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ASSESSMENT OF THE EFFECTIVENESS AND SAFETY OF HEPATITIS A VACCINES IN THE CONTROL OF HEPATITIS A VIRUS INFECTION: A GLOBAL PERSPECTIVE

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ABSTRACT

Hepatitis A virus (HAV) is a highly contagious pathogen responsible for acute liver inflammation and significant global disease burden. While the Hepatitis A vaccine has been proven to be a safe and effective preventive measure—inducing protective antibodies in over 95% of recipients and offering long-term immunity for up to 30 years—there remains a need to critically assess its implementation and impact across various populations and geographic regions. Existing research predominantly focuses on clinical efficacy and safety profiles, yet there is limited evaluation of vaccine coverage disparities, long-term public health outcomes, and integration with other immunization programs. This review aims to synthesize current knowledge on the types, effectiveness, and safety of Hepatitis A vaccines while identifying gaps in vaccine accessibility, uptake among high-risk populations, and the role of combination vaccines in improving coverage. Addressing these gaps is essential for optimizing immunization strategies and sustaining the global reduction in HAV incidence.

Keywords: Hepatitis A vaccine, inactivated virus vaccine, Vaccine recommendations, Public health impact, Vaccine development

INTRODUCTION

Hepatitis A virus (HAV) is a highly contagious, non-enveloped, positive-sense single-stranded RNA virus that primarily affects the liver, causing acute hepatic inflammation and dysfunction. Transmission typically occurs through the fecal–oral route, often via ingestion of food or water contaminated with feces from an infected person. Although hepatitis A is usually self-limiting, it can lead to severe complications, particularly among adults, older individuals, and those with pre-existing liver conditions. The virus was first identified in 1973 by Stephen Feinstone, Albert Kapikian, and Robert Purcell, a milestone in the differentiation of hepatitis A from other viral hepatitides (Shouval, 2021). Historically, descriptions of epidemic jaundice—possibly due to HAV—date back to ancient Greek medicine, but it was not until the 20th century that hepatitis A was clinically distinguished from hepatitis B and C, with the development of specific serologic assays in the 1970s ,(CDC, 2021).

HAV remains endemic in many low- and middle-income countries (LMICs), particularly in sub-Saharan Africa, where poor sanitation, unsafe water, and inadequate hygiene practices facilitate its transmission. In Nigeria, several studies confirm the widespread nature of HAV. El-Yuguda *et al*., (2016) reported high seroprevalence rates among school-aged children in northeastern Nigeria, reflecting early-life exposure due to substandard sanitary conditions. Similarly, research in Cross River State found anti-HAV antibodies in 55.2% of children, suggesting ongoing community-level transmission, (Okonko *et al.,* 2015). Despite the known burden, hepatitis A has often been overshadowed by chronic hepatitis B and C infections, which are more likely to cause long-term liver disease. However, HAV outbreaks—often affecting hundreds or thousands—remain a serious concern in areas with limited vaccine coverage, underscoring the need for proactive and sustained preventive strategies.

Vaccination is currently the most effective method for preventing hepatitis A. Inactivated hepatitis A vaccines have shown exceptional immunogenicity, with over 95% of recipients developing protective antibody levels after two doses (WHO, 2022). These vaccines are considered safe and provide long-term immunity for at least 20 years, with some studies suggesting lifelong protection. In addition to monovalent HAV vaccines, combination vaccines that include HAV with hepatitis B (such as Twinrix) are also available and offer logistical advantages in public health programs. Nevertheless, uptake of the hepatitis A vaccine varies widely across countries and within populations. In many endemic regions, including Nigeria, hepatitis A vaccination is not routinely included in national immunization schedules, and public awareness about its benefits remains limited, (Adeyemi *et al.,* 2020). This lack of integration into public health systems represents a critical gap in the fight against HAV.

