

Clinician's Perspective on the Use of Hepatitis A Vaccine in Indian Children

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ABSTRACT

Hepatitis A, a waterborne endemic disease, is an important cause of acute viral liver disease in Indian children. Although self-limiting in most cases, hepatitis A can rarely cause life-threatening acute hepatic failure. It is the most common attributable cause for acute liver failure in children in countries of high endemicity. Changing epidemiology of hepatitis A in India has resulted in the coexistence of heterogeneous pockets of exposed and unexposed individuals in different social classes and regions. Epidemiological transition has also resulted in higher risk of hepatitis A infection and complications in older children and adults. Vaccines are the time tested and effective measures for prevention of hepatitis A infection; however, despite available vaccines, hepatitis A remains an important public health problem in India because of low vaccination coverage. Currently, two types of vaccines are available for prevention of hepatitis A: live attenuated vaccine and killed/inactivated vaccines. Live vaccine provides robust and long-term immunogenicity due to both humoral and cellular responses, unlike mostly humoral response with killed vaccines. Differences also exist in the schedule and route of administration of these vaccines. Live attenuated vaccine is administered subcutaneously and offers several advantages over killed vaccine including convenience, potential for better compliance, less cost due to single-dose administration and less pain. In patients with bleeding disorder, subcutaneous administration can result in less chances of bleeding when compared with intramuscular administration. Moreover, published long-term immunogenicity data in Indian subjects are available only with live vaccine. In this article, we discuss the clinician's perspective on the use of hepatitis A vaccine in Indian children.

Keywords: Hepatitis A, Immunogenicity, Killed/inactivated vaccine, Live vaccine.

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INTRODUCTION

Hepatitis is a major public health concern in developing countries including India. Among different types, hepatitis A is more common¹ and highly endemic in many Asian countries.

India is considered as a hyperendemic country,² but large nationwide exact data on prevalence of hepatitis A are lacking due to improper surveillance system. Age group and socioeconomic status of family are important factors for infection with hepatitis A virus (HAV). The reported seropositivity for hepatitis A among children between 18 months and 10 years of age is 37.5% with range from 20.6 to 60.9%.³ Another study reported higher seroprevalence in rural and urban areas (90.9 vs 77.1%, respectively) and children from all socioeconomic strata (lower social class 87.2% vs higher social class 54.5%).⁴ Hepatitis A virus is transmitted through feco-oral route and represents an important cause of acute viral liver disease and most common cause of fulminant hepatic failure among children in India,⁴ which can be life-threatening. The coexistence of heterogeneous pockets of exposed and unexposed individuals in different social classes and regions within country makes population prone for outbreaks.²

As clinicians, we see so many cases of hepatitis in school-going age group. However, epidemiology of disease is underestimated, as we routinely do not conduct hepatitis A viral markers studies in these patients of jaundice. Due to this, it is very difficult to judge the real magnitude of hepatitis A in community. Many of the hepatitis cases particularly in developing country like India in resource-limited setting are just detected by urine for bile salt–bile pigment and treated on an outpatient basis. Although many clinicians do not consider hepatitis A as a disease of adverse or grave outcome, it definitely affects the family with unwanted and unexpected medical expenses and loss of school working days, which is very important

