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The doses of 10 μg should replace the doses of 5 μg in newborn hepatitis B vaccination in China: A cost-effectiveness analysis

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ABSTRACT

Objective: To identify whether Chinese current series of three 5 μg doses for newborn hepatitis B vaccination should be replaced by the series of three 10 μg doses.
Methods: A cost-effectiveness analysis was conducted from the societal perspective based on the constructed decision tree-Markov model. Model parameters were estimated from published literatures, government documents and our surveys. The expected cost and effectiveness were compared between the 3-dose 5 μg series (the 5 μg strategy) and the 3-dose 10 μg series (the 10 μg strategy), and the incremental cost-effectiveness ratio (ICER, additional cost per quality-adjusted life-years gained) was calculated. Threshold values of the efficacy difference of the two series for the ICER = 0, 1 and 3 times per capita gross domestic product were analyzed under different scenarios to understand whether the 10 μg strategy should replace the 5 μg strategy according to the recommendation of World Health Organization.
Results: The 10 μg strategy would be cost-saving compared with the 5 μg strategy under the base-case scenario. Under keeping all the other parameters at the base-case values or further adjusting any one of them to the value most unfavorable to the 10 μg strategy, as long as the efficacy of 3-dose 10 μg series was slightly higher than that of 3-dose 5 μg series, the 10 μg strategy would be cost-effective, highly cost-effective, or even cost-saving. Even under the most pessimistic scenario, i.e. all the other parameters, but the discount rate, at the values most unfavorable to the 10 μg strategy, the 10 μg strategy would be cost-effective if the efficacy difference reached higher than 1.23 percentage point.
Conclusion: For newborn hepatitis B vaccination in China, the 10 μg strategy should be cost-effective, even more possibly highly cost-effective or cost-saving compared with the current 5 μg strategy. The doses of 10 μg should be considered to replace the doses of 5 μg in newborn hepatitis B vaccination in China.

1. Introduction

Hepatitis B virus (HBV) infection has long been a health problem in China. The first and second nationwide serosurveys in 1979 and 1992, respectively, showed that 9.05% and 9.75% of Chinese population were positive for HBV surface antigen (HBsAg) [1]. Routine hepatitis B vaccination for newborns was recommended by the Chinese Ministry of Health in 1992, and was fully integrated into the National Children Immunization Program in 2002. This strategy has achieved significant impact on controlling HBV transmission in children. According to the third nationwide serosurvey in 2006 [2], the HBsAg prevalences in children aged 1–4 years and 5–14 years have reduced from 9.67% and 10.74% in 1992 to 0.96% and 2.42% in 2006, respectively. However, a high rate of 7.18% is still held by the total population in China [2].

During the past two decades in China, the series of three 5 μg doses was recommended in newborn hepatitis B vaccination. With the economic development and the self-production capacity expansion, China has been able to afford its universal newborn hepatitis B vaccination even with a larger dose. A number of researches have demonstrated that increasing the dose can achieve stronger immunity for hepatitis B in children and adults [3–5]. The doses of 10 μg have been used in children in some countries and regions [6]. Therefore, we want to know whether Chinese current series of three 5 μg doses for newborn hepatitis B vaccination should be replaced by the series of three 10 μg doses. We performed a model-based

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cost-effectiveness analysis from the societal perspective to answer this question. This work will help improve the newborn hepatitis B vaccination strategy in China and add to the body of evidence for maximizing the power of the current vaccines.

2. Methods

2.1. Decision tree-Markov model

We constructed a decision tree-Markov model based on the published literatures [7–9], using the software of TreeAge Pro 2012 (TreeAge Software, Inc., MA, USA). A cohort born in 2013 was assumed to be enrolled following the two alternative newborn hepatitis B vaccination strategies: the current series of three 5 μg doses at birth, 1 and 6 months of age (the 5 μg strategy) and the hypothetical series of three 10 μg doses at the same age points (the 10 μg strategy). The current monovalent recombinant hepatitis B vaccines produced by China were considered in this study. The decision tree part of the model was used to simulate the compliance and efficacy of the strategies and perform the comparison between the two strategies. The Markov part of the model was used to simulate HBV infection and progression and as the calculator to calculate the health and economic outcomes of HBV infection in a lifetime horizon. Other strategies were not considered because in China only the 3-dose series is recommended up to now and hepatitis B immunoglobulin is used at a very low proportion due to the "self-select and self-pay" policy.