Given the persistent endemicity of HAV in Nigeria and other LMICs, this study aims to evaluate the current landscape of hepatitis A vaccination strategies, with a focus on their effectiveness, accessibility, and integration into existing public health frameworks. While the clinical efficacy of the vaccine is well-established, research gaps remain regarding vaccine implementation in resource-limited settings—particularly with respect to distribution equity, uptake among high-risk groups, and the long-term population-level impact. Addressing these challenges is vital for informing national policy, improving vaccination coverage, and ultimately reducing the incidence and outbreaks of hepatitis A.

Early Developments and Vaccine Discovery

The first descriptions of hepatitis A date back to ancient times, but significant progress in understanding the virus was made in the 20th century. The vaccine that prevents hepatitis A is known as the hepatitis A vaccine, (Maurice, 2021).

It lasts for at least 20 years, and possibly for the rest of a person's life, and it works in about 95 percent of cases. Starting after the age of one, two doses are advised if administered. It is administered via muscle injection. In 1991 and 1995, respectively, the European Union and the United States approved the first hepatitis A vaccination. It is listed as an essential medicine by the, (WHO, 2023).

Maurice Hilleman and his colleagues at Merck & Co. created the vaccine Vaqta, which was licensed in the United States in 1995. Children who lived in high-risk locations were gradually given the vaccination starting in 1996. Its use was expanded to regions with higher infection rates in 1999. In an effort to eradicate the virus countrywide, the vaccine is strongly advised for all children aged 12 to 23 months in the United States as of 2007. Despite being approved in Europe in 1991, GlaxoSmithKline's Havrix license was first granted by (Maurice, 2021).

All children older than one year, individuals whose sexual activity puts them at risk, those with chronic liver disease, those receiving treatment with clotting factor concentrates, those working in close proximity to the virus, and those residing in areas where an outbreak is occurring should be vaccinated, according to the US Centers for Disease Control and Prevention, (CDC, 2021). Since hepatitis A is the most prevalent vaccine-preventable virus contracted while traveling, people should get vaccinated before visiting regions where the infection is prevalent, such as the Indian subcontinent, Africa, Central America, South America, Asia, and Eastern Europe, (Tulchinsky TH, 2018; Nelson *et al.,* 2020). For optimal protection, the vaccination is administered in two doses to the upper arm muscle. Six to twelve months after the first dose, a booster should be administered, (CDC, 2007). About two to four weeks following the initial vaccine, protection against hepatitis A starts to take effect, (NHS, 2006; CDC, 2007). The duration of protection is at least 15 years, and if the booster is given, it is predicted to last at least 25 years, (Ott *et al.,* 2012).

Both vaccines provide substantial protection for at least two years with the inactivated vaccine and at least five years with the attenuated vaccine, according to a Cochrane analysis. The assessment found that while the inactivated vaccine is safe, more reliable data is needed to evaluate the attenuated vaccine's safety, (Irving, *et al.,* 2012).

Commercial vaccines

There are a number of marketed hepatitis A vaccinations. Depending on how hepatitis A antigen is quantified in their goods, different manufacturers have different definitions for (U) nits. Sanofi Pasteur manufactures Avaxim.

Hepatitis A virus inactivation generated in MRC-5 cells, 160 U of antigen adsorbed on aluminum hydroxide (0.3 mg Al) are present in each dose, (Wayback, 2010). Crucell is the maker of Epaxal. Also offered under the VIROHEP-A and HAVpur brand names. In addition to the hepatitis A antigen, this vaccine contains virosomes, which are synthetic particles made of influenza proteins and synthetic lipids. Aluminum is not present in it, (Wayback, 2010).

The inactivated hepatitis A virus produced in MRC-5 cells is produced by GlaxoSmithKline's Havrix, which contains 1440 ELISA units of viral antigen adsorbed on aluminum hydroxide (0.5 mg Al) per adult dose. The pediatric (child) doses contain half as much viral antigen and aluminum, (VAQTA, 2012). While Merck's Vaqta contains 50 U of antigen adsorbed onto 0.45 mg of aluminum (as aluminum hydroxyphosphate sulfate) in an adult dose, and the child dose contains half as much aluminum (VAQTA, 2012).