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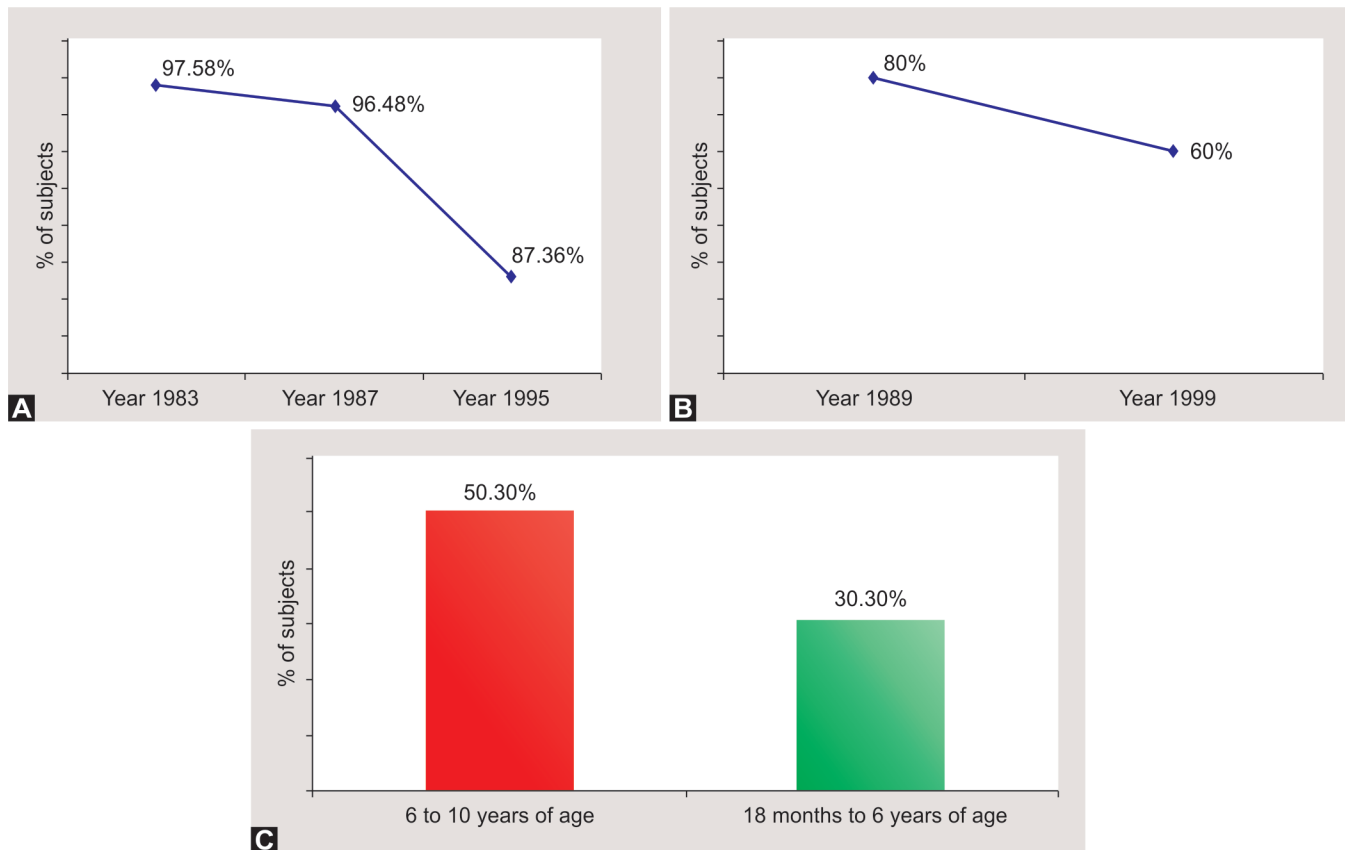
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in today's competitive world. We also need to consider loss of working days of working parents to take care of their sick children.

EPIDEMIOLOGICAL SHIFT IN PATTERN OF HEPATITIS A

India has undergone significant socioeconomic development in last few years² and with economic transition and improvement in standard of living and hygiene conditions, there has been a change in the epidemiological pattern of the disease (Fig. 1).^{2,5,6} The age of acquiring hepatitis A is shifting from early childhood to adolescent and younger adult age group.⁷



Figs 1A to C: Changing age-related pattern of hepatitis A prevalence in India: (A) Anti-HAV prevalence among children from 5–10 years;⁵ (B) Anti-HAV positivity among children aged <10 years;⁶ (C) Seroprevalence of hepatitis A in children in different age groups³

