

H2 strain attenuated live hepatitis A vaccines: protective efficacy in a hepatitis A outbreak

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Subject headings hepatitis A/prevention and control; vaccines, attenuated; vaccines, inactivated; viral hepatitis vaccines; disease outbreaks; protective efficacy

Zhao YL, Meng ZD, Xu ZY, Guo JJ, Chai SA, Duo CG, Wang XY, Yao JF, Liu HB, Qi SX, Zhu HB. H2 strain attenuated live hepatitis A vaccines: protective efficacy in a hepatitis A outbreak. *World J Gastroentero*, 2000;6(6):829-832

Abstract

AIM To investigate the protective efficacy of H2 strain attenuated live hepatitis A vaccines (H2-strain vaccines) in hepatitis A (HA) outbreaks.

METHODS With the permission of their parents, 5551 pre-school and grade 1-3 primary school children were inoculated with 1 dose ($10^{6.5}$ TCID₅₀) of H2-strain vaccines in a nonrandomized, controlled trial conducted in Fucheng County, Hebei Province in May 1997. Another 6485 children in the same grades and compatible in gender and age were enrolled as controls. Epidemiological and serological survey was conducted to evaluate the protective efficacy of the vaccines. ELISA was used to detect serum IgM anti-HAV.

RESULTS HA outbreak started in early May 1998, peaked in the middle of the same month, and lasted about 80 days. Overall 302 HA cases were found, 192(63.58%) were 5-9 years old. One vaccinee and 25 control cases were found to have hepatitis A, which account for 0.28% (1/356) and 5.92% (25/422) of all vaccinees and controls in the 14 villages, respectively. The

protective efficacy of vaccines was 95.27% (95% CI: 85.83%-104.72%). In subjects tested for anti-HAV IgM from 13 villages, 1(0.40%) overt and 11(4.06%) asymptomatic HAV cases were found in 271 vaccinees, but 21(6.69%) of overt and asymptomatic ones were found in 314 controls.

CONCLUSION H2 strain vaccines were excellent in preventing overt hepatitis A, but not so effective in preventing asymptomatic hepatitis A virus infection. A booster dose might be needed to get permanent reliable immunity.

INTRODUCTION

Hepatitis A (HA) is the most common infectious diseases in China. Its notified incidence rates in recent years were 10-20 per 100 000. As severe under-reporting existed, the real incidence rates were possibly 10-fold higher than the notified rates. Community-wide outbreaks occurred at intervals of 5-10 years. The development of HA vaccine made this disease preventable. Two kinds of HA vaccines are available now in China: inactivated HA vaccine and live attenuated HA vaccine. Inactivated HA vaccine, with good tolerance, stability and immunogenicity, proved to be a good selection in developed countries^[1-3]. But most Chinese people refuse them for its considerably high cost. Live attenuated HA vaccine, with only about 1/10 expenses of the inactivated ones, proved to be the best alternatives. China-made H2 strain live attenuated HA vaccine (H2-strain vaccine), has been studied and on trial for more than 10 years, now is the best available one in China. Previous studies showed that it was safe, immunogenetic and had satisfactory preventive effect on sporadic HA^[4,5].

In May 1997, a controlled trial was performed in Fucheng County of Hebei Province, China, 5551 children were inoculated with H2 strain vaccine. Another 6485 children were set as controls. One year later, an outbreak of HA occurred in this county. We conducted an epidemiological and serological survey on this outbreak to evaluate the preventive effect of H2 strain vaccine on HA outbreaks.

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Supported by national ninth five-year study program for tackling key scientific problems, No.03-01-01

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Received 2000-06-28 Accepted 2000-07-16

METHODS

Vaccination

The H2 strain HA vaccine ($10^{6.5}$ TCID₅₀, 1mL) used were produced by Zhejiang Academy of Medical Sciences. Subjects were children from pre-school class and grade 1-3 primary school who had no history of viral hepatitis or HA vaccination. One dose of vaccine was inoculated to each of the 5551 children with the permission of their parents. Another 6485 children who were in the same grade but refused to accept the vaccines were enrolled as controls. The two groups were compatible in gender and age. The vaccinations were finished in May 1997.