The Markov model (the details shown in Appendix Fig. 1) consisted of eight health states: susceptible to HBV; immune due to infection or vaccination; asymptomatic carrier; chronic hepatitis; compensated cirrhosis; decompensated cirrhosis; hepatocellular carcinoma; and death. The model was run with a cycle length of one year for 91 cycles (i.e. from birth to 90 years old) in order to cover lifelong experiences of the vast majority of the cohort members, like done in some previous studies [10]. Liver transplantation was not considered as a health state because of the few applications relative to the large patient population in China. Acute HBV infection, as a transient process, was covered in the susceptible state (the details shown in Appendix Fig. 2).

2.2. Model parameters

Base-case values and ranges of parameters used in the model were estimated from published literatures, government documents and our surveys. They were described below and summarized in Table 1.

2.2.1. Vaccine coverage and efficacy

Ninety percent of newborns would receive a full 3-dose vaccination for hepatitis B after birth according to the latest National Health Survey in 2008. This parameter was adjusted between 80% and 95% based on its shift among the regions. The 10 μg strategy was assumed to have the same coverage as the 5 μg strategy. The non-full vaccinations were ignored in the model because of the very low proportion in newborns. Eighty-five percent of newborns who receive the 3-dose 5 μg series would obtain the protection to HBV infection according to the domestic reports [11,12]. A wide range of 70–95% was given to this parameter because of the potential large uncertainty resulted from the shift of the timely birth dose coverage among the regions [13].

Few studies have reported the efficacy difference between the 3-dose 10 μg series and the 3-dose 5 μg series. A few small randomized control trials from China showed that the 3-dose 10 μg series had a higher efficacy in preventing the mother-to-infant transmission than the 3-dose 5 μg series [14,15], but the differences were not statistically significant. A large observational study from China reported a highly significant efficacy difference between the two different dose series in preventing the mother-to-infant transmission [16], but confounding factors were not controlled. However, some studies demonstrated that the 3-dose 10 μg series could induce a significantly higher antibody concentration and seroconversion rate than the 3-dose 5 μg series in children [4,14,17]. A latest observational study from China which enrolled more than 13 thousand infants found that the antibody geometric mean concentration and seroconversion rate were significantly different between the two different dose series (10 μg: 1778.28 mIU/ml and 97.69%; 5 μg: 354.81 mIU/ml and 82.94%), and the differences remained stable after controlling for some confounding factors [17]. We made a subjective judgment based on these reports: the 3-dose 10 μg series had a 3 percentage point higher protection than the 3-dose 5 μg series. We adjusted this parameter from 0 to 6% in sensitivity analyses. The protection obtained from vaccination was considered lifetime [18], and the adverse events of vaccination were ignored in the model [19].

2.2.2. Incidence of HBV infection

Due to the incomplete information and poor quality of the reported acute hepatitis B incidence data in China, we estimated the annual incidence of HBV infection in susceptible individuals at different ages (i.e. the age-dependent force of HBV infection) based on the nationwide serosurvey data by three steps. First, we estimated the initial age-dependent force (point estimates and 95% CI estimates) from the serosurvey data in 1992 by a modified simple catalytic model. The serosurvey in 1992 was performed just before the recommendation of routine hepatitis B vaccination for newborns was announced, and the data could characterize natural HBV infections without vaccination. The total and age-specific prevalences of HBV infection in 1992 were consistent with the results of the nationwide serosurvey in 1979 [1]. Second, we estimated an average annual decline of the force of HBV infection from 1992 to 2006 in the total population by the theoretical expression of the force of infection and the difference of the total HBsAg prevalence between 1992 and 2006. This parameter was determined at 2.16%. It was increased by up to 50% in sensitivity analyses in consideration of the potential underestimation. Third, using this annual decline we adjusted the estimates of the initial age-dependent force to obtain the current estimates in 2013. The details were showed in Appendix. The point estimates of the age-dependent force were used as the base-case values, and the 95% CI estimates were used in sensitivity analyses. The decline of the force of HBV infection was considered during the whole time horizon of analysis and 2.16% was used consistently as the base-case value.

2.2.3. Outcome and transition probabilities of HBV infection

Outcome probabilities of acute HBV infection and annual transition probabilities related to chronic HBV infection were determined according to published literatures home and abroad, which had been used in some hepatitis B-related economic evaluation studies. The estimate of hospitalization rate among those with symptomatic acute infection also referred to a previous expert interview we did [20]. A wide range was given to each of these parameters to cover the majority of reported data. For those considered to be age-dependent, we adjusted the age-specific base-case values simultaneously by ±50% in sensitivity analyses.

Population-based age-specific mortality rates were obtained from China Population & Employment Statistics Yearbook, 2014. The rates were transformed to the probabilities by the formula embedded in TreeAge to predict deaths due to the other causes.

2.2.4. Costs

The cost of the 3-dose 5 μg series was determined at 17 Chinese dollar (CN$), shifting between 14 and 20 CN$, according to