Original article

Hepatitis A virus vaccination strategy and pre-immunization screening of Bangladeshi children

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Abstract:

Background: HAV infection is endemic in many developing countries like India, Pakistan, Nepal etc. Several seroprevalence studies show high rates of sero-positivity among children by sub-clinical infection. Therefore mass vaccination against HAV has not been recommended in endemic countries. ***Objective***: To determine whether routine hepatitis A vaccination is indicated for all Bangladeshi children & also to know whether pre-vaccination screening is necessary. ***Materials & Methods***: Serum samples from 254 children aged between 1-15 years were tested for antibody (IgM & IgG) against hepatitis A virus (HAV) to determine the seroprevalence of HAV antibody and do a cost-benefit analysis for decision making about vaccination against HAV among the children of Bangladesh. ***Results***: Hepatitis A virus antibody was positive in 141 (55.5%) of 254 children. Age-specific sero-prevalence was 13 (23.2%) of 56 in 1-3 year,64 (55.2%) of 116 in 3-5 year, 39 (70.9%) of 55 in 5-10 year & 25 (92.6%) of 27 in 10-15 year age group. Cost benefit analysis showed that the total cost of screening followed by vaccination was almost 1.8 times less than the total cost of vaccination of all children without screening. ***Conclusions***: Majority of the children were found sero-positive against HAV around 15 year of age. Therefore mass vaccination against HAV may not be required for Bangladeshi children.

Key words: Hepatitis A virus (HAV); HAV seroprevalence; HAV vaccine

DOI: http://dx.doi.org/10.3329/bjms.v14i1.21561
Bangladesh Journal of Medical Science Vol. 14 No. 01 January'15. Page: 65-69

Introduction

Hepatitis A virus (HAV) infection occurs throughout the world but most common in developing countries.[1] In these countries with high endemicity, 90% of the population is infected by 10 years of age.[2] Here children are continuously exposed to the virus, which confers lifelong immunity.[3] In many developing countries like India, Pakistan, Nepal several sero-prevalence studies have shown high rates of sero-positivity among child by sub-clinical infection[4-9]. Therefore, mass vaccination against HAV has not been recommended in endemic countries.[10] Furthermore, Hepatitis-A vaccine is expensive. In Bangladeshi children, limited data are available regarding the sero-prevalence of HAV antibody.[11] In this context, the present study was designed to see the prevalence of HAV antibody (IgG & IgM) among children of different age group and to perform a cost benefit analysis study before formulating a vaccination strategy for the children of Bangladesh.

Materials & Methods

A cross sectional observational study was conducted from July 2008 to June 2009. Blood was collected at blood collection centers of Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital & Dhaka Shishu (Children) Hospital (DSH). A total of

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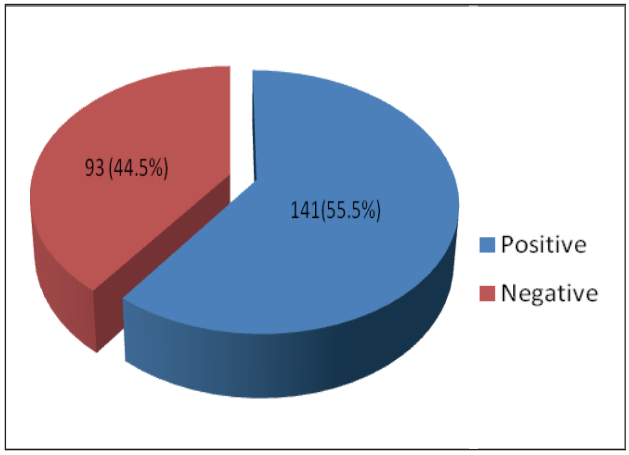
254 children aged 1-15 years (boys=139 & girls=115), who had no previous history of jaundice or hepatitis or Hepatitis A vaccination but attended OPD of these two hospitals for other illnesses were included in this study. The sample size was determined by the prevalence rates of neighburing countries with a similar socioeconomic condition (e.g., India & Pakistan) as there are no previous data on HAV prevalence particularly in the children of Bangladesh. With prior written consent, clinical history and relevant data were recorded and 2 ml of blood was collected from each of the study cases. Serum was separated, stored at -20°C and were tested for HAV antibody (IgG & IgM) by ELISA using the ELISA kit (DiaSorin Italy, ETI-AB-HAVK PLUS, no136, 01/2009) at the Department of Virology laboratory of BSMMU, Dhaka. The cut-off value was determined by the mean absorbance of the calibrator values. The presence or absence of anti-HAV was determined by comparing the absorbance values of unknown samples with the absorbance values below/above the cut-off values of the controls. For cost benefit analysis, pre-vaccination screening price was 2$ for each child & vaccine price along with vaccination charge was 15$ (Per dose).