Criteria of diagnosis

Overt HAV infection or HA ① Those with symptoms and signs of acute hepatitis (fever, jaundice, anorexia, vomiting, abdominal discomfort, etc.), elevated serum alanine aminotransferase (ALT) levels and a positive test for serum anti-HAV IgM; ② with negative anti-HAV IgM for untimely serum collection, with significant epidemiological contact history to HA and without positive test results of hepatitis B, diagnosed by town clinics or higher level hospitals.

Asymptomatic or subclinical HAV infection Those who were seropositive for anti-HAV IgM but had no symptoms of hepatitis.

Novel HAV infection Those who were diagnosed as overt or asymptomatic HA cases.

Collection of HA cases

In order to avoid under-reporting, special persons were designated to be in charge of reporting HA cases in each village, school or town clinic, on the basis of previously existed infectious diseases reporting system. HA cases were collected mainly through the following ways: ① routine infectious disease notification; ② periodical review the results of outpatient and laboratory examinations in local hospitals; ③ periodical meeting of designated physicians in the town or village; and ④ direct visit to villages and schools where HA cases were found by trained specialists.

Interview of HA cases

All the HA cases from the trial population and some others from HA amassed villages were interviewed by specialists. A questionnaire was filled out for each case and his/her parents. Three mL serum sample was drawn from each of them for the detection of anti-HAV IgM.

Serological study

A serological survey was performed on trial populations from 13 villages (including 10 of the 14 villages with HA cases and 3 other villages). Serum

samples were obtained from 80.2% (271/338) of the vaccinees and 83.3% (314/377) of the controls. Serum anti-HAV IgM was detected by ELISA kits made by Beijing Wantai Bio-medical Limited Company, batch number: 8080104.

Analysis

All data from epidemiological survey or serological test were input into FoxBASE database. ANOVA (variances to be homogeneous) or Kruskal-Wallis one way analysis (variances to be different) was used to compare the means. Chi square test was used to compare the rates by more than two. Mantel-Haenszel (M-H) test or Fisher exact 1-tailed test was used to compare two rates. All these analyses were done by EPI INFO 6.0 software. Calculation of vaccines' protective efficacy (VE): $VE = (P_1 - P_2) / P_1 \times 100$. The 95% confidence intervals (95% CI) of $VE = VE(\%) \times 1.96 \times (1/P_1^2 \times P_2 Q_2 / N_2 + P_2^2 / P_1^2 \times P_1 Q_1 / N_1)^{1/2}$. P_1 and N_1 are the morbidity rate and sample number of control group, $Q_1 = (1 - P_1)$; P_2 and N_2 are the morbidity rate and sample number of vaccine group, $Q_2 = (1 - P_2)$.

RESULTS

Status of vaccination

With 307 003 population, Fucheng county was divided into 10 administrative towns, or further, 615 administrative villages. The distribution of vaccine group and control group was shown in Table 1. There were 5551 subjects in the vaccine group, which account for 1.8% of the whole population or 7.74% of the 1-15 year-old children in the county.

Table 1 Status of H2 strain vaccines vaccination in Fucheng county in May 1997

Towns	No. of villages	Whole population	Population aged 1-15	No. of trial villages	Vaccine group	Control group
Fucheng	79	50847	11815	28	1224	1457
Manhe	38	26958	6563	31	560	920
Gucheng	76	40083	8375	44	694	1087
Cuimiao	84	40818	8931	40	1155	1133
Matou	82	37005	8817	32	653	352
Xiakou	56	29030	7123	14	265	297
Wangji	58	21468	5607	32	431	525
Dabai	46	19154	4369	16	201	344
Jianqiao	39	17440	4437	8	196	109
Jiangfang	57	24200	5717	10	172	260
Total	615	307003	71754	255	5551	6485

Features of the outbreak

Cases of HA found during the first 9 months of 1998 are shown in Table 2. The incidence rates remained in sporadic level during the first 4 months (<10 cases each month) and an increasing tendency could be noticed in April. The morbidity began to rise significantly in the first ten days of May (46 cases), peaked on the next ten days (154 cases), lowered to sporadic level on the last ten days of June, and another small peak appeared on the second ten days

in July. The outbreak lasted about 80 days with 302 HA cases found. The incidence rate was 98.37/100 000. Two hundred and eighty-seven cases (95.03%) were found in the main outbreak period about 50 days (from the beginning of May to the second ten days of June), nine cases found in the second ten days of July might be secondary cases.

