

# 甲型肝炎减毒活疫苗(LA-1株)大规模免疫长期效果观察

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## Long-term immunogenicity and protective efficacy of a live attenuated hepatitis A vaccine (LA-1 strain)

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## Abstract

**AIM:**To evaluate the long-term protective efficacy following a large scale immunization with a live attenuated hepatitis A vaccine (the LA-1 strain) and immune persistence of the vaccine with different immunization schedules.

**METHODS:**A randomized controlled double-blind study was conducted in 212 985 children between 1.5 and 10 years of age from 8 counties in Guangxi province (10 0735 in vaccine group and 112 250 in control group). Vaccine group was received one dose of HAV vaccine of 10<sup>6.75</sup> TCID<sub>50</sub> (LA-1 strain, China). Surveillance of the incidence of hepatitis A in the two groups was started 1 month after vaccination. To evaluate the persistence of antibodies, 156 children of

6-9 years old with hepatitis A antibody negative were divided into 3 groups with equalities in age and sex. Group A was given one dose of the vaccine, Group B and C were immunized according to 0,6 and 0,12 schedules respectively. During follow-up of every individual, the blood specimens were collected at 6, 12, 24 and 36 months after immunization in Group A and 12, 24 and 36 months after first dose and 1 month after second dose in Group B and C. Anti-HAV levels were expressed as GMTs in mIU/ml by serial immunoglobulin dilutions (WHO standard) and HAVAB-Imx kit (Abbott Lab, USA).

**RESULTS:**During a follow-up for 36 months, 71 cases of symptomatic HAV infection were found in the control and 2 in the vaccine group (63.25/10<sup>6</sup> vs 1.99/10<sup>6</sup> respectively). The protective efficacy was estimated at 96.85 % with 95 % lower confidence limit of 92.4%. The antibody positive rate in Group A after 6-24 months was 88.6-91.4 %, the GMT was 105-106 mIU/ml, but each of those decreased to 80.0 % and 99.20 mIU/ml after 36 months. GMT reached to the top in Group B and C 1 month after the second dose, 1 024.63 mIU/ml and 3 463.21 mIU/ml respectively. But during the time from top GMT to 24<sup>th</sup> month, the GMT of Group B and C decreased rapidly to about 59.4 % and 83 % respectively, and it continually declined slowly at 36<sup>th</sup> month to 459.68 mIU/ml and 506.23 mIU/ml, which were 6 % and 15 % lower than that at 24<sup>th</sup> month. It showed that the antibody level in Group B and C after 2 doses were significantly higher than that in Group A from beginning to end, at 36<sup>th</sup> month the GMT of Group B and C were 4.6 times and 5.1 times to that of Group A, and the antibody positive rate (97 %) was higher than that of Group A (80 %) at the same time.

**CONCLUSION:**A single dose of live attenuated hepatitis A vaccine can come into being high and persistent protection against hepatitis A. Booster dose induces an immune response which persists for at least three years in 97 % of the subjects. The high GMT still present at month 36 predicts a long-term persistence of antibody.

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## 摘要

**目的:**观察甲型肝炎减毒活疫苗(LA-1株)大规模接种的长期保护效果和不同免疫程序的免疫持久性。

**方法:**212 985例1.5-10岁儿童随机分成疫苗组和对照组。疫苗组每人接种1针甲肝疫苗,接种1 mo后观察两组甲肝发病情况。6-9岁的甲肝抗体(抗HAV)阴性儿童156例按年龄和性别均衡分为A、B、C组, A组接种1剂疫苗, B组按0、6 mo、C组按0、12 mo程序分别接种2剂疫

苗, 然后随访各组抗 HAV 变化。

结果:甲型肝炎 3 a 累积发病率在对照组为 63.25/10 万(71/112 250), 疫苗组为 1.99/10 万(2/100 735), 保护率 96.85 % (95 %CI 下限为 92.44 %)。A 组免疫后 6、12、24、36 mo 抗 HAV 阳性率分别为 91 %、89 %、89 %、80 %, 抗体几何平均滴度(GMT)分别为 106、105、106、99 mIU/ml; B 组 7、12、24、36 mo 的阳性率分别为 100 %、98 %、95 %、98 %, GMT 分别为 1204、773、489、459 mIU/ml, C 组 12、13、24、36 mo 的阳性率分别为 82 %、100 %、100 %、97 %, GMT 分别为 92、3 463、596、506 mIU/ml。B、C 组在第 36 个月的 GMT 分别是 A 组的 4.6 倍和 5.1 倍, 阳性率高于同期 A 组(P = 0.008)。

