Review Article


Epidemiological transition of hepatitis A in India: Issues for vaccination in developing countries

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Received February 1, 2008

With improvement in economic and living conditions of the communities, the age of acquiring hepatitis A virus (HAV) infection is shifting from early childhood to adolescence and young adulthood. Such epidemiological shift leads to an increased incidence of symptomatic HAV infection, including heightened risk of liver failure. Data from India indicate that the population is no longer homogeneous for its HAV exposure profile. Occasional outbreaks of HAV and higher proportions of symptomatic cases are reported amongst older children and adults from different regions of the country. However, the heterogeneous exposure to HAV defies widespread use of the vaccine. The challenge is to recognize the susceptible pockets and take pre-emptive steps. In regions with rapid improvement in living standards and environmental hygiene, there is a need for regular surveillance through structured protocols that are able to identify early signs of epidemiological shift. This review discusses relevant issues and concerns to influence decision making for HAV vaccination in such transition societies.

Key words Developing countries - epidemiological transition - hepatitis A - vaccination

Hepatitis A virus (HAV) infection in early childhood is mostly asymptomatic or mildly symptomatic. In the absence of specific anti-viral drugs, it requires only supportive management. The relative frequency of symptomatic hepatitis and asymptomatic infection has been reasonably well characterized and appears to be strikingly age dependent. With improvement in socio-economic conditions and its consequences, early childhood exposure to the virus has decreased. Hence, there has been a gradual shift in the age of acquiring the infection from early childhood to adulthood in different parts of the world. Concomitantly, there was an increase in symptomatic cases and in severe clinical outcomes including liver failure. The social and economic burden of this morbidity and mortality led to the development of several vaccines. In 2005, encouraged by the huge success of targeted vaccination, the US American Advisory Committee on Immunization Practices recommended universal childhood HAV vaccination in all children aged between 12-23 months in the United States.

The peak age of seroprevalence is shifting from the 1st decade of life to the 2nd and 3rd decades. This shift in age of acquiring infection from childhood to older age groups is termed as epidemiological shift. In a country like India with an extensive variations and heterogeneity in the determinants of acquiring anti-HAV antibodies, a unified approach for vaccination would appear epidemiologically inappropriate. These populations are likely to co-exist within same geographic areas,
having diverse economic and social classes. The age of acquiring HAV infection by populations living in cleaner environments is different from others. Hence, the differences in living conditions of populations within the same geographic regions, besides varying economic and social classes need careful attention while formulating any policy recommendations. In this review we discuss the considerations and rationale for prescribing HAV vaccine in India, as an example of a country where epidemiological transition is likely to occur; also highlighting the reasons for the impasse and suggesting the possible options.

**Hepatitis A epidemiological shift: The Indian scenario**

The seroepidemiology of hepatitis A has been described based on the distribution of anti-HAV IgG, IgM and total anti-HAV antibodies, singly or in combination across the age groups. In high endemicity regions, majority of HAV infection is acquired in early childhood. We discuss the situation in India where there are early and sporadic symptoms of epidemiologic transition, since we feel that such situations would be prevalent in some other developing economies of the world that are changing from high to intermediate and low endemicity states.

An overview of the seroprevalence profile of HAV antibodies in Indian children and adults available from published literature has been compiled in the Table.

This is by no means an exhaustive compilation, since a lot of data would be available in unpublished reports and proceedings. Number of children in various studies was variable and notably, fewer in very young age groups. Not withstanding the gaps in the available data, some general observations can be made.

About 15 years ago, the cord blood anti-HAV antibody levels in newborns was nearing 100 per cent, which in turn reflected the maternal antibody prevalence. In recent studies, this level has come down to 50-60 per cent. Some of the studies also show that seroprevalence of HAV antibodies was lowest in 6 months to 2 yr age group and, maximum exposure to HAV occurred in 2-5 yr age. These observations may be the first indication of epidemiological shift in the age of acquiring anti-HAV antibodies in the community at large. But the available data do not show a consistent decline in childhood HAV seroprevalence rates and increased susceptibility to HAV in young adults.