Combination vaccines

Hepatitis A and B vaccine is a vaccine against hepatitis A and hepatitis B. Hepatitis A and typhoid vaccine is a vaccine against hepatitis A and typhoid, (WHO, 2023).

Key milestones include:
- 1940s: Hepatitis A was differentiated from hepatitis B based on its incubation period.
- 1970s: Serologic tests were developed, allowing for definitive diagnosis.
- 1973: The Hepatitis A virus was
- 1979: The hepatitis A virus was isolated.
- 1995: Hepatitis A vaccines were first licensed in the United States, (WHO, 2023).

Prophylax is against HAV Infection Hepatitis A Vaccines

All three vaccines are inactivated and licensed by the U.S. Food and Drug Administration (FDA): Havrix in 1995, Vaqta in 1996, and Twinrix in 2001. The single-antigen vaccines Havrix and Vaqta, as well as the combination vaccine Twinrix (containing both HAV and HBV antigens), contain HAV antigen and are licensed in the United States.

Vaccine Preparation

The preparation of inactivated HepA vaccines is comparable to that of inactivated poliovirus vaccine (Misumi *et al.,* 2021 and Ayouni *et al.,* 2021). An adjuvant made of aluminum is present in HepA vaccinations. Vaqta is made without a preservative, whereas Havrix and Twinrix contain 2-phenoxyethanol as a preservative, (WHO, 2023).

Thimerosal is not a preservative found in any of the HepA vaccines that are authorized in the US. Enzyme-linked immunosorbent assay (ELISA) units of HAV antigen are used to express the final vaccine potency (per dose) for Havrix and Twinrix. Units of HAV antigen are used to express the antigen content of Vaqta. Additional details on how to prepare the HepA vaccine are included in the manufacturer's package inserts, (Viray *et al*., 2018).

Vaccine Storage and Shipment

According to (Ezeanalue *et al.*, 2018), the HepA vaccine should not be frozen and should be transported and stored between 36°F and 46°F (2°C and 8°C). Additional information is included in the manufacturer's package inserts, (Viray *et al*., 2018).

Route of Administration

Depending on the age of the recipient, the vaccine should be injected intramuscularly into the deltoid muscle of the upper arm or the anterolateral portion of the thigh (Ezeanalue *et al.,* 2018). Use a needle length that is suitable for the individual's size and age (Ezeanalue *et al*., 2018). HepA vaccinations ought to be given in a separate anatomic location when given in conjunction with other vaccinations or immune globulin (IG). (e.g., separate limbs) (Ezeanalue *et al.,* 2018). The dose is deemed genuine and does not require repetition if the HepA vaccination was given subcutaneously, accidentally, or for a medical purpose, (Ezeanalue *et al.,* 2018).

Vaccination Schedule and Dosage

Vaqta

Two formulations of Vaqta are licensed. Individuals who are 12 months to 18 years old should receive 25 units of HAV antigen per dosage in a two-dose schedule, whereas those who are 19 years of age or above should receive 50 units per dose, (Viray *et al*., 2018).

Havrix

Additionally, Havrix has two formulation licenses. In a two-dose plan, individuals 12 months to 18 years old should take 720 ELISA units each dose; those 19 years of age and over should receive 1,440 ELISA units per dose, Maurice Hilleman, (2021).

Twinrix

Twinrix can be used by adults who are at least eighteen years old. According to Viray *et al.,* (2018), Twinrix includes 20 µg of reco and 720 ELISA units of HAV antigen, which is half of the adult dose. Recombinant HBV surface antigen protein (the same as the adult dose of Engerix-

B) Twinrix's primary immunization is given in three doses at 0 months, 1 month, and 6 months, which is the same timetable as single-antigen HepB vaccination. Both HAV antigen and HBV surface antigen antibody responses following three Twinrix doses are comparable to those observed following separate, regular administration of the single-antigen vaccinations, (Czeschinski *et al*., 2021). The Twinrix packaging insert contains more details (Viray *et al.,* 2018). Twinrix can be given on an accelerated schedule of three doses at 0, 7, and 21–30 days before to travel or any other possible exposure, followed by a booster dose at 12 months to provide long-term protection, (Viray *et al*., 2018).