Most (255, 84.44%) HA cases were found in Gucheng town where the incidence rate reached 638.18/ 100 000. Others were found in Jianqiao (19 cases), Jiangfang (19 cases), Fucheng (6 cases), Manhe (2 cases) and Wangji (1 case) towns. The incidence rates in the 5 towns were 108.95, 78.51, 11.80, 7.42 and 4.66 per 100 000, respectively. No case was found in the other 4 towns.

The mean age of all HA cases was 8.81 years±6.87 years(ranged 1 year-63 years,median 7 years, most cases (252, 83.44%) aged 3 years-11 years and 192(63.58%) aged 5 years-9 years. More male cases were found than female ones (1.65:1) Table 3.

We tested 127 1-15 year old HA cases and 112 (88.19%) were anti-HAV IgM positive. The results are shown in Table 4. The mean ages of the 4 groups were not statistically different ($F=2.03$, $P>0.05$, ANOVA). Following the prolonging of the interval between HA attack and interview, decreasing trends were observed in anti-HAV IgM positive rate ($r=-0.7811$, $P>0.05$, linear correlation) and S/CO of anti-HAV IgM ($r=-0.9948$, $P<0.01$, linear correlation), the former being not statistically significant.

Table 2 HA cases found during the first 9 months in 1998

Months	First ten days	Second ten days	Last ten days	Total
January	1	0	0	1
February	1	3	3	7
March	2	3	0	5
April	5	0	4	9
May	46	154	48	248
June	26	13	3	42
July	3	9	3	15
August	3	3	2	8
September	0	1	0	1

Table 3 Age and sex distribution of HA cases found in Fucheng County during the HA outbreak in 1998

Age	Male	Female	Total
1	2	1	3
2	2	1	3
3	7	4	11
4	12	3	15
5	20	16	36
6	31	19	50
7	28	17	45
8	20	10	30
9	18	13	31
10	12	6	18
11	9	7	16
12-14	13	4	17
15-24	10	7	17
25-34	2	3	5
35-63	2	3	5
Total	188	114	302

Table 4 Results of serum IgM anti-HAV in 138 1-15 year old HA cases found in the HA outbreak in Fucheng, 1998

Days between HA attack and interview	No. of tested	Age (mean±SD)	Positive		
			No	%	S/CO(mean±SD)
1-29	12	6.33±2.57	12	100.00	10.33±1.22
30-59	46	8.11±2.39	44	95.65	7.12±2.50
60-89	61	7.36±2.52	49	80.33	5.09±2.71
90-119	8	7.13±1.25	7	87.50	2.80±2.24
Total	127	7.52±2.45	112	88.19	6.31±3.04

Protective efficacy of vaccines (VE)

In the HA outbreak, twenty-six HA cases were found in trial population, one in vaccine group and 25 in control group. They were distributed in 14 trial villages. The incidence rates of vaccine group and control group in the 14 villa ges were 0.28%(1/356) and 5.92%(25/422), respectively. The VE was 95.27% (95% CI: 85.83%-104.72%), Table 5.

Table 5 Incidence rates of the trial population in the 14 villages invested

Villages	Vaccine group			Control group		
	No. of Subjects	No. of HA cases	Incidence rate	No. of Subjects	No. of HA cases	Incidence rate
Dongni	17	0	0.00	29	1	3.45
Dongyi	32	0	0.00	34	3	8.82
Fuzhuang	0	0	0.00	9	1	11.11
Gengzhuang	5	0	0.00	10	3	30.00
Gucheng	48	0	0.00	62	3	4.84
Haitun	19	0	0.00	20	1	5.00
Houxong	32	1	3.13	26	2	7.69
Lihui	35	0	0.00	27	1	3.70
Liqiao	48	0	0.00	23	2	8.70
Liuhui	16	0	0.00	26	1	3.85
Liunan	35	0	0.00	40	2	5.00
Mengzhuang	4	0	0.00	49	3	6.12
Qiansong	40	0	0.00	42	1	2.38
Dainan	25	0	0.00	22	1	4.55
Total	356	1	0.28	422	25	5.92

We tested 80.2%(271/338) subjects of vaccine group and 83.3%(314/377) subjects of control group in 13 villages. The sampling rates of the two groups were not significantly different ($\chi^2=1.16$, $P>0.28$, M-H test). Results are shown in Table 6.