Epidemiological change has implications on the clinical presentation and risk of complications including increased risk of liver failure.⁷ In children below 6 years of age, the disease is asymptomatic, while chances of symptoms and severity of disease increase with increasing age.^{3,8} A recent study from Pune reported significant reduction in anti-HAV positivity in the population from lower middle socioeconomic status and increase in higher socioeconomic status. The rise in anti-HAV positivity in higher socioeconomic status population reflects vaccine- and infection-induced antibodies, whereas in lower middle socioeconomic status only infection-induced antibodies are seen. This emphasizes the need for creating awareness about hepatitis A in general population, especially in lower and middle socioeconomic class population. However, there is a huge need gap for vaccination to eradicate hepatitis A.⁹

According to the World Health Organization (WHO) position paper¹⁰ published in 2012, transition from high to intermediate endemicity of hepatitis A leads to increased risk of clinically significant hepatitis. Overall, epidemiological data, difficulty in diagnosis of infection in small children due to asymptomatic nature or non-specific symptoms,⁴ and risk of disease severity with increasing age underline the importance of prevention of hepatitis A in the community.

MANAGEMENT OF HEPATITIS A

Because of the absence of specific treatment for hepatitis A,^{8,11} prevention is crucial aspect of its management. Patients with hepatitis A infection should be advised bed rest⁸ and receive

supportive care including hydration and nutritional support. Symptomatic treatment for severe vomiting and high grade fever may be required in these patients. Considering the risk of adverse events, paracetamol should be carefully administered during symptomatic stage of acute hepatitis.¹¹

PREVENTION OF HEPATITIS A

Improvement in the personal hygiene, community hygiene, and water system with proper sanitation system, avoidance of contaminated food, and administration of vaccine against hepatitis A and, only in certain cases, immunoglobulins² are the important measures for prevention of hepatitis A. As far as individual protection in a particular child is concerned community measures to improve sanitation may not be effective when compared with protection from effective vaccination. Because of its effectiveness, vaccination represents an important armamentarium for prevention of hepatitis A infection and associated complications. Epidemiological data highlight the need of vaccination in all population irrespective of socioeconomic strata.³

HEPATITIS A VACCINES

Many clinicians question the need of hepatitis A vaccine with an argument that majority of children will be seropositive due to subclinical or natural infection. However, with changing epidemiology of the country particularly in urban areas where due to better hygiene, sanitation, and better quality of living, children do not get exposure to natural infection till they grow up and enter

school-going age group. If they get infection once they are grown up, they are likely to get severe disease, and there are increased chances of complications too.

We feel that hepatitis A vaccine is especially needed for people in higher socioeconomic class. Affordability of vaccine is also not a concern in this population. When it comes to the discussion of one dose vs two doses in clinical practice, it is always advantageous to have one dose of effective vaccine, which makes place for another vaccine in the already crowded immunization schedule in 12–18 months of age group.

According to the WHO, vaccination should be considered for the prevention of hepatitis A. Susceptibility of people and the level of exposure are the important parameters for consideration of vaccination. Due to poor sanitation system and hygiene when compared with developed countries, vaccination against hepatitis A is important in Indian population. In some countries, vaccination is recommended for high-risk population (i.e., recreational drug users, travel to endemic countries, men having sex with men, and those with chronic hepatic disease).¹² In the very recent updates of recommendations from the Advisory Committee on Immunization Practices of Centers for Disease Control and Prevention, United States, hepatitis A vaccination is advised in all children at age 1 year, people with unstable housing or experiencing homelessness, persons who are at increased risk for infection, persons who are at increased risk for complications from hepatitis A, and any person wishing to obtain immunity (protection).¹³

In India, two types of vaccines, formaldehyde inactivated (killed) and live attenuated vaccine, are available for prevention of hepatitis A.