In 2001, trends of age related HAV seroprevalence in the urban (higher and lower middle income categories) and rural populations around Pune were reported. There were significant declines in the positivity of HAV antibodies in children between 6-10 (85 to 30%) and 11-15 (92 to 45%) years of age, belonging to the higher income class in the urban areas, between the period of 1982 and 1998 respectively. Some decline was also seen in the younger age groups in the rural areas. However, there were no changes seen in children belonging to the lower middle income families. Similarly, from Mumbai sero-positivity among children and adults from high socio-economic group was reported as 64.5 per cent, compared to 85.3 per cent in individuals from low socio-economic class, the difference was statistically significant (P<0.001). Several studies done in different parts of the country do not demonstrate major differences in the HAV seroprevalence in relation to socio-economic status.

The lowest HAV antibody seroprevalence rates in India have consistently been reported from Kerala; Mathews et al. and Mall et al. have reported the lowest seroprevalence rates of 4.5 and 10.3 per cent respectively in children below 5 yr. This is in contrast to studies from across the country which have shown the seroprevalence to be between 60-80 per cent in children below 5 yr. An epidemic of hepatitis A in the age range of 2-75 yr was reported from central Kerala (Koothattukulam) in 1998. Out of 399 cases of acute hepatitis A, majority (65%) were in the age range of 15-33 yr. In 2004, an epidemic of hepatitis A occurred in Kottayam district of Kerala, and mainly involved young adults. There was contamination of the drinking water by the nearby non-functional and leaking sewage plant. These events clearly demonstrated that certain geographic regions of the country showed features of intermediate HAV endemicity.

Recently some studies from India have reported an increase in symptomatic cases of HAV among older populations, so as to substantiate epidemiological shift. In a study from a specialty hospital which caters to patients from the upper and middle socio-economic classes in South Delhi, trends of acute sporadic viral hepatitis A over a period of 5 yr in patients aged 13-20, 21-30 and >30 yr showed an increase in proportion of acute hepatitis due to HAV infections up to 3 times.
Similarly, a public tertiary care hospital from another part of the same city reported an increase of acute hepatitis A cases among adults (>15 yr) from 3.4 to 12.3 per cent during 1999-2003\textsuperscript{24}. In contrast, a decrease in the proportion of adult patients with acute hepatitis A attending the Liver Clinic in a tertiary level government hospital, catering mainly to lower and middle income group patients in the same city was observed over 8 yr (12.5% in 1992; 8% in 2000)\textsuperscript{13}. In a study from Rajasthan (western India), HAV was reported to be the predominant cause of acute viral hepatitis in the adult population (32.1%)\textsuperscript{25}. Chadha \textit{et al}\textsuperscript{26} reported trends of acute viral hepatitis (AVH) and fulminant liver failure (FHF) from four hospitals in