Hepatitis A Vaccination Schedule

- All children age 12 through 23 months and all children and adolescents age 2 through 18 years who have not previously received HepA vaccine
    - 2-dose series at 0, 6–18 months (Vaqta)
    - 2-dose series at 0, 6–12 months (Havrix)
- Adults age 19 years or older with risk factors
    - 2-dose series at 0, 6–18 months (Vaqta)
    - 2-dose series at 0, 6–12 months (Havrix)
    - 3-dose series at 0, 1, 6 months (Twinrix)

3-dose series with doses at 0, 7, 21–30 days, and booster 12 months after dose 1 (Twinrix, accelerated), (WHO, 2023).

The pediatric formulations of Havrix and Vaqta vaccines are approved for people's age 12 months through 18 years. The adult formulations are approved for people's age 19 years or older. Both vaccines are approved as a 2-dose series. The second dose of Vaqta is administered 6 through 18 months after the first dose, and the second dose of Havrix is administered 6 through 12 months after the first dose, Patravale *et al.,* 2012).

HepA-HepB (Twinrix) is licensed for person's age 18 years or older and administered as a 3-dose series at 0, 1, and 6 months. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 5 months. Twinrix is approved for people's age 18 years or older and can be used in persons in this age group with indications for both hepatitis A and hepatitis B vaccines. Twinrix is also approved using an alternative schedule with doses at 0, 7, and 21–30 days and a booster dose 12 months after the first dose, (CDC, 2022).

All children should receive hepatitis A vaccine at age 1 year (i.e., 12 through 23 months). Vaccination should be completed according to the licensed schedules. All children and adolescents age 2 through 18 years who have not previously received HepA vaccine should be vaccinated (i.e., children and adolescents are recommended for catch-up vaccination). Adults age 19 years or older with risk factors should receive the adult formulation of HepA vaccine. Persons at increased risk for HAV infection, or who are at increased risk for severe disease from HAV infection, should be routinely vaccinated, (WHO, 2023).

TRAVELERS

Vaccination of Groups at Increased Risk

- Persons age 6 months or older traveling to or working in countries with high or intermediate endemicity of HAV infection
    - <6 months or contraindicated for vaccine: IG
    - 6–11 months: 1 dose of HepA vaccine (does not count toward routine 2-dose series)
    - 12 months–40 years and partially vaccinated or unvaccinated: 1 dose of HepA vaccine

    - >40 years, immunocompromised, or chronic liver disease: 1 dose of HepA vaccine when travel is considered; if traveling in less than 2 weeks, 1 dose of HepA vaccine and may be administered IG in a separate limb
- International adoptees and persons who anticipate close personal contact with an international adoptee
    - Adoptees: Consider testing for anti-HAV IgG and IgM to guide decision-making
    - Contacts: 2-dose series as soon as adoption is planned
- Persons experiencing homelessness, persons with chronic liver disease, persons with HIV: Routine vaccination, (WHO, 2022).

Persons at increased risk for hepatitis A should be identified and vaccinated. HepA vaccine is recommended for people's age 6 months or older traveling to or working in countries where they would have a high or intermediate endemicity of HAV infection. These persons should be vaccinated, or receive IG if too young or contraindicated for vaccine, before departure. For travelers who are partially vaccinated already (i.e., did not receive a full vaccine series), a dose should be administered before travel, if needed, according to the vaccine schedule. If the first dose was given within the past 6 months, a second dose is not needed before travel. HepA vaccine should be administered to infant's age 6 through 11 months traveling outside the United States when protection against HAV is recommended, (WHO, 2022). The travel-related dose for infant's age 6 through 11 months does not count toward the routine 2-dose series. Therefore, the 2-dose HepA vaccination series should be initiated at age 12 months with the appropriate dosage and schedule. Healthy people's age 12 months through 40 years who are planning on traveling to an area with high or intermediate hepatitis A endemicity and who have not received HepA vaccine should receive a single dose of HepA vaccine as soon as travel is considered and should complete the HepA vaccine series with the appropriate dosage and schedule, (Yin *et al.,* 2020).