Inactivated/killed Vaccine

Two brands (HavrixTM 720 and Avaxim[®] 80U) of inactivated hepatitis A vaccines are available as injectable formulations in India. These vaccines are administered intramuscularly. The mechanism of protection against infection and side effects are similar for both the available vaccines.¹² Two doses of inactivated vaccine are required for long-lasting protection against the disease.¹³

Live Vaccine

Only one live hepatitis A vaccine (Biovac ATM) is available in India and is administered subcutaneously. Single dose of live vaccine is adequate for providing long-term immunity.¹⁴ Single dose has shown to induce and maintain long-term immune response.¹⁵ Almost all recipients develop protective levels of antibodies within 1 month of single-dose administration of hepatitis A vaccine.¹²

Both inactivated and live attenuated hepatitis A vaccines are safe and effective in providing protection in children and adults.¹⁰ No vaccine (inactivated or live) is licensed for children less than 1 year of age.¹² Scientific evidence on long-term immunogenicity is available for both types of hepatitis A vaccines. Several global studies^{16–18} (Zhuang et al. 2001, Zhuang et al. 2005, Zhuang et al. 2010) have proven effectiveness of live vaccine by demonstrating high rates of seroprotection ranging from 80 to 81%.

There is global data on 20-year and 17-year follow-up with inactivated vaccine¹⁹ and live vaccine,¹⁵ respectively, marking durable protection with both types of vaccines. Live vaccine is well studied in Indian subjects. Published evidence on long-term follow-up in Indian subjects is available only with live attenuated vaccine. A 10-year follow-up study from India showed long-term immunity after single-dose administration of live attenuated hepatitis A vaccine.²⁰ In this long-term follow-up study,²⁰

98.1% subjects showed seroprotective titer of IgG antibodies (>20 mIU/mL). The geometric mean titre (GMT) of anti-HAV antibodies among seroprotected children was 100.5 mIU/mL. No significant safety concern was reported in the study. Other studies^{21,22} from India have also reported immunogenicity and safety of live attenuated hepatitis A vaccine.

A comparative study by Zheng et al. was unable to identify differences between inactivated and H2 strain live hepatitis vaccine in terms of seroconversion proportion and GMT at 7 and 28 days.²³

Overall, both vaccines provide long-term, possibly life-long protection in children and adults.¹⁰

Despite availability of vaccine and supporting evidence, the coverage and uptake remains suboptimal because of vaccine hesitancy among parents. Vaccine hesitancy is an outcome of complex interactions between several factors including compliance, convenience, cost, fear of injection (with injectable vaccines), complacency, and duration of protection. It is, therefore, important to consider and understand differences between live and inactivated vaccine while selecting vaccine for a child in individual practice.

Comparison between Live and Inactivated Hepatitis A Vaccines

Single dose of live attenuated vaccine offers the following advantages over inactivated hepatitis A vaccine.

- **Compliance:** Clinicians and parents have an option of choosing between single-dose vaccine (live attenuated vaccine) and two-dose (killed vaccine) vaccine for protection against hepatitis A. Higher the number of doses, more is the reluctance to comply. People often prefer vaccine with less number of doses. That is one of the reasons for combination vaccines to come into existence. Number of injections is a barrier for complying with vaccination schedule. Suboptimal compliance is known with multidose vaccines. A large retrospective study evaluating the Vaccine Safety Datalink population from 1996 through 2004 reported suboptimal compliance with multiple-dose vaccination. Among subjects with different age groups who received first dose of hepatitis A vaccine ($n = 594,917$), only 40–50% received the second dose.²⁴ Another study from the United States evaluating vaccination coverage of hepatitis A vaccine among adolescents from 13 to 17 years also suggested reduced coverage with two or more than two doses when compared with only one dose.²⁵ These data clearly suggest that noncompliance increases the chance of missing the second dose of vaccine and which can have impact on long-term immunity of the vaccine recipient. Needle fear is another documented reason for noncompliance with vaccination.²⁶ Single-dose administration of live attenuated vaccine (with single prick) helps in better acceptance than two injections of inactivated vaccine.
- **Convenience:** Convenience can be viewed from both health-care provider and parent's point of view and live attenuated vaccine offer advantage to both. Live attenuated vaccine is convenient for health-care provider because of greater ease of subcutaneous administration when compared with intramuscular injection. Similarly, it can have impact on convenience on the part of vaccine provider in the form of reduced risk of inadvertently damaging deeper structures with subcutaneous administration when compared with intramuscular injection. Single dose which saves time and money for traveling to the clinic and reduces number of pricks to the kid for second dose offers convenience to parents. Parents and