<table>
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<tr>
<th>Author/Year/Reference</th>
<th>Region/City</th>
<th>Age groups studied</th>
<th>No. of subjects tested (N)</th>
<th>Proportion with anti-HAV antibodies (%)</th>
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<tr>
<td>Tandon \textit{et al} 1984\textsuperscript{4}</td>
<td>North/Delhi</td>
<td>Neonates, Till 5 yr, 5-10 yr</td>
<td>25, 73, 52</td>
<td>100, 68, 90</td>
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<tr>
<td>Mittal \textit{et al} 1998\textsuperscript{8}</td>
<td>North/Delhi</td>
<td>Newborn, &lt;6 mo-24 month, 2-5 yr, &gt;5-10 yr</td>
<td>36, 166, 91, 67</td>
<td>50.6, 76.9, 79.1</td>
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<td>Thakur \textit{et al} 1998\textsuperscript{6}</td>
<td>North/Delhi</td>
<td>1-8yr, 9-12 yr, 13-16 yr</td>
<td>170, 181, 86</td>
<td>35.8, 59, 77</td>
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<tr>
<td>Das \textit{et al} 1998\textsuperscript{7}</td>
<td>North/Delhi</td>
<td>11-20 yr, 21yr</td>
<td>93, 302</td>
<td>60.2, 64.2</td>
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<td>Dutta \textit{et al} 2000\textsuperscript{4}</td>
<td>North/Delhi</td>
<td>0-0.5 yr, 0.5-2 yr, &gt;2-5 yr, &gt;5-12 yr</td>
<td>30, 90, 90, 210</td>
<td>60, 21, 66, 86.6</td>
</tr>
<tr>
<td>Das \textit{et al} 2000\textsuperscript{9}</td>
<td>North/Delhi</td>
<td>19-45 yr</td>
<td>500</td>
<td>71.2</td>
</tr>
<tr>
<td>Jindal \textit{et al} 2002\textsuperscript{10}</td>
<td>North/Delhi</td>
<td>18-21 yr</td>
<td>91</td>
<td>5.1</td>
</tr>
<tr>
<td>Batra \textit{et al} 2002\textsuperscript{11}</td>
<td>North/Delhi</td>
<td>4-7, 8-11, 12-18</td>
<td>206, 574, 644</td>
<td>86, 91, 97</td>
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<td>Aggarwal \textit{et al} 1999\textsuperscript{13}</td>
<td>North/Lucknow</td>
<td>0-5 month, 6-10 month, 11-18 month</td>
<td>28, 22, 23</td>
<td>68, 91, 96</td>
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<td>Arankalle \textit{et al} 1995\textsuperscript{13}</td>
<td>West/Pune</td>
<td>&lt;0.6 yr, 0.7-1.5 yr, 1.6-15 yr</td>
<td>0, 11, 186</td>
<td>67, 18, 93.3</td>
</tr>
<tr>
<td>Chadha \textit{et al} 1999\textsuperscript{14}</td>
<td>West/Pune</td>
<td>0-3 month, 4-6 month, 7-48 month, 49-72 month</td>
<td>38, 30, 365, 66</td>
<td>94.7, 56.7, 28.2, 90.9</td>
</tr>
<tr>
<td>Dhawan \textit{et al} 1998\textsuperscript{15}</td>
<td>West/Mumbai</td>
<td>0-3 yr, 4-10 yr, 11-15 yr, ≥16yr</td>
<td>75, 143, 66, 386</td>
<td>50.7, 73, 83.3, 84.4</td>
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<tr>
<td>Mathews \textit{et al} 1998\textsuperscript{16}</td>
<td>South/Kerala</td>
<td>1-5 yr, 6-10 yr, ≥11-15 yr</td>
<td>89, 94, 186</td>
<td>4.5, 8.6, 48.3</td>
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<tr>
<td>Mohanavilli \textit{et al} 2003\textsuperscript{17}</td>
<td>South/Chennai</td>
<td>0-2 yr, &gt;2-6 yr, &gt;6-12 yr</td>
<td>19, 77, 86</td>
<td>31.6, 83.1, 94.1</td>
</tr>
<tr>
<td>Joshi \textit{et al} 2000\textsuperscript{18}</td>
<td>South/Hyderabad</td>
<td>0-5 month, 6-20 month, ≥21month</td>
<td>21, 49, 20</td>
<td>14, 59.1, 95</td>
</tr>
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Pune (western India) during 1994-1997 (group A) and 1978-1981 (group B). Amongst children, there was an increase in AVH cases from 51.4 per cent in group B to 81.6 per cent in group A, while in the adult subjects it increased from 3.5 to 10.6 per cent. The proportion of children with AVH in group B was significantly more in those aged below 10 yr compared to group A. This probably indicated to a shift in age of acquiring HAV infection to older children in the recent years. Out of 276 subjects in group A, only 56 were from high socio-economic class, while almost all of the 266 patients in group B were from low socio-economic class. In adults from the upper socio-economic class, there was a five time increased risk of acute hepatitis A, while no such trend was observed in children. Although, the sample size and study design was not appropriate for detecting statistically significant differences, the trends are obvious. Around the same period a study from Indore, a town in the neighbouring central part of India showed that younger children belonging to high socio-economic class had increased frequency of acute hepatitis A. Differences in findings between these two cities (around the central-western part of India) may reflect, albeit crudely, differences in the stage of economic and civic development.

These studies indicate towards an evolving epidemiologic shift occurring in certain areas and population groups of the country. The varied study design and methodology followed in most studies do not allow for their comparison and extrapolation beyond their sampling frame. However, one has to be cautious in regions with rapid economic development where pockets of susceptible older children and adults may emerge. HAV outbreaks, like the one observed in Shanghai in 1988, represent a transition from an endemic HAV transmission to an epidemic pattern.

The severity of HAV associated infection increases, irrespective of the age, in those who have another underlying chronic liver disease (CLD). Thus, it appears that vaccination would minimize the risk of accelerated liver disease in individuals with established CLD. However, in HAV endemic regions, like India, the seroprevalence of anti-HAV antibodies has been shown to be above 95 per cent in patients with CLD, irrespective of its aetiology. This has been shown to be similar to the individuals without CLD, and thus routine HAV vaccination of these patients is not warranted. In a matched study of adult patients with CLD and those without, HAV superinfection as a cause of acute exacerbation of chronic liver disease was not seen. However, whether the same will be applicable in children with CLDs is not known, since the acquisition of anti-HAV antibodies is still ongoing.

