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Brief Reports

Research on optimal immunization strategies for hepatitis B in different endemic areas in China

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INTRODUCTION

At present hepatitis B vaccine immunization is an unique effective measure for controlling hepatitis B. It is important to determine optimal immunization st rategy for controlling HB and to rationally allocate health resources. From t he angle of health economics, cost-effective analysis (CBA) is used for the eva luation of economic benefit of the immunization strategies implemented in different endemic areas of HB in China in order to provide the evidences for decision-making and revision of the current HB immunization strategy.

MATERIALS AND METHODS

Basic data

The data for low and medium endemic areas of HB, involving morbidity and mortality of HB and liver cancer, cost of HB vaccine administration, overage personal income, GNP, and expenses for medical treatment of patients with acute, chronic hepatitis B and hepatocellular carcinoma, were collected from the medical literature[1,2]. The corresponding data related to heavy endemic area were obtained from the survey.

Definition of immunization strategies and protective effectiveness

The principal immunization strategies currently implemented in China and their effectiveness, which were used as the basis for evaluation, were selected from the related literature[3,4] for the sake of fair comparison between the different endemic areas. The definition of these strateg ies is as follows: ① Low-dose immunization strategy is defined as without maternal predelivery HBeAg and HBsAg screening, and infancy vaccination with three or four doses (one dose of booster) of 10 μg plasma-derived hepatitis B vaccine, and yielding a protective effectiveness of 85%. ② Based on maternal predelivery HBeAg and HBsAg screening, high-dose immunization strategy is known as infancy vaccinatio n with one of the following regimens: infant with maternal HBeAg- and HBsAg-negative only receives three doses of 10 μg plasma-derived hepatitis B vaccine; infant with maternal HBeAg and/or HBsAg-positive receives one dose of 30 μg and two doses of 10 μg plasma-derived hepatitis B vaccine; or three doses of 20 μg plasma-derived hepatitis B vaccine and one dose of hepatitis B immune globin (HBIG); or three doses of 20 μg and one dose of 10 μg (for booster) plasma-derived hepatitis B vaccine. All provided a protective effectiveness of 90%.

Definition of heavy, medium and low endemic areas

The range of HBsAg-positive rate for heavy, medium and low endemic areas of HB is defined as over 11%, from 5% to 10%, and less than 4% respectively. Longan County, Jinan City and Beijing were selected as the representative areas for the heavy, medium and low endemic levels of HB in China, respectively. The HBsAg- positive rate for the whole population and pregnant women was 18. 0% and 11.9% in Longan County, 7.59% and 5.40% in Jinan City, and 2.0% and 1.4% in Beijing, respectively. The data collected from these three places were used for CBA.

Study methods

CBA method was used to compare the data of economic benefit between the different places. Comprehensive weighted score analysis (CWSA) was made for determining the optimal immunization strategy. Definition and calculation formula relative to four scales for evaluation of the strategies are as follows: (a) proportion of individuals with HBsAg

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carriage prevented among imm unized population: HBsAg-positive rate before immunization-HBsAg-positive rate after immunization = HBsAg-positive rate before immunization × protective effectiveness; (b) net benefit (NB) = total benefit-total cost; (c) benefit cost