Table 6 Comparison between vaccine group and control group on HAV infection features

Groups	No. of Subjects	IgM anti-HAV(+)		Clinical HA cases		Subclinical infection		Novel infection		Clinical/subclinical ratio
		No.	%	No.	%	No.	%	No.	%	
Vaccine	271	12	4.4	1	0.4	11	4.1	12	4.4	1:11
Control	314	39	12.4	21	6.7	21	6.7	42	13.4	1:1
Relative risk		2.8		18.1		1.7		3.0		6.0
95%CI		1.5-5.3		2.5-133.9		0.8-3.4		1.6-5.6		0.9-40.2
χ^2		11.7		16.0		1.9		13.9		
P value		<0.001		<0.001		>0.5		<0.001		<0.01
Statistical method		M-H		M-H		M-H		M-H		Fisher

From Table 6 we found that anti-HAV IgM positive rate, HA incidence rate, HAV novel infection rate and ratio between HAV overt infection and asymptomatic infection were all significantly higher in control group than in vaccine group. HAV asymptomatic infection rate in control group was also higher than in vaccine group, but not statistically significant.

DISCUSSION

H2-strain vaccine was developed by Zhejiang Academy of Medical Sciences and proved to be safe and immunogenic^[6,7]. Its VE on sporadic HA was studied in a few trials. The results showed that it was dose-dependent. In early years, the titre of live HA vaccines was considerably low ($10^{5.0-5.5}$ -TCID₅₀) and the VE was only 79% - 90%^[8]. Researchers recommended $\geq 10^{6.5}$ TCID₅₀ as a standard dose in recent years. Large-scale trial showed that a dose of H2-strain vaccine $10^{7.0}$ TCID₅₀ induced 94.84% anti-HAV seroconversion and 100% VE^[5]. Our study showed that a dose of H2-strain vaccine ($10^{6.5}$ TCID₅₀) could induce >95% VE in HA outbreak. The result was comparably satisfactory.

Although only 1 HA case was found in vaccine group, 11 subclinical HAV infection cases were observed. This was understandable considering the low geometric mean titre (GMT, about 100mIU/mL)^[5] of serum anti-HAV after inoculation of live vaccines. We concluded that the vaccine was not so effective in preventing HAV infection as in preventing overt HA. The natural HAV infection 1 year after vaccination might act as a natural booster dose and induce life-long immunity. This was an ideal result. But the result might be different if the outbreak comes a few years later. The necessity of a booster dose, therefore, remains to be further studied.

The occurrence of the HA outbreak showed that 7.74% coverage of HA vaccine in children aged 1-15 year's was not enough to prevent HA outbreaks. Since the beginning of reporting viral hepatitis (HV) by type in 1990, only 1 HA outbreak

(1992, the incidence rate was 176/ 100 000) was observed in Fucheng County. The HA incidence rates remained at sporadic level between 1993 and 1997 (4.89-44.63/100 000). The accumulation of susceptible subjects might be the basic reason for the HA outbreak in 1998.

Although HA cases were found in 6 of the 10 towns in the county, most cases were found in Gucheng Town. Another HA outbreak will probably occur in the other 9 towns in a few years. So HA vaccination was still needed in Fucheng County. As the outbreak occurred in summer and most cases were less than 10 years of age, we suggested that another vaccination program be performed among children aged below 10 in next spring in the county except Gucheng town.

The fairly high positive rate (88.19%) of serum anti-HAV IgM in cases tested within 4 months after the attack showed that it was feasible to use anti-HAV IgM as an index in the retrospective study of HA outbreaks which occurred in recent 4 months.

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Edited by You DY and Ma JY