A preformed semi structured data collecting form was used as a data collection instrument. Data were collected by researcher and analyzed by Statistical Package for social Science (SPSS) version 11.5 program. P value of <0.05 was considered as statistically significant.

Results

Hepatitis A virus antibody (total) was found positive in 141 (55.5%) of 254 children (Fig:I)

Fig: I Anti-HAV positivity among all children



Total 172 children from 1-5 year age group, 55 children from 5-10 year age group and 27 children from 10-15 year age group were taken. Boys were 139 & girls 115 so male:female ratio was 1.2: 1. Age distribution of the children positive for HAV antibody shows that with the advancement of age, anti-HAV positivity increases. Anti-HAV of 1-5 year age group was found to be 44.7%, it gradually increased to 70.9% in 5-10 year age group and finally to 92.6% in 10-15 year age group. Anti-HAV positivity of 5-10 year age group was significantly higher than that of 1-5 year age group (p=0.001) and antibody positivity of 10-15 year age group was significantly higher than that of 5-10 year age group (p=0.026). (Table 1.1).

Table 1.1 Anti-HAV positivity with age

Age (yrs)	n	HAV antibody		χ^2	p-value
		Positive	Negative		
1 – 5	172	77 (44.7)	95 (55.3)	11.397	0.001
5 – 10	55	39 (70.9)	16 (29.1)	4.970	0.026
10 – 15	27	25 (92.6)	2 (7.4)		

#Data were analysed using Chi-square (X^2) Test

Figures in the parentheses denote corresponding percentage

Table 1.2 shows anti-HAV positivity in children aged 1-5 year. Anti-HAV was found 18.9% in 1-2 year age group, 31.6% in 2-3 year age group, 53.1% in 3-4 year age group & 56.7% in 4-5 year age group.

Table 1.2 Seroprevalence of antibodies in children aged 1-5 year

Age (yrs)	n	HAV antibody		χ^2	p-value
		Positive	Negative		
1 – 2	37	7 (18.9)	30 (81.1)	1.129	0.467
2 – 3	19	6 (31.6)	13 (68.4)	2.536	0.111
3 – 4	49	26 (53.1)	23 (46.9)	0.153	0.696
4 – 5	67	38 (56.7)	29 (43.3)		

Data were analysed using Chi-square (X^2) Test;

Figures in the parentheses denote corresponding percentage

Table 1.3 shows, total number of subjects were 254. Current cost of 2 doses of vaccine is 15$×2=30$. Anti-HAV assay by ELISA costs 2$ per test. Total cost of vaccination of all the 254 children without screening is (30$×254) 7620$. On the other hand total cost of screening all the children is (2$×254) 508$. After screening of all the 254 children, 113 were found anti-HAV negative, who needed vaccination. Cost of vaccination of these 113 children is (30$×113) 3390$. Thus, total cost of vaccination after prior screening is (508$+3390$) 3898$. Therefore the cost of vaccination without screening is almost 2 (1.95) times more than the cost of vaccination after screening (Table 1.3). Therefore, it is worthwhile to screen the individuals before recommending hepatitis A vaccine.