ratio (BCR) =

here, the signal B, denotes benefit; C_t, cost; *r*, discount rate; *t*, time; *n*. lifetime saved. (d) Direct BCR (DBCR) was known as a BCR which only involved the expenses of medical treatment in hospital. The basic principle and procedure of CWSA: First, four kinds of standards, A,B,C,D, used for assessment of every strategy to endemic areas of HB were defined in terms of different weight score (from 0 to 4) of 4 scales. Standard A was designated as comprehensive effectiveness in four scales: 4 scores (very important) to scale I (HBsAg) which denoted the reduced proportion of HBsAg-positive rate between pre- and post-vaccination; 1 score (less important) to scale II (NB); 3 scores (important) to scale III (BCR), and 2 scores (fairly important) to scale IV (DBCR). Standard B: 4 scores to scale HBsAg; 3 scores to scale NB; 2 scores to scale BCR; and 1 score to scale DBCR. Standard C: 4 scores to scale HBsAg; 3 scores to scale NB; 3 scores to scale BCR; and 0 score (not important) to scale DBCR. Standard D: 0 score to scale HBsAg; 4 scores to scale NB; 4 scores to scale BCR; and 3 scores to scale DBCR. Then, the score rank for four sca les was calculated according to their corresponding value in each strategy, the maximal score of any scale in all strategies was 10. The calculation of the score rank was that a measured or estimated value of the scale in each strategy was divided by the greatest measured or estimated value of this scale among all strategies being compared, then multiplied by 10. The total comprehensive scores for each strategy was calcu lated by the following formula: score rank for each strategy × weighted score for each scale. Finally, based on the same standard, for example, B, the total comprehensive scores for all strategies were compared to screen a stra tegy with maximal scores. The strategy possessing greatest total comprehensive scores in all standards evaluated was considered as the optimal one.

Data analysis

All data was analyzed with the software of version SAS 6.0 and Excel 5.0.

RESULTS

Benefit from hepatitis B vaccination of different strategies in differ ent endemic areas

Benefit of the low-dose strategy in three places CBA was conducted based on the actual epidemiologic data of Longan County, Shanghai and Jinan City, and assuming that after the implementation of the infancy low-dose strategy same protective effectiveness of 85% and coverage of 100% could be yie lded in these places. The results indicated that the outstanding benefit was obtained for all places inspite of their different economic development level a nd different endemicity. Longan had a lower value of benefit scales compared with Shanghai and Jinan except the DBCR scale. The greatest value of dif ference between BCR and BCR excluding the cost of liver cancer was found in Long an (Table 1).

Table 1 Benefit of HB vaccination of the low-dose strategy for three places with different economic development level and different endemicity

	Place		
	Longan	Shanghai	Jinan
HBsAg-positive rate before vaccination (%)	18.0	10.2	7.6
No. of neonates in 1987	7666	12 000	18 519
Direct benefit*	286	345	562
Indirect benefit*	683	1571	1852
Total benefit*	969	1916	2414
Total cost*	18	22	42
Net benefit*	951	1893	2372
BCR	52.7	85.8	57.9
DBCR	15.5	15.4	13.5
BCR excluding cost of liver cancer	23.6	67.9	34.8
DBCR excluding cost of liver cancer	9.2	14.2	10.1
HBsAg-positive rate after vaccination (%)	3.1	2.2	1.5

*10 000 Yuan RMB.

Comparison of benefit from different strategies in three places Assuming that different immunization strategies had been implemented in each place, the results of CBA for three places showed that the low-dose strat egy in Longan and Shanghai would provide the highest values in both scales, BCR and DBCR; the high-dose strategy (30 μg + 10 μg × 2 regimens) in Jinan would yield a slightly higher BCR value compared with the low-dose strategy, 55.35 *vs* 54.52; and if exclud ing the influence of difference of economic level between the places (assuming that average personal income for three places was the same i.e.10 000 in 1998), Longan would have a greater economic benefit, BCR, than Shanghai and Jinan.

Determination of the optimal immunization strategy in different endemic areas of HB

Analysis of sensitivity Based on the assuming parameters invo lving birth number (10 000), coverage (100%), screening proportion (90%), and sensitivity for screening (90%), the influence of changing endemicity level and strategies on benefit was determined. The results indicated that if the same immunization regimen and strategy was adopted, rank of NB value for every strategy would be seen in order of medium, heavy and low endemic

areas; if BCR of the changing immunization strategies in same endemic area was compared, the low-dose strategy for all endemic areas would yield the greatest BCR and DBCR compared with other strategy, leading to BCR value of 49.91, 54.53 and 37.68 for heavy medium and low endemic area respectively; and DBCR of 14. 63, 12.69 and 5.61 for corresponding three endemic areas. No matter which stra tegy was taken, the greatest difference between DBCR and the BCR excluding liver cancer might be seen certainly in the heavy endemic area; the high-dose strategy would yield the greatest NB compared with other strategy in any endemic area.