结论:甲肝减毒活疫苗(LA-1株)1针免疫有高而持久的保护效果和免疫原性; 2针免疫可显著提高其免疫持久性; 0、6 程序与 0、12 程序的长期免疫效果相同。

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<http://www.wjgnet.com/1009-3079/11/693.asp>

## 0 引言

我国是病毒性肝炎高流行区, 其中甲型肝炎病毒(HAV)感染居各型肝炎病毒之首<sup>[1]</sup>。甲型肝炎(简称甲肝)是儿童肝炎和肝炎暴发流行的主要型别<sup>[2,3]</sup>, 较长时期内预防甲肝的暴发或流行任务仍十分艰巨<sup>[1]</sup>。用甲型肝炎疫苗实施主动免疫已证明是预防和控制甲型肝炎的最有效手段<sup>[4-10]</sup>。我国研制的甲肝减毒活疫苗 LA-1 株在滴度达到  $10^{6.75}$ TCID<sub>50</sub> 时, 经大规模人群观察, 安全性、近期免疫原性和保护效果良好, 与国外甲肝灭活疫苗近期效果相似<sup>[11]</sup>。本文报告该疫苗在农村地区儿童中大规模接种的长期保护效果和不同免疫程序的免疫持久性, 为甲肝疫苗免疫策略的制订提供科学依据。

## 1 材料和方法

1.1 材料 广西农村人群中甲型肝炎感染率为 84 %, 感染上升速度最快年龄段在 1-5 岁。本课题所在的 8 个县(市)甲肝年发病率 1991/1995 年 2-9 岁人群中约为 30/10 万 - 170/10 万, 对其中两个县 1-10 岁儿童 9 400 人免前血清学调查, 甲型肝炎易感率为 80-85 %。

### 1.2 方法

1.2.1 疫苗保护效果的研究 在柳城县和隆安县采用个体随机分组方法, 对 114 588 名 1.5-10 岁的儿童按个体出生月份单数或双数随机分成甲肝疫苗接种组(58 955 名)和对照组(55 633 名), 其中 7 316 名为经血清学筛查确定的甲肝易感(即血清抗 HAV-IgG 阴性)儿童: 接种组和对照组分别为 3 771 名和 3 545 名; 在田阳等 6 县(市)对 120 105 名 1.5-10 岁儿童不做免前筛检, 以行政村

或班级为单位, 按整群随机方法分成甲肝疫苗组(63 488 例)和对照组(56 617 例)。疫苗组每人接种 1 针甲肝疫苗。儿童家长、现场的疫苗接种工作人员均不了解分组情况。免后 1 mo 开始对两组的甲型肝炎发病情况随访 3 a。凡有症状和/或体征、谷丙转氨酶(ALT)异常、抗 HAV-IgM 阳性者, 确诊为临床甲型肝炎病例。

1.2.2 不同免疫程序研究 在柳城县 1 个小学疫苗组中, 对血清抗 HAV-IgG 阴性的 156 名儿童分为 A、B、C 3 个组, 各组人数分别为 35、62、59 人, 平均年龄分别为 7.6 岁、6.6 岁、7.3 岁, 男女之比分别为 0.8 : 1、0.8 : 1、1.4 : 1。A 组接种 1 剂甲肝疫苗; B 组按 0、6 mo 程序, C 组按 0、12 mo 程序分别接种 2 剂甲肝疫苗。A 组于接种后 6 mo、12 mo、24 mo、36 mo, B 组和 C 组均在第 2 针接种后 1 mo、首针接种后 12 mo、24 mo、36 mo 定人随访采血, 无菌分离血清, 冻存于 -20 °C, 空运至实验室检测血清甲肝抗体(抗 HAV-IgG)。检测工作均在 2 wk 内完成。血清一般不反复冻融, 以保证标本中抗体滴度不因反复冻融而下降。

1.3 疫苗 疫苗为卫生部长春生物制品研究所生产的甲型肝炎减毒活疫苗 LA-1 株, 每剂含量  $10^{6.75}$ TCID<sub>50</sub>。接种部位在上臂皮下。