Table 1.3: The cost benefit analysis of hepatitis A virus vaccination strategies

Vaccine strategy	Total 254 children	Number of ELISA tests	Cost of ELISA 2$ per test	Number of vaccinees	Cost of vaccine 15$ per dose × 2	Total cost
Without screening	254	0	0	254	7620$	7620$
With screening	254	254	508$	*113	3390$	3898$

*113 were found negative for anti-HAV

Discussion

Acute viral hepatitis caused by HAV is an acute, self-limiting infection.[12] Hepatitis A virus infection is very common in early childhood and most of the infections are asymptomatic or mildly symptomatic.[13] Immunity that develops following natural infection is stronger and persists longer than that develops following vaccination.[14]

Three epidemiological patterns of endemicity (low, intermediate and high) are observed worldwide. Each pattern has a different rate of infection, prevailing age of infection, and transmission model. HAV epidemiological pattern are highly dependent on age and level of hygiene. The distribution of HAV seroprevalence by age group may reflect current hepatitis A endemicity in countries and regions. The countries with low endemicity include Japan, Singapore, Hongkong and Taiwan whereas those with moderate endemicity include Thailand, Malaysia and Sri Lanka. Countries with high endemicity for HAV infections include India, China, Nepal, Bangladesh, Pakistan, Myanmar and Philippines.[15] In many developing countries of Africa, Asia and Latin America, most infections occur by 5 years of age where seroprevalence approach 90-100% by 10-15 years of age.[1] In Africa, Hendricks et al.[16] showed anti-HAV positivity of >90% among the 5-10 year age group among lower class black children.

India, China, Nepal, Pakistan and Bangladesh are included in high endemic zone[15] and a large number of populations acquire immunity through subclinical infections in early life.[17] During the last 5 years several reports from countries in southern Asia, Latin America and Europe showed a decreasing seroprevalence of protective antibody against hepatitis A virus.[18]

In the present study the average prevalence of anti-HAV was 55.5%. Only 44.7% individuals were positive at the age range of 1-5 years. Anti-HAV seroprevalence increased with age from 44.7% in 1-5 year age group to 92.6% in the 10-15 year age group. It was also observed that in 1-5 year age group (younger children), about one third of children were anti-HAV positive by 2-3 year of age and more than half by 3 years of age. Similar results were also observed in other studies in Bangladesh. Ahmed et al.[19] found a high prevalence (74.8%) of anti-HAV among Bangladeshi children and adult. He also reported anti-HAV positivity of 38% in 1-5 year age group, 75.2% in 5-10 year age group, 80.4% in 11-15 year age group and 98.5% in 15-20 year age group. Saha et al.[11] also reported anti-HAV positivity of 40.4% in 1-5 year age group which gradually increased to 98.4% in >30 year age group. Another study by Sheikh et al.[20] reported anti-HAV positivity of 100% in 15-20 year age group. These findings are similar to the findings of our neighbouring coun-

tries. Mall et al.[2] from India (Calcutta) reported 40% anti-HAV positivity in 1-5 year age group and through gradual increase in age the prevalence reached to 97% in the >16 year age group.

A recent study by Kamath et al.[5] reported anti-HAV positivity of 61.6% in 5-10 year age group and 97% in 11-15 year age group in Chennai, India. Agboatwalla et al.[8] & Sawayama et al.[21] also reported similar results from Pakistan (94.1% seropositive by the age of 5 years) and Nepal (91.1% seropositive) respectively. Anti-HAV positivity was found 94.1% in 1-5 year age group at Rawalpindi and 99% in two rural villages in Nepal. In Africa, Raharimanga et al.[14] reported that the overall seroprevalence of anti-HAV was 92.2%. In 8-10 year age group it was 83.7% and in 10-24 year age group it was 95.5%.

