Review Article

Inactivated TZ84 strain hepatitis A vaccine and its impact: A narrative review

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ABSTRACT

Hepatitis A (HepA) represents a significant global public health challenge. At present, there is no definitive treatment available for managing HepA. Before the availability of HepA vaccines, hepatitis A virus (HAV) infection had emerged as a leading cause of fulminant hepatic failure and a significant indication for liver transplantation in children living in Argentina, Brazil, the Republic of Korea, and India. Inactivated HAV vaccines have demonstrated a high level of immunogenicity. In addition, there is evidence supporting the use of inactivated HepA vaccines in immunocompromised individuals and as post-exposure prophylaxis. Recently, the inactivated TZ84 strain hepatitis A vaccine, which has shown superior immunogenicity for up to 30 years and fewer adverse reactions when compared with other inactivated HepA vaccines, has become available in India. Moreover, the TZ84 strain of the inactivated HAV vaccine has the potential to control community-wide outbreaks. This narrative review offers an overview of the existing evidence concerning immunization against HepA in India, with a particular emphasis on the TZ84 strain of the inactivated HAV vaccine.

Key words: Childhood immunization, Hepatitis A, Inactivated vaccine, Pediatric hepatitis, Public health, Vaccine immunogenicity

Hepatitis A (HepA), a type of vaccine-preventable viral hepatitis, continues to pose a significant threat to global public health as it epitomizes a leading cause of mortality around the world [1,2]. HepA epidemiology indicates that the regions of sub-Saharan Africa and South Asia, including India, experience the brunt of the disease, and hepatitis A virus (HAV) antibodies may be present in more than 90% of individuals by the age of 10 years [1]. In recent times, the notion of transitional epidemiology has surfaced in relation to HepA. Nations undergoing swift development, coupled with enhancements in sanitation practices and access to clean water, have observed a decrease in the prevalence of HAV among young children. However, there has been an increase in the occurrence of HAV-related illness and death among older children and adults [3]. HAV infection accounts for 10%–30% of all cases of acute viral hepatitis, and acute liver failure (ALF) is documented in 1%–2% of HAV-infected individuals [4,5].

HAV infection is typically contracted through the fecal–oral route [6,7]. The primary mode of transmission typically involves close contact, such as within households or through sexual contact, with individuals who are infected with HAV. Furthermore, there have been instances of HepA outbreaks linked to the consumption of food items imported from countries where HepA is prevalent [3]. HepA has been known to spread through contaminated food, with implicated food items including shellfish, salads, sandwiches, vegetables, fruits, frozen berries, and various other raw or undercooked foods [6,8-10].

The clinical presentation of HepA includes initial non-specific prodromal symptoms such as mild fever, muscle pain, loss of appetite, general discomfort, nausea, and vomiting. After these initial symptoms, specific signs of liver dysfunction become apparent, such as dark urine, pale stools, jaundice (yellowing of the skin and eyes), and yellowing of the white part of the eyes (scleral icterus) [11]. Immunocompromised individuals are at risk of experiencing more severe forms of the disease, as well as enduring extended periods of viremia in their bloodstream and continued viral shedding in their feces. In addition, HepA can manifest in various non-typical ways, including relapsing HepA, cholestatic hepatitis, autoimmune hepatitis, and extrahepatic symptoms. Complications reported following an infection of HepA include acute renal injury, fulminant hepatic failure (FHF), ALF, relapsing HepA, gall bladder wall thickening, acuteon-chronic liver failure, gastrointestinal bleeding, intracerebral bleeding, hypoglycemia, encephalopathy, prolonged cholestasis, coagulopathy, ascites, thrombocytopenia, pleural effusion, increased duration of hospitalization, and increased mortality rates [12]. Approximately 6–10% of cases of HepA exhibit a biphasic or relapsing form [13].

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India is known to have a large burden of HepA (with at least one outbreak reported annually in 23 states) [14]. Recent research has drawn attention to shifts in the epidemiology and the overall disease impact of HepA in the Indian subcontinent. These changes have notably impacted distinct demographic groups, leading to an increased incidence of severe HepA instances among vulnerable adolescents and adults [5,15]. A seasonal variation in HepA is noticed in India and the surrounding regions, with a peak in the incidence of the disease during the monsoons (June to September) [16,17].

The major HAV outbreaks in India over the past few years are demonstrated in Table 1.

At present, there is no definitive treatment for HepA. The recuperation process from symptoms following infection can have an extended duration, spanning weeks or even months [12]. Before the availability of HepA vaccines, HAV infection had emerged as a leading cause of FHF and a significant indication for liver transplantation in children living in Argentina, Brazil, the Republic of Korea, and India [1]. Vaccination against HepA is therefore an integral part of the prevention and control of viral hepatitis. According to the World Health Organization (WHO), the best approach to thwart HAV infection is to enhance sanitation and promote immunization [27]. Besides, it has also been suggested that the implementation of HAV vaccination programs for children is of paramount importance in countries transitioning to or at intermediate endemicity levels to protect susceptible adults and adolescents who are at increased risk for severe HepA infection and associated complications [6].

Since 1992, safe and effective inactivated HepA vaccines have been widely available in developed nations that have helped protect at-risk populations and prevent outbreaks [6]. At present, there are two types of HepA vaccines available for clinical use: Formaldehyde ("killed") or inactivated HepA vaccine (HepA-I) and live attenuated HepA vaccine (HepA-L), both of which contain HAV cultured in different human and non-human mammalian cells [28,29].

This review aims to highlight the immunization strategies against HepA and provide a detailed overview of the TZ84 strain, inactivated HepA vaccine.

INACTIVATED TZ84 HEPA VACCINE

The HepA vaccine containing an inactivated TZ84 strain of HAV was first produced in Asia [30]. The vaccine is presently authorized for use in over 30 countries and regions. It is cultured in 2BS human fetal lung diploid cells and is preservative free [31]. After cultivation, it is refined by chromatography, rendered inactive by formalin, and adsorbed onto aluminum hydroxide [30].

The effectiveness and safety of this vaccine have been confirmed through numerous studies conducted in diverse settings. In a randomized controlled trial among school-aged children who were previously seronegative to HAV, it was observed that the inactivated TZ84 strain HepA vaccine had very high seropositive rates 12- and 24-month after vaccination. The inactivated TZ84 strain HepA vaccine-receiving group had 94.4% seroprotection compared to 73% seroprotection in the inactivated HM-175 strain HepA vaccine-receiving group and 64% in the group receiving vaccine containing live attenuated H2 strain of HAV after 12 months. After 24 months of vaccination, the seropositive rate of the TZ84 group was 95.6%, the HM-175 group was 72%, and the H2 group was only 63%. The same study speculated that the inactivated TZ84 strain HepA vaccine may contain more virus antigen than the HM-175 strain-inactivated HepA vaccine and that could be the reason for the greater immunogenicity [32]. This study by Zhang *et al*., also demonstrated that the inactivated TZ84 strain vaccine remained more immunogenic than both the H2 live strain vaccine and the inactivated HM-175 strain vaccine, even at 24 months following vaccination [32].

These findings were corroborated by an Indian study conducted on 467 vaccine-naïve children in India between 1 and 15 years of age. The study aimed to compare the immunogenicity and safety of the inactivated TZ84 strain HepA vaccine with those of the inactivated HM-175 strain HepA vaccine. While the participants in both groups achieved 100% seroconversion, significantly higher geometric mean concentration (GMC) of antiHAV immunoglobulin G (IgG) antibodies at day 210 was observed in the TZ84 strain group (40139.65 mIU/mL [95% confidence interval [CI]: 32889.82, 48987.55 mIU/mL]) compared with the HM-175 strain group (18167.84 [95% CI: 14451.70, 22839.55] mIU/mL). Fewer adverse reactions were noted in the subjects who received the inactivated TZ84 strain HepA vaccine (10.77%) than in those who received the inactivated HM-175 strain HepA (11.92%). These results therefore suggest that in the Indian population, the inactivated TZ84 strain HepA vaccine induced higher immunogenicity than the inactivated HM-175 strain HepA vaccine [33].

Table 1: HepA outbreaks in India over the past two decades

Year	Geographical location	Number of documented cases	Source of infection	References
2005	Kerala	1180	Contaminated water	[18]
2009	Pune	179	Contaminated water	[19]
2011	Punjab	83	Contaminated water	[20]
2014	Mylapore village, Kerala	45	Contaminated water	[21]
2015–2017	Kashmir	393	Contaminated water	[22]
2016	Kerala	223	Food from a newly opened hotel	[23]
2016	Kerala	562	Contaminated food	[24]
2020	Aligarh	183	Contaminated water	[25]
2020	Tamil Nadu	23	Contaminated water	[26]

HepA: Hepatitis A

A study by Wang *et al.* aimed to assess the immunogenicity and long-term persistence of the inactivated TZ84 strain and HM-175 strain HepA vaccines. At 15 years of follow-up, GMC in children receiving the inactivated TZ84 strain HepA vaccine was significantly higher than that in children receiving the inactivated HM175 strain HepA vaccine across time intervals ranging from 1 month to 15 years following the completion of the full vaccination regimen [34]. The TZ84 strain group also had higher seroconversion rates than the HM175 strain group at most time points during the study period. At 7 months, the seroconversion rates for both groups were 100%, whereas the seroconversion rates for the TZ84 strain group were consistently stable, with the minimum rate remaining >90% throughout the follow-up period. The seroconversion rates in the HM175 strain group were relatively less stable, as indicated by the lower limits of rates falling <90% at 112 months and 186 months. Thus, the inactivated TZ84 strain HepA vaccine may potentially exhibit a superior ability to sustain protective levels of anti-HAV antibodies compared with the inactivated HM-175 strain HepA vaccine, even 15 years after vaccination [34].

Although sporadic studies have demonstrated the efficacy of single doses of the inactivated TZ84 strain HepA vaccine, primary immunization with this vaccine comprises a two-dose schedule, with the second dose being administered 6 months following the first dose. The possibility of interchanging inactivated HepA vaccines was evaluated in an interchangeability and tolerability trial between the inactivated TZ84 strain and the inactivated HM-175 strain HepA vaccines. While GMCs were highest in patients who received 2 doses of the inactivated TZ84 strain vaccine (8905.5 [95% CI: 7566.5–10,481.5] mIU/mL), high antibody concentrations were also achieved in the group that received the inactivated HM-175 strain vaccine as first dose followed by the inactivated TZ84 strain vaccine as the second dose (4165.8 [95% CI: 3478.1–4989.5] mIU/mL). The antibody titers were found to be at least 2 doses of the inactivated HM-175 strain vaccine. The results of the trial thus confirmed that inactivated HAV vaccines could be interchangeable, thereby allowing for flexibility in vaccine selection. Therefore, if the primary objective is to achieve heightened antibody levels, it is advisable to consider a vaccination regimen comprising either two doses of the inactivated TZ84 strain HepA vaccine or a regimen involving the first dose with the inactivated HM-175 strain vaccine followed by a second dose with the inactivated TZ84 strain vaccine. The capacity to interchange these vaccines represents a crucial aspect for health-care professionals in addressing challenges related to limited vaccine availability [35].

INACTIVATED AND LIVE HEPA VACCINES: UNDERSTANDING THE DIFFERENCES

Cellular memory immune responses

A strong humoral and T cell-mediated immunity is offered by formaldehyde-inactivated vaccines [36]. A Cochrane review from 2012 concluded that inactivated HepA vaccines provide remarkable protection against clinical HepA and play a significant role in conferring seroprotection through anti-HAV IgG antibodies [37]. Administration of a single dose of an inactivated vaccine induces cellular memory immune responses that closely resemble those elicited by a natural infection. Consequently, the first vaccine dose itself effectively primes the immune system through an early proliferative T-cell response. As a result, after the initial administration of a priming dose of a two-dose inactivated vaccine, the second (booster) dose leverages the existing cell-mediated immune memory to elicit a swift humoral antibody booster response in individuals of all age groups. This response leads to a minimum 20–30-fold surge in antibody levels within 10–14 days [10]. A 2020 systematic review also found that GMCs of anti-HAV antibodies were significantly higher at 7–8 years after vaccination in children who received two doses of the HepA vaccine compared with those who received only one dose. Thus, the administration of two doses of the inactivated vaccine provided long-term protection, resulting in effective immunity [38].

Defense against HepA: Post-exposure prophylaxis (PEP)

Many countries have opted to utilize inactivated HepA vaccines for both pre- and PEP [21]. As highlighted in Table 1, several large outbreaks of HepA in various parts of India have been reported, which, in most cases, were due to contamination of water with sewage. The use of inactivated vaccines helps mitigate the potential risk of the live attenuated virus reverting to a virulent state [29,39,40]. Moreover, research suggests that a vast majority of subjects seroconvert within 2 weeks of vaccination. This prompt response implies that immunization against HepA can be administered as early as possible, within the 28-day incubation period of the infection. As a result, timely administration of an inactivated HepA vaccine following exposure can lead to effective disease prevention [30]. The use of inactivated vaccines as PEP has proven to be beneficial in preventing secondary cases of HepA outbreaks, with their effectiveness being equivalent to that of prophylactic Ig administration [41].

A review by Wu *et al*. reported that a single dose of the inactivated TZ84 strain HepA vaccine has the potential to arrest a community-wide outbreak of HepA, provided that a sufficient number of susceptible individuals are inoculated, resulting in herd immunity. In addition, it can forestall an epidemic in localities where only a limited number of cases of HAV infection have been reported [30].

In a study conducted to examine the efficacy of live HepA vaccines during an outbreak, the live vaccine failed to demonstrate a protective effect. A significant difference was not observed in the infection rate between the vaccinated and control groups. The potential explanation for this phenomenon could be attributed to the extended duration of antibody induction associated with the live vaccine, whereby seroconversion attains its peak approximately 2–3 months following administration. In contrast, the period of antibody induction for the inactivated HepA vaccine

is notably brief, lasting only 2 weeks. Hence, the efficacy of the inactivated HepA vaccine in conferring protection against HepA after exposure or an outbreak is widely acknowledged [30].

SECURING HEALTH: THE RELIABILITY AND SAFETY OF INACTIVATED HEPA VACCINES

The safety and tolerability of inactivated HepA vaccines in the pediatric population have been well established [32,35,42]. The common adverse reactions observed following vaccination include injection site reactions (such as pain and erythema) and mild systemic reactions (such as fever, irritability, lack of appetite, fatigue, and headache) [43]. Notably, the safety of inactivated HepA vaccines has been consistently established with more than 20 years of use and several hundred million doses being administered. The occurrence of serious adverse events related to these vaccines has been very rare, despite the presence of some short-term reactogenicity [10].

With live attenuated HepA vaccines, on the other hand, there is a risk of horizontal transmission. A Cochrane review indicated concern over the theoretical possibility of virulent atavism, which refers to the reversion of the live attenuated HAV strain in this vaccine to its original "wild form" [37]. A primary study of the H2-derived live attenuated HepA vaccine found that attenuated HAV was present in the stools of vaccinated individuals for 8–30 days after vaccination. The observation suggests the presence of a weakened form of HAV in the feces, although in significantly lower quantities than the wild strain. Furthermore, a Chinese study done among children aged 4–7 years residing in a boarding school found that administration of a live attenuated HepA vaccine was associated with increased horizontal transmission of HAV, with the virus being recovered from 70% of feces samples of children whose roommates had received the live vaccine (H2 strain) [28]. The potential for horizontal transmission through live attenuated HepA vaccine and its implications for HepA elimination in nations where this vaccine is used warrants additional surveillance [28,44,45].