1.4 检测 免前用 ELISA 检测筛选抗 HAV-IgG, 试剂盒购自浙江省医科院。免后随访血清抗 HAV-IgG 用 Abbott 公司的 IMx mEIA 试剂及相应的自动检测仪检测, 以同时检测的不同浓度 WHO 标准抗体单位制成标准曲线, 换算出每毫升血中抗体毫国际单位(mIU/ml)。疑似病例的抗 HAV-IgM 检测用上海实业科华生物技术有限公司的 ELISA 试剂盒。

## 2 结果

2.1 保护效果 观察 3 a, 在随访对象 234 693 人中, 共报告疑似病例 248 例, 经实验室确诊, 73 例为临床甲型肝炎病例。其中对照组和疫苗组分别为 71 例和 2 例, 3 a 累积发病率分别为 63.25/10 万(71/112 250)和 1.63/10 万(2/122 443), 保护率 97.42 %, 95 %可信度下限为 93.4 %。

2.2 不同免疫程序的抗体水平 3 a 动态观察 A 组儿童在接种后 6-24 mo 的抗体阳性率和抗体几何平均滴度(GMT)基本维持在同一水平(88.6-91.4 % 和 105-106 mIU/ml), 第 36 个月时略有下降, 阳性率为 80.0 %, GMT 较第 24 个月下降 6 %, 为 99.20 mIU/ml(表 1)。

表 1 甲型肝炎减毒活疫苗(LA-1株)1针免疫后 3 a 的抗体变化(A组)

免疫后(mo)	检测数	抗-HAV		抗-HAV GMT	
		阳性数	阳性率 %	mIU/ml	95 % CI
6	35	32	91.4	106.31	69.77-162.00
12	35	31	88.6	105.09	73.15-141.22
24	35	31	88.6	105.77	74.97-149.23
36	35	28	80.0	99.20	71.75-137.16

B组(0、6 mo程序)和C组(0、12 mo程序)的抗体均在第2针接种后1 mo达到高峰, 然后各组GMT均呈先快后慢趋势下降, 第24个月, 分别比峰值下降了59.4%和83%,

第36个月较第24个月分别下降了6%和15%; 第36个月时B、C组的抗体水平趋于相同, 阳性率分别为97.6%和96.94%, GMT分别为459.68 mIU/ml和506.23 mIU/ml(表2).

表2 甲肝减毒活疫苗(LA-1株)2针免疫后3 a的抗体变化(B组、C组)

免疫后时间(mo)	B组(0、6 mo程序)					C组(0、12 mo程序)				
	n	S	SP(%)	GMT(mIU/ml)	GMT95 %CI	n	S	SP(%)	GMT(mIU/ml)	GMT95 %CI
7-	55	55	100	1 204.63	876.48-1 655.65	-	-	-	-	-
12-	54	53	98.1	773.15	43.15-1 100.54	60	49	81.7	91.92	66.15-127.00
13-	-	-	-	-	-	31	31	100.0	3463.21	2561.0-4 683.26
24-	56	53	94.6	489.12	339.85-703.98	34	34	100.0	596.57	456.47-779.66
36-	41	40	97.6	459.68	306-688.86	32	31	96.9	506.23	337.15-760.11

表3 甲肝减毒活疫苗(LA-1株)不同免疫程序的抗体水平比较

程序		A组	B组	C组
		1针	2针(0、6)	2针(0、12)
峰值	阳性率(%)	91.4	100	100
	GMT(mIU/ml)	106.31	1 204.63	3 463.21
免后24 mo	阳性率(%)	88.6	94.6	100.0
	GMT(mIU/ml)	105.77	489.12	596.57
免后36 mo	阳性率(%)	80.0	97.6	96.9
	GMT(mIU/ml)	99.20	459.68	506.23

由表3可比较不同免疫程序的抗体水平. 抗体阳性率峰值在B、C组均为100%, A组高为91.4%; 在GMT峰值上, B组是A组的11.3倍, C组是A组的32.6倍、B组的2.9倍. 在第36个月, B组和C组的GMT虽然已较峰值显著下降, 但仍分别是A组的4.6倍和5.1倍, 抗体阳性率为97%左右, 也高于同期A组(80%,  $\chi^2=7.11$ ,  $P=0.008$ ).