Persons older than age 40 years, persons with immunocompromising conditions, and persons with chronic liver disease planning on traveling to an area with high or intermediate HAV endemicity should receive a single dose of HepA vaccine as soon as travel is considered. Persons traveling in less than 2 weeks should receive the initial dose of HepA vaccine and simultaneously may be administered IG in a different anatomic injection site (e.g., separate limbs), (Vivaxim, 2020). The HepA vaccine series should be completed according to the routine schedule. Travelers for whom vaccine is contraindicated, who choose not to receive HepA vaccine when it is indicated, and persons younger than age 6 months old should receive IG. Persons traveling for up to 1 month should receive a single dose of IG (0.1 mL/kg). Persons traveling for up to 2 months should receive IG at 0.2 mL/kg. Persons traveling for 2 months or longer should receive IG at 0.2 mL/kg repeated every 2 months for the durati`on of travel. Infants age <6 months traveling for 2 months or longer should receive IG at 0.2 mL/kg repeated every 2 months for the duration of travel or until the infant is administered HepA vaccine (i.e., at age ≥6 months), (Twinrix and FDA, 2019).

International Adoptees and Persons Who Anticipate Close Personal Contact with an International Adoptee

Screening asymptomatic people for hepatitis A is generally not recommended; however, clinicians may decide to test internationally adopted children for anti-HAV IgG and IgM to identify those who may be acutely infected and shedding virus and to make decisions regarding HepA vaccination, (Vivaxim, 2020). HepA vaccination is recommended for all previously unvaccinated persons who anticipate close personal contact (e.g., household contact or regular babysitting) with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the United States. The first dose of the

2-dose HepA vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee, (Vivaxim, 2020).

Persons Experiencing Homelessness

All people's age 1 year or older experiencing homelessness should be routinely vaccinated against hepatitis A. HepA vaccine should be integrated into routine preventive services for persons experiencing homelessness. A homeless person is defined as an individual: who lacks housing (without regard to whether the individual is a member of a family), including an individual whose primary residence during the night is a supervised public or private facility (e.g., shelter) that provides temporary living accommodations and an individual who is a resident in transitional housing; without permanent housing who may live on the streets; stay in a shelter, mission, single-room occupancy facility, abandoned building or vehicle; or in any other unstable or nonpermanent situation; who is "doubled up," a term that refers to a situation where individuals are unable to maintain their housing situation and are forced to stay with a series of friends or extended family members, (Twinrix and FDA, 2019).

Persons with HIV

All persons with HIV infection age 1 year or older should be routinely vaccinated with HepA vaccine. Because the response to the vaccine might be reduced in persons with HIV infection who are immunosuppressed, post-vaccination serologic testing should be performed for all persons with HIV infection at least 1 month after completing the HepA vaccine series, (McNeil *et al.,* 2014). HepA vaccination is not routinely recommended for health care personnel, persons attending or working in child care centers, food service establishments and food handlers, or persons who work in liquid or solid waste management (e.g., sewer workers or plumbers). These persons have not been shown to be at increased risk for HAV infection. In addition, transmission of HAV from infected food handlers to susceptible consumers or restaurant patrons in the workplace is rare. As of 2020, persons who receive blood products for clotting disorders (e.g., hemophilia) are no longer specifically recommended to receive HepA vaccine, (Havrix*,* 2024).