Potential approaches for HAV vaccination

Issues related to HAV vaccination in regions with epidemiologic shift need to be discussed in light of the existing WHO recommendations.

Role of improving sanitation and personal hygiene: Marked reduction in virus transmission in most developed countries came several decades ago due to improvement in living standards, better sanitation and environmental states in addition to higher income. Same trend was observed in several developing countries with increasing economic prosperity during the 1990s e.g., Singapore, Malaysia, Thailand and other South East Asian countries. These changes occurred without the vaccine, underscoring the critical importance of environmental and personal hygiene and sanitation to prevent faecal-oral transmission of pathogens. This is an essential pre-requisite for the success of any HAV vaccination programme so as to curb the transmission of the virus in the environment.

Potential options of using the HAV vaccine: Strategies to immunize and protect against HAV infection can be broadly seen in three perspectives. First option is to have a high risk immunization strategy so that individual/group is the focus, and vaccine is administered with the routine immunizations. Secondly, the intervention is designed to avoid outbreaks of HAV among susceptible population, wherein mass vaccination in the susceptible population is done. Thirdly, to vaccinate all children irrespective of their individual risk status of acquiring HAV infection, with the ultimate aim of eliminating the infection from the community. All these options are likely to prevent/minimize the risk of HAV disease in susceptible adults.

Surveillance for HAV infections and decision to vaccinate

Although at present there is lack of evidence for recommending universal vaccination against hepatitis A in India, it appears from the data that the population is no longer homogenous. Differences in exposure may be due to the levels of socio-economic status of the family and stage of development of the place of residence. The challenge is to identify these pockets and monitor them on a regular basis for HAV seroprevalence and disease. Monitoring the population would also provide information on enlarging clusters of susceptible older children and adults. The vaccine will be useful in such
individuals and populations who remain unexposed to the HAV infection during early childhood.

Outbreaks of HAV are likely to occur among people residing in cleaner environments such as industrial townships, upper class housing complexes, student hostels, etc. Occasionally, unique segments of the population may emerge as susceptible pockets. As an example, children of domestic helpers who are born and stay in cleaner urban environments may have HAV exposure profile like the children of households where their parents are working. Geographic regions with known HAV outbreaks should be kept under close surveillance.

HAV infection in children below 5 yr of age is mostly asymptomatic. Individuals and population segments who are likely to remain susceptible beyond 5 yr of age can be offered vaccination with pre-immunization screening. 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. The following equation can be used to decide when it will be more efficient to do antibody screening before giving the vaccine. It takes into account the cost of vaccination and screening for HAV antibodies and HAV seroprevalence:

\[ A \leq B + A (1-x) \]

A= total cost of vaccine including the cost of manpower; B= total cost of testing for HAV-antibodies and \( x= \) HAV antibody positive fraction of the population. (i.e., seroprevalence). For example, the current cost of two paediatric doses of HAV vaccine in India is almost 2000 INR (US$ 50), while HAV antibody assay is available for approximately 900 INR (US$ 23) per test. At current prices, if the reported or estimated prevalence of HAV antibody in a particular age group and region is >50 per cent, it is worthwhile to screen the individuals before recommending the HAV vaccine. On the other hand, if the probability of an individual having been exposed to HAV is <50 per cent at a particular age, vaccination can be offered without screening for antibodies.

Research requirements to facilitate policy development

Well structured and uniform protocols to monitor the HAV seroprevalence and disease burden are necessary to capture the changing exposure profiles of the population. The use of seroprevalence data alone does not indicate anything about the disease burden and hence is not useful with respect to evaluating potential vaccination strategies. The protocols should include (i) characterization of geographic regions; (ii) cross-sections of socio-economic classes within the same region; (iii) indicators to capture environmental hygiene, and (iv) stage of economic development.

Conclusions

Available data indicate that there are pockets of susceptible population within different regions of India among older children and adults. Heterogeneous pockets of susceptible and exposed individuals may co-exist in rapidly developing societies. Thereafter, small localized or large outbreaks of HAV infection will remain a threat in such areas. The situation demands that relevant guidelines be evolved for HAV vaccination in these susceptible pockets and communities by characterizing them appropriately.

Competing interests

The views expressed by the authors do not reflect those of the organizations they are currently affiliated to. We declare no conflict of interest.

References


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