### 3 讨论

实施甲肝疫苗接种是减少甲型肝炎发病的最有效手段<sup>[12]</sup>. 国外甲肝灭活疫苗在泰国40 119例5-15岁儿童(易感率75%, 年发病率119/10万)中以随机对照方法观察3针免疫的保护效果, 随访5-10 mo, 保护率为97%(95%CI, 87-99%)<sup>[13]</sup>; 在美国的甲型肝炎高流行区对儿童实施甲肝疫苗常规免疫6 a, 疫苗保护率为98%(95%CI, 86-100%)<sup>[14]</sup>. 国产甲肝减毒活疫苗(LA-1株)滴度为 $10^{5.5}$ TCID<sub>50</sub>时, 在广西28 679例中小学生整群随机对照观察中, 1针免疫后第3年的保护率为78.8%<sup>[15]</sup>. 由于疫苗的滴度对于疫苗的保护效果至关重要, 近年来我国规定甲肝减毒活疫苗应不低于 $10^{6.5}$ CCID<sub>50</sub><sup>[16]</sup>. 本文在234 693例儿童中观察甲肝减毒活疫苗LA-1株在滴度达到 $10^{6.75}$ TCID<sub>50</sub>后1针免疫的第3年保护率为97.42%(95%可信限下限93.4%), 显著高于滴度为 $10^{5.5}$ TCID<sub>50</sub>时的3 a保护效果<sup>[15]</sup>, 与国外的甲肝灭活疫苗的保护效果<sup>[13,14]</sup>相似.

提示该疫苗滴度达到 $10^{6.75}$ TCID<sub>50</sub>时, 可获得高而持久的保护效果.

疫苗对甲型肝炎控制的有效期限取决于疫苗所能提供的保护期限<sup>[17]</sup>, 而后者与疫苗刺激产生的抗体水平密切相关. 甲肝灭活疫苗1针免疫时, 产生的抗体水平仅能提供短时间的保护, 而2针免疫后刺激的高水平抗体水平可提供长期保护<sup>[18]</sup>. 本文中, 甲肝减毒活疫苗接种2针后, 抗体GMT峰值达到1024mIU/ml(0、6 mo程序组)和3463mIU/ml(0、12 mo程序组), 与国外甲肝灭活疫苗2针免疫后达到的GMT峰值相当<sup>[19-23]</sup>, 第3年仍有97%的抗体阳性率和较高水平的抗体滴度, 预示着抗体有长期存在的可能. 尽管2针免疫诱导的抗体GMT达到峰值后会有大幅度回落, 但当他降至一定水平趋于稳定时, 抗体滴度在免疫后3 a仍达到1针的5倍左右, 抗体阳性率(97%)也显著高于1针(80%). 提示2针免疫可显著提高甲肝减毒活疫苗的免疫持久性, 与国产甲肝减毒活疫苗H<sub>2</sub>株观察结果一致<sup>[24]</sup>.

甲肝减毒活疫苗以不同程序进行2针免疫后, 所诱导的抗体水平在达到峰值后都呈先快后慢地下降, 与甲肝灭活疫苗以0、6 mo和0、12 mo程序免疫后的抗体滴度变化动态<sup>[25-29]</sup>相同. 说明虽然减毒活疫苗和灭活疫苗的免疫机制不同, 但以相同免疫程序接种后, 二者的抗体水平变化趋势是相似的. 本文中疫苗1针免疫后抗体缓慢下降趋势则与刘景晔 et al<sup>[30]</sup>在儿童中对该疫苗1针免疫后随访3 a观察到的抗体动态趋势一致.

甲肝减毒活疫苗(LA-1株)以不同程序免疫2针后, 抗体GMT峰值在0 mo、12 mo程序组显著高于0 mo、6 mo程序组, 与Vidor et al<sup>[31]</sup>对甲肝灭活疫苗的观察结果相同. 3 a随访结果显示, 甲肝减毒活疫苗0 mo、6 mo程序和0 mo、12 mo程序免疫效果是一样的. 虽然抗体滴度峰值在0 mo、12 mo程序组(3 463mIU/ml)显著高于0 mo、6 mo程序组(1 024 mIU/ml), 但随着免疫年限延长, 两组抗体水平趋于接近, 随访36 mo, 抗体滴度已十分接近(459.68 mIU/ml和506.23 mIU/ml), 抗体阳

性率亦如此(97.6%和96.9%)。说明甲肝减毒活疫苗(LA-1株)以这两种免疫程序均可产生良好的长期免疫效果。

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#### 4 参考文献

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