Comprehensive weighted score analysis Total comprehensive scor e for each strategy of different endemic areas were calculated according to four scales of standard, A, B, C, D. The results indicated that when the goal of e xpectation (representative of standards A, B, C) was to decrease HBsAg-positive rate in general population, the low-dose strategy yielded the highest total co mprehensive score. Even through ignoring the decrease of HBsAg-carriage, i.e. only concerning the economic benefit (representative of standard D), the low-dose strategy still yielded the highest total comprehensive score in different endemic areas. But whichever the four standards, the regimen of 10 μg ×3 + HBIG classified into the low-dose strategy always had the least comprehensive score, compared with any regimen of both low and high-dose strategies. The details are shown in Table 2.

Table 2 Comprehensive weighted score analysis of the immunization strategies in different endemic areas

Endemic-area	Immunization strategy	Standard			
		A	B	C	D
Heavy	10 μg × 3	97.3	96.2	96.2	107.9
	10 μg × 4	84.7	88.5	88.5	90.2
	10 μg × 3 + HBIG	83.4	89.9	89.9	86.5
	30 μg + 10 μg×2*	93.1	95.9	95.9	100.4
	20 μg × 3 + 10 μg*	90.6	94.3	94.3	96.8
	20 μg × 3 + HBIG*	91.4	94.8	94.8	97.9
Medium	10 μg × 3	97.3	96.2	96.2	107.9
	10 μg × 4	84.7	88.5	88.5	90.2
	10 μg × 3 + HBIG	80.5	88.1	88.1	82.4
	30 μg + 10 μg×2*	92.6	95.6	95.6	99.6
	20 μg × 3 + 10 μg*	90.2	94.1	94.1	96.3
	20 μg × 3 + HBIG*	91.2	94.7	94.7	97.7
Low	10 μg × 3	97.3	96.3	96.3	108.0
	10 μg × 4	84.7	88.5	88.5	90.2
	10 μg × 3 + HBIG	78.1	86.6	86.6	79.0
	30 μg + 10 μg × 2*	90.8	94.5	94.5	97.1
	20 μg × 3 + 10 μg*	88.3	92.9	92.9	93.6
	20 μg × 3 + HBIG*	89.6	93.7	93.7	95.4

*High dose strategy.

DISCUSSION

The results of CBA and sensitivity analysis on the actual data from Longan, Shan ghai and Jinan indicated that the low-dose strategy yielded higher NB and BCR in Shanghai and Jinan with higher level of economic development; and DBCR in Longan was slightly higher than that in Shanghai and Jinan after excluding indirect benefit; and the distribution of HBsAg-positive rate in these three places was positively correlated with their DBCR, suggesting that the higher the endemicity level was, the bigger the DBCR obtained; the difference between BCR and BCR exclud ing expenses of liver cancer in Longan was the greatest compared with thatin other two places, and the half of total expenses was used for the treatment of liver cancer in Longan, revealing that a significant economic benefit would be obtained in hyperendemic area of liver cancer assuming that the morbidity of liver cancer could be prevented through the HB vaccination. It is demonstrated from the results mentioned above that the low-dose regimen is an optimal strategy in economic benefit and hepatitis B control for areas with different endemic and economic levels/ However, the strategy, i.e., the maternal HBVMs screening before d elivery and high dosage vaccination (30 μg + 10 μg × 2), should be adopted to im prove the protective effectiveness of HB vaccine. Also, the results of CWSA use d for determining an optimal strategy demonstrated that for any endemicity level the low-dose strategy yielded the maximal comprehensive score compared with other strategies, providing same conclusion with CBA based on the actual data.

It is recommended that in different endemic areas of hepatitis B in China, the high-dose strategy is suitable for the econom ically developed areas in obtaining better protective effectiveness in decreasing HBsAg-positive rate. However, the low-dose strategy is optimally used for poor rural areas based on its outstanding economic benefit and better protection against HBV.

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