children can be benefitted due to convenience of less frequent pain reported with subcutaneous administration. Thus, in terms of convenience, live attenuated vaccines scores over inactivated vaccine. Route of administration can have impact on vaccine hesitancy because of number of visits. Convenience of vaccine is crucial in overcoming hesitancy, improving acceptance rate, and governing compliance of immunization.

- **Potential for lower risk of adverse events:** Concerns for side effects is another barrier for vaccine acceptance. Both live attenuated vaccine and killed vaccines are well tolerated and have minimal risk of adverse events/complications. Mild local site reactions can occur after injection of vaccine in few subjects. Due to single-dose administration, the risk of procedure-related adverse events is reduced by 50% with live attenuated vaccine unlike killed vaccine which needs to be given as two-dose schedule. A study among children receiving *Haemophilus influenzae* type b vaccine reported less frequent pain with subcutaneous route when compared with intramuscular route.²⁷ Hepatitis A live vaccine is administered subcutaneously; hence, it may be less painful than intramuscular administration.
- **Risk of bleeding:** Bleeding is not a major adverse event in normal subjects but can be a concern in patients with hemolytic disorders. Although head-to-head vaccine-related clinical trials comparing risk of bleeding with intramuscular vs subcutaneous route of administration are not available, medication via intramuscular route is avoided in patients with bleeding disorder (e.g., idiopathic thrombocytopenic purpura) because of possibility of bleeding into the skin.^{28,29} There is also a risk of hematoma formation at the site of vaccination.³⁰ Subcutaneous route is an option in such cases.²⁸⁻³⁰ According to the Department of Health, Australian Government,³¹ subcutaneous route may be used instead of intramuscular route for vaccination of individuals with hemophilia or those receiving anticoagulants. The British Columbia Centre For Disease Control recommends subcutaneous route over intramuscular route in people with bleeding disorders if the efficacy of vaccines is same.³² This translates into advantage of less risk of bleeding with subcutaneous route of administration with live vaccine when compared with intramuscular administration.
- **Immune response:** Live and killed vaccines differ in stimulation of the immune system. Live attenuated vaccines provide both cellular and humoral immunity and hence result in better immune responses and long-lasting immunity. Inactivated vaccines produce weaker immune response³³ because most activity is due to humoral response and very less due to cellular immunity. Chances of waning of immune protection achieved with single dose in two-dose schedule of killed vaccine are more than live vaccine. Live vaccines due to the presence of memory cells can provide long-term immunity when vaccinated person is exposed to infection even after many years of vaccination even if antibody titers are not up to the WHO recommended level of 20 IU. A long-term follow-up study showed antibody persistence and immunological memory even after 17 years of single-dose live vaccine administration.¹⁵
- **Cost-effectiveness:** Cost is one of the significant considerations in health care, especially for vaccination. Less frequent dosing of live vaccine can probably lead to lowered cost of hepatitis A vaccination. Additionally, expenses are also incurred in travel to the clinic/hospital for receiving vaccine. This travel cost obviously gets doubled up with inactivated vaccine requiring two-dose regimen.

Differences between live attenuated vaccine and inactivated vaccine in terms of immune protection, dosage administration, cost, compliance, and adverse events are listed in Table 1.