Vaccine Interchangeability

Limited data indicate that vaccines from different manufacturers are interchangeable. Completion of the series with the same product is preferable. However, if the originally used product is not available or not known, vaccination with either product is acceptable. For both vaccines, the dosage of the second dose should be based on the person's age at the time of the dose, not the age when the first dose was given. The minimum interval between the first and second doses of hepatitis A vaccine is 6 months, (WHO, 2023). There is no maximum interval for either vaccine. A second dose given at 12 months or longer after the first dose need not be repeated. Single-antigen hepatitis A and hepatitis B vaccines may be used in conjunction with Twinrix to form a complete series of these vaccines. Because the hepatitis B component of Twinrix is equivalent to a standard adult dose of hepatitis B vaccine, the schedule when vaccinating against hepatitis B is the same regardless of which hepatitis B vaccine (i.e., single-antigen or Twinrix) is used for which dose. Because the hepatitis A component of Twinrix is equivalent to a pediatric dose of hepatitis A vaccine, a series mixing the single-antigen hepatitis A vaccine and Twinrix is more complex. A person age 19 years or older who receives 1 dose of Twinrix may complete the hepatitis A series with 2 doses of adult formulation hepatitis A vaccine separated by at least 5 months. A person who receives 2 doses of Twinrix may complete the hepatitis A series with 1 dose of adult formulation hepatitis A vaccine 5 months after the second dose. A person who begins the hepatitis A series with single-antigen hepatitis A vaccine may complete the series with 2 doses of

Twinrix or 1 dose of adult formulation hepatitis A vaccine. Person's age 18 years should follow the same schedule using the pediatric formulation, (Twinrix and FDA, 2019).

Post-exposure Prophylaxis (PEP)

HepA vaccine should be administered as soon as possible, within 2 weeks of exposure, to all unvaccinated persons age 12 months or older who have recently been exposed to HAV. In addition to HepA vaccine, co-administration of IG (0.1 mL/kg) is recommended under certain circumstances and for people's age 40 years or older based on the provider's risk assessment. Considerations regarding decision to use IG, vaccine, or both should include the ability of the person to develop a protective level of antibodies after receipt of HepA vaccine, the magnitude of the risk for HAV transmission from the exposure, and the availability of IG and vaccine, (Yin *et al.,* 2020).

Unvaccinated persons who are immunocompromised or have chronic liver disease and who have been exposed to HAV within the past 14 days should receive both IG (0.1 mL/kg) and HepA vaccine simultaneously in a different anatomic site (e.g., separate limbs) as soon as possible after exposure. When the dose of HepA vaccine administered for post-exposure prophylaxis is the first dose the exposed person has received, a second dose should be administered 6 months after the first for long-term immunity; however, the second dose is not necessary for PEP. IG (0.1 mL/kg) is recommended for post-exposure prophylaxis for children younger than age 12 months and for persons for whom vaccine is contraindicated.

Booster and Challenge Doses

By producing an anamnestic response, a dose of the HepA vaccine can be used to detect the existence of vaccination-induced immunologic memory. A dose of HepA vaccine given following a primary vaccination series to provide quick protective immunity against significant infection (i.e., infection that results in serologic test results positive for HAV, clinically significant disease, or both) has been referred to as a "booster dose" or "challenge dose." (Viray *et al*., 2018).

Vaccine Performance Detection of Anti-HAV after Vaccination Correlate of protection

An immune response (i.e., IgG anti-HAV titer) that causes and is statistically associated with protection is known as the correlate of protection (Plotkin *et al*., 2020). Anti-HAV levels are expressed as milli-international units per milliliter (mIU/mL) and are assessed against a reference IG reagent from the World Health Organization. The achievement of a measurable and quantifiable post-vaccination IgG anti-HAV level of ≥10 mIU/mL by conventional tests is known as seroconversion, or response to vaccination, (Viray *et al.,* 2016; Plotkin *et al.,* 2020). When IgG anti-HAV levels continue to be higher than the correlate of protection, serocorection—which is regarded as a stand-in for clinical protection—persists. Since IG is 90% effective at preventing hepatitis A and very low levels of anti-HAV are found in IG patients, the exact lower limit of anti-HAV required to prevent HAV infection has not been established, but it is probably rather low,