Immunocompromised individuals may face an elevated risk of experiencing severe complications due to HAV infection. Research indicates that the inactivated HepA vaccine is a safe option for immunocompromised individuals and is readily accessible [28,29]. Studies also indicate that live vaccines are contraindicated for severely immunocompromised individuals as severe systemic reactions may develop against the vaccine strains [28,46].

ADMINISTRATION OF THE INACTIVATED TZ84 STRAIN HAV VACCINE

Administration of the inactivated TZ84 strain HepA vaccine is uncomplicated as it is approved for intramuscular delivery and recommended to be administered in two doses [28]. It is available in prefilled syringes (PFSs) and vials. The PFSs are advantageous due to their ease of use, enhanced precision in dosing (premeasured dosages can reduce dosing errors and increase patient compliance), and ability to ensure safe administration. Prefilled cartridges exhibit a comparatively lower susceptibility to fracturing or shattering as opposed to conventional glass counterparts, and they exhibit a notable degree of precision, thereby enhancing their safety profile. In an Indian study conducted by Kasi *et al.* to evaluate the effectiveness of vaccine administration through PFS compared to traditional vials, it was noted that the utilization of PFS led to a 2-fold increase in the rate of vaccine administration by health-care professionals. This increase was primarily ascribed to the reduction in vaccination time associated with PFS. In addition, it was found that the occurrence of handling errors and associated health hazard risk (HHR) were three times lower when using PFS compared with vials [47].

PROTECTING COMMUNITIES: STRATEGIC IMMUNIZATION INNOVATIONS

A position paper by the WHO stated that the inclusion of HepA vaccination is integral to a comprehensive strategy aimed at preventing and managing viral hepatitis. This strategy should complement other measures such as outbreak control, ensuring access to safe water, and promoting sanitation and hygiene practices [48]. In the Indian subcontinent, the evolving seroepidemiology of HepA, driven by improvements in sanitation, has led to a notable shift. This shift exposes a greater proportion of older children, adolescents, and young adults to an elevated risk of HepA infection. Consequently, it increases the average age at which infections occur, potentially leading to a paradoxical rise in severe cases among susceptible older age groups and an amplified risk of outbreaks [12,27]. This evolving scenario underscores the heightened significance of large-scale HepA vaccination efforts. The need for such vaccinations has become even more imperative in light of these changing dynamics, highlighting the importance of HepA vaccination as a preventive measure.

CATCH-UP VACCINATION FOR COMPREHENSIVE PROTECTION

Although routine vaccination of children against HepA has been implemented, a significant proportion of the population remains unvaccinated, thereby posing a potential risk of HAV infection to adolescents and adults. One of the significant benefits of catch-up vaccination for HepA is the prevention of infection in susceptible individuals, leading to improved public health outcomes, and it is particularly significant for individuals planning to travel to regions with a high prevalence of HepA [49]. The WHO, therefore, states that, in nations experiencing socioeconomic advancements, the widespread implementation of HAV vaccination is expected to yield costeffective results. Furthermore, the WHO recommends the use of catch-up immunization strategies guided by age-specific seroprevalence data [48].

CONCLUSION

Studies have reported a shift in the seroprevalence of HAV in the Indian population, thereby emphasizing the importance of

effective vaccination against HAV infection in India to prevent disease incidence in the community and reduce the impact of disease. Inactivated HepA vaccines have proven efficacy and safety in providing long-lasting protection among vaccinated children. Moreover, the inactivated TZ84 strain HepA vaccine has shown encouraging results in the Indian population by demonstrating higher immunogenicity. There is also robust evidence highlighting the long-term immunogenicity and safety of the inactivated TZ84 strain HepA vaccine in healthy children. The rapid seroconversion obtained by the inactivated TZ84 strain vaccine further supports its usefulness as a noteworthy HepA vaccine for immunizing children in India.

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