In the present study, it was evident that the cost of vaccination with screening is more than 2 times cheaper (3898$) than the cost of vaccination without screening (7620$). As such, these findings suggest to screen the individuals before recommending hepatitis A vaccination. Ahmed et al. [19] also observed that the cost of vaccination with screening was almost three times cheaper (US$3418) than the cost of vaccination without screening (US$8928). It is to be economically worthwhile, the cost of vaccinating a group of people must be equal to or less than the cost of testing the entire group plus the cost of vaccinating the non-immune group[22]. In India also reported that, if anti-HAV positivity is >50% in a particular age group, then it is advisable to screen the individual before HAV vaccination. On the other hand, when the chance of positivity is <50% in a particular age group, then vaccination can be offered without screening for antibodies. [13] It is evaluated that in India, selective vaccination of high risk populations, based on their serological evidence of HAV antibody, could be a rational and cost effective approach. [23] In a developed country like Argentina reported that universal vaccination against HAV was cost effective. [24]

Conclusions

In the studied children anti-HAV positivity was more than 50% after 3 years of age and finally increased to more than 90% after 10 years of age. So, high proportion of children in the present study acquired HAV antibody since early childhood and anti HAV positivity increased with increase in age. On cost benefit analysis, the cost of vaccination with screening was almost 2 times cheaper than the cost of vaccination without screening. Therefore mass vaccination or vaccination without prior knowledge regarding the serostatus could be an unnecessary immunological assult & may not be a suitable strategy for Bangladesh in lieu of the present socioeconomic condition. Assult

Recommendations

Based on the present study, it may be recommended that in children less than 3 years of age vaccination without prior screening can be done. However in children of ?3 years of age, pre-vaccination screening should be done prior to vaccination as this is cost effective, safe and more rational.

Further community based studies with larger sample size are required before giving a final recommendation for routine HAV vaccine to children of Bangladesh.

Limitations of study

Small sample size, selection biasness and absence of socio-economic status are the three limitations of this study.

Acknowledgement

Prof. C. A. Kawser, PhD, Chairman of Pediatrics, BSMMU.

Prof. Samir K. Saha, PhD, Head, Dept. of Microbiology, BICH, DSH.

Reference:

1. Pickering LK, Snyder JD. Viral hepatitis. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson Textbook of Pediatrics. 17th ed. Saunders Elsevier, New Delhi; 2004. P 1324-32.

2. Mall ML, Rai RR, Philip M, Naik G, Parekh P, Bhawnani SC et al. 'Seroepidemiology of hepatitis A infection in India: changing pattern'. *Indian Journal of Gastroenterology* 2001**; 20**: 132-35.

3. Kaw HW, Aschcavai M, Redekar AG. 'The persistence of IgM antibody after acute clinical Hepatitis A'. *Hepatology* 1984; **4**: 933-6. http://dx.doi.org/10.1002/hep.1840040525

4. Chadha MS, Lole KS, Bora MH & Arankalle, VA. 'Outbreaks of hepatitis A among children in Western India'. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2009; **1088**: 1-6.

5. Kamath SR, Sathiyasekaran M, Raja TE & Sudha. 'Profile of viral hepatitis A in Chennai'. *Indian Pediatrics* 2009; **46**: 642-3.

6. Joshi N, Rao S, Kumar A, Patil S & Rani S. 'Hepatitis A vaccination in chronic liver disease: Is it really required in a tropical country like India?' *Indian Journal of Microbiology* 2007**; 25**(2); 137-39. http://dx.doi.org/10.4103/0255-0857.32720

7. Hussain Z, Das BC, Hussain S, Murthy NS & Kar P. 'Increasing trend of acute hepatitis A in north India: Need for vaccination of high-risk population for vaccination'. *Journal of Gastroenterology and Hepatology* 2006; **21:** 8 9 - 9 3 . http://dx.doi.org/10.1111/j.1440-1746.2006.04232.x 8. Agboatwalla M, Isomura S, Miyake K, Yamashita T, Morishita T & Akram DS. 'Hepatitis A, B and C seroprevalence in Pakistan'. *The Indian Journal of Pediatrics* 1994; **61:** 545-9. http://dx.doi.org/10.1007/BF02751716

9. Anish K & Xavier S. 'Is hepatitis A vaccination necessary in Indian patients with cirrhosis of liver?' *Indian Journal of Gastroenterology* 2003; **22**(2): 54-58.