POSTEXPOSURE PROPHYLAXIS

Immune serum globulin is useful for postexposure prophylaxis.¹¹ It is recommended to give within 2 weeks of exposure to subjects less than 1 year or more than 40 years of age, those with immune deficiency and chronic liver disease. Availability and cost are the challenges for the use of serum immunoglobulins.³⁵ According to the WHO, hepatitis A vaccine should be considered instead of passive prophylaxis with immune globulin for the pre- as well as postexposure prophylaxis.¹⁰

Live or killed vaccine can be an option for postexposure prophylaxis against hepatitis A. Hepatitis A vaccine is given as postexposure prophylaxis for healthy people between age group of

Table 1: Comparison between live attenuated vaccine and inactivated vaccine available in India

	<i>Inactivated vaccine</i>	<i>Live attenuated vaccine</i>
Type of vaccine	Formaldehyde inactivated HAV vaccine ¹⁰	Live HAV H2 strain vaccine ¹⁴
Route of administration	Intramuscular ¹⁰	Subcutaneous ¹⁰
Number of doses	2 doses ¹⁰	1 dose ¹⁰
Dosage schedule	First dose after 1 year of age and second dose usually 6 months (may be increased to 18–36 months) after the first dose ¹⁰	Single dose after 1 year of age ¹⁰
Minimum age for administration	1 year ¹⁰	1 year ¹⁰
Immunogenicity (28 days postvaccination) ²³		
Seroconversion	93%	98%
GMT	67 mIU/mL	47 mIU/mL
Data on long-term protection	Available. ¹⁹ No published Indian data	Available. ¹⁵ Indian as well as global evidence available
Adverse reactions	Mild local reactions (short duration), mild systemic reactions ³⁴	Similar to inactivated vaccine, ²³ less frequent pain ²⁷ and risk of bleeding with subcutaneous route
Convenience	2 doses (2 times travel to the clinic/hospital)	More convenient because of single dose
Compliance	Lower; also will have chances of missing second dose ²⁴	High because of single dose
Cost	Cost can be more due to more number of doses; additional cost of travel to the hospital/clinic for second dose	Probably less due to less number of doses

1 and 40 years.² Immunogenicity of the vaccine may be decreased in people with very old age. To achieve best response, vaccine should be given within 14 days of exposure.²³

As per the WHO position paper,¹⁰ single dose of live attenuated vaccine is used in national immunization program of many countries, and it also mentions that live vaccine is required as single dose, whereas inactivated vaccine is required to be administered with two doses to have a long-term protection against HAV.¹⁰ This is based on the high efficacy of vaccine achieved after single-dose administration. Anti-HAV antibodies are found in up to 88% of the vaccines after 15 years of vaccination without significant safety concerns. Now, even 17- to 20-year follow-up data on immunogenicity are available for these vaccines.¹⁵

Both vaccines are included in Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices-recommended immunization schedule (2018–2019) for children aged 0 through 18 years. This recommendation also recommends single-dose schedule for live vaccine and two-dose schedule for killed vaccine.³⁶

CONCLUSION

Hepatitis A is a significant concern in developing countries like India because of lack of proper sanitation systems and coexistence of heterogeneous pockets of exposed and unexposed individuals in different social classes and regions. Prevention of the disease by vaccination is an important measure for avoiding complications of hepatitis A. Both live attenuated and inactivated vaccines are available for prevention of hepatitis A. Live attenuated vaccine provides robust and long-term immunity because of cellular and humoral responses. Convenience, compliance, and cost are known important barriers for vaccination. Evidence of published long-term immunogenicity data in Indian population coupled with practical advantages of convenience of single-dose administration, compliance, single prick, and less cost makes live attenuated vaccine a better choice than inactivated vaccine from clinician's and patient's perspective. Further comparative pharmacoeconomic studies need to be conducted to conclusively demonstrate these potential advantages.

DISCLOSURE

Dr Archana Karadkhele, Dr Gaurav Puppalwar, and Dr Rishi Jain are the salaried employees of Wockhardt Ltd. Dr Chetan Trivedi, Dr Bhaskar Shenoy, Dr Sanjay Marathe, and Dr Nishchal Bhat are consulting pediatricians and vaccinators.

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