(Stapleton *et al.,* 2020; Winokur *et al.,* 2021). Anti-HAV concentrations obtained during active induction by vaccination or passive transfer by IG are 10–100 times lower than those generated in response to a spontaneous infection, (Lemon *et al.,* 2022). Because vaccine-induced antibody levels are typically high and few illnesses have been found among vaccinated individuals, clinical investigations have produced little information from which a minimal protective antibody level can be calculated. (Vaccine failure, for example). The threshold for human protection against HAV infection has been suggested to be between 10 and 33 mIU/mL using several tests (Lemon *et al*., 2022). However, one study suggested that any detectable level of IgG anti-HAV would suggest protection, (Stapleton *et al.,* 2020). The lower limit of detection of the specific assay being employed has traditionally been regarded as the protective level because there is no absolute

protected level identified; post-vaccination studies use ≥10 mIU/mL as the minimum protection level, (Nalin *et al*., 2021).

IgM anti-HAV after vaccination.

IgM anti-HAV can be detectably produced by HepA vaccination, especially if the test is performed a few weeks after the vaccine. Eight to twenty percent of adults have been shown to have IgM anti-HAV two to three weeks after receiving a single dose of the vaccination (Shouval *et al.,* 2023; CDC, 2023). People should only be tested for IgM anti-HAV if they are symptomatic and suspected of having a HAV infection in order to minimize false-positive results, (Nelson *et al.,* 2020).

Immune Globulin

By passively transferring antibodies, IG offers protection against hepatitis A. (See GamaSTAN package insert) GamaSTAN is a sterile, preservative-free intramuscular IG solution used for prophylaxis against infections caused by the HAV, measles, varicella, and rubella viruses (Grifols *et al*., 2019). The only FDA-approved IG product for hepatitis A prophylaxis is GamaSTAN. The dosage of IG was modified in 2017 to account for the decline in IgG anti-HAV potency, (Nelson *et al.,* 2020; Tejada *et al*., 2021), probably as a result of plasma donors' declining prevalence of prior HAV infection (Barzaga, 2019). GamaSTAN can be given at any time in between doses or concurrently with inactivated vaccinations or toxoids in a different anatomic location (such as distinct limbs) (Ezeanolue *et al*., 2018). However, it is unknown how IG preparations affect the response to specific live-virus vaccinations, and antibodies in Gama STAN may conflict with live-virus vaccines like the varicella and measles, mumps, and rubella (MMR) vaccines. (Grifols *et al.,* 2019). Additional information is included in the GamaSTAN package insert. When MMR and varicella vaccinations are advised, they should be given at least two weeks before to (Ezeanolue *et al.,* 2018) or at least six months following the administration of hepatitis A IG, (Ezeanolue *et al*., 2018; Grifols *et al.,* 2019).

Vaccine-Induced Seroprotection

Immunogenicity in Infants

According to the information now available, children under the age of two who do not have a positive acquired maternal antibodies respond immunogenic to inactivate HepA vaccinations. After receiving the HepA vaccine, all of these kids developed protective antibody levels; however, the final geometric mean concentrations (GMCs) varied according on the dosage and timing (Descenclos *et al.,* 1993; Wheeler *et al.,* 2020). Following vaccination, the GMC was lower among infants (less than 12 months old) who passively acquired maternal antibodies (Wheeler *et al.,* 2020).

Immunogenicity in Youngsters and Teens

Studies employing various formulations and vaccination regimens have shown that HepA vaccines are highly immunogenic when given to children and adolescents. One month following the first dosage, 97% to 100% of individuals between the ages of 2 and 18 had protective antibody levels, and 100% had protective levels with high GMCs one month following the second dose. (Grifols *et al.,* 2019).

Immunogenicity in Adults

When given in accordance with the suggested schedules, all licensed HepA vaccinations are highly immunogenic in adults over the age of 18 (Van *et al*., 2015; Ezeanolue *et al.,* 2018; Nalin *et al*., 2021; McMahon *et al*., 2023;). There is little information on when protective antibodies must develop. The immunogenicity and safