HBsAg-positive mothers: offering a booster to individuals who tested negative for HBsAg, or offering a booster to individuals who tested negative for both HBsAg and anti-HBs. Testing provided a two-fold role in these scenarios—to identify individuals who would benefit from vaccination, and to refer those who are HBsAg-positive to appropriate treatment. Model parameters were based on published values, and on expert opinion when published data were not available. Extensive sensitivity analysis was carried out on costs of testing and vaccination, compliance with testing, vaccine efficacy, utility weights and natural history, and model validation was performed against data on the incidence of hepatocellular carcinoma and liver cirrhosis in chronic HBV patients. Taking a societal perspective, both strategies were found to be cost-saving compared to no testing (for either HBsAg or anti-HBs) and no booster (current recommendations). Both strategies were predicted to reduce the lifetime risk of HBV-related death by 20–30% and both had similar cost-effectiveness ratios compared to no testing and no booster. Due to the higher cost associated with testing for anti-HBs in addition to HBsAg, the strategy involving screening for HBsAg and anti-HBs was slightly less favourable (both more expensive and less effective) compared to screening for HBsAg only; however the authors note that patients are often anxious to know their anti-HB status, which could make this strategy more acceptable than one without anti-HB status testing. The most influential parameters

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identified in sensitivity analysis were costs associated with the treatment of chronic hepatitis and utility assumptions for patients with chronic hepatitis; however, even in the 'worst case' scenario explored in sensitivity analysis (where all parameters were simultaneously set to the least favourable values), cost-effectiveness ratios remained below the GDP per capita for China.

It has been estimated that each year in China 0.75–1 million children are born to HBsAg-positive mothers (Cui et al., 2017b). Wang/Shi et al. note that awareness of HBsAg status in China has been reportedly over 70% for more developed areas in China, which could result in up to 700,000 additional doses of HBV delivered each year in China if the recommendation to offer a booster was made nationally. However, as vaccinated cohorts age, the number of HBsAg-positive mothers will decrease. HBsAg sero-prevalence surveys have reported declines in prevalence of almost 50% for individuals aged 20–29 years in 2014 compared to 1992 (Cui et al., 2017a). Wang/Shi et al. also note that the National Health and Family Planning commission recommended that vaccinated infants would be offered a HBV dose 1–2 months after they completed the third dose if seronegative for HBsAg and anti-HBs <10 mIU/ml from 2017 onwards, which would change the effectiveness of strategies considered in their cost-effectiveness analysis once these children reach age 10.

Some simplified model assumptions were made by Wang/Shi et al. For instance, the impact of the existing infant vaccination program was not modelled explicitly, but rather captured in a simplified way based on an observed 2.16% reduction observed over 1992–2006 in 1–59 year-olds. Some limitations of the earlier study by Wang et al. (2017) have been identified (Zhou, 2018; Qu et al., 2018). One limitation is that it was uncertain as to whether the individuals who experienced breakthrough infection were adequately vaccinated as infants, including how many had received all three doses and how many received the first dose within 24 h of birth, which has implications as to whether it would be more effective to invest resources into increasing appropriate timing and coverage in infants, as opposed to investing resources in booster vaccination. The protective effect of booster vaccination in the development of chronic HBV infection for individuals born to HBsAg-positive mothers was not significant ($p = 0.074$). Furthermore, the study was not randomised, which lends itself to potential selection bias. An earlier Cochrane review concluded that "*there were no eligible randomised clinical trials to be included in the review. There is no scientific evidence to support or reject the need for booster doses . . . We need evidence, based on randomised clinical trials to formulate future booster policies.*" (Poorolajal et al., 2010).

The current results from Wang/Shi et al. suggest that offering a booster to children aged 10 years who were born to HBsAg-positive mothers and screen HBsAg-negative could be cost saving. It will be important, however, to confirm the earlier findings on breakthrough infection reported by Wang et al. by randomising individuals at age 10 years to receive either a booster vaccine or no booster, provided these individuals received full-dose timely vaccination at birth and were born to HBsAg-positive mothers.

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