10. WHO. 'Department of communicable disease surveiliance and response', Hepatitis A 2000; 1-39.

11. Saha SK, Setarunnahar S, Shakur S, Hanif M, Habib MA, Dutta SK et al. 'Seroprevalence of hepatitis A infection by age group and socioeconomic status of Bangladesh'. 13th International Congress on Infectious Diseases Abstracts, *Poster Presentations* 2008; **16**(43): 101-02.

12. Feinstone SM, Gust ID. Hepatitis A virus. In: Richman DD, Whitley RJ, Hayden FG, editors. Clinical Virology. 2nd ed. ASM press, Washington D.C; 2002. P 1019-32.

13. Arora NK & Mathur P. 'Epidemiological transition of hepatitis A in India: Issues for vaccination in developing countries'. *Indian Journal of Medical Research* 2008; **128:** 699-704

14. Raharimanga V, Carod JF, Ramarokoto CE, Chertien JB, Rakotomanana F, Talarmin A et al. 'Age specific seroprevalence of hepatitis A in Antananarivo (Madagascar)'. *BMC Infectious Diseases* 2008; **8**(78): 1-6.

15. Kar P. 'Is there a change in seroepidemiology of hepatitis A infection in India?' *Indian Journal of Medical Research* 2006; **123:** 727-29.

16. Hendrickx G, Herck KV, Vorsters A, Wiersma S, Shapiro C, Andrus JK et al. 'Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology'. Journal of Viral Hepatitis 2008; 15: 1-15. http://dx.doi.org/10.1111/j.1365-2893.2008.01022.x

17. Arankalle VA, Devi KLS, Leo KS, Shenoy KT, Verma V & Haneephabi M. 'Molecular characterization of hepatitis A virus from a large outbreak from Kerala, India'. *Indian Journal of Medical Research* 2006; **123:** 760-69.

18. Batra Y, Bhatkal B, Ojha B, Kaur K, Saraya A, Panda SK & Acharya SK. 'Vaccination against hepatitis A virus may not be required for school children in Northern India: results of a seroepidemiological survey'. *Bulletin of the World Health Organization* 2002; **80(**9): 728-31.

19. Ahmed M, Munshi SU, Nessa A, Ullah MS, Tabassum S & Islam MN. 'High prevalence of hepatitis A virus antibody among Bangladeshi children and young adults warrants pre-immunization screening of antibody in HAV vaccination strategy'. *Indian Journal of Medical Microbiology* 2009**; 27**(1): 48-50.

20. Sheikh A, Sugitani M, Kinukawa N, Moriyama M, Arakawa Y, Komiyama K et al. 'Hepatitis E virus infection in fulmimant hepatitis pattern and an apparently healthy population in Bangladesh'. *American Journal of Tropical Medicine and Hygiene* 2002; **66**(6): 721-24.

21. Sawayama Y, Hayashi J, Ariyama I, Furusyo N, Kawasaki T, Kawasaki M et al. 'A ten year serological survey of hepatitis A, B and C viruses infections in Nepal'. *Journal of Epidemiology* 1999**; 9**(5): 350-54. http://dx.doi.org/10.2188/jea.9.350

22. Mathur, P & Arora, NK. 'Considerations for HAV vaccine in India', *Indian Journal of Pediatrics* 1999; **66**: 111-2 0 . http://dx.doi.org/10.1007/BF02752368

23. Gupta, A & Chawla, Y. 'Changing epidemiology of hepatitis A Infection', *Indian Journal of Medical Research* 2008; **128:** 7-9.

24. Gentile, A. 'The need for an evidence based decision making process with regard to control of hepatitis A', *Journal of Viral Hepatitis* 2008**; 15**: 16-21. http://dx.doi.org/10.1111/j.1365-2893.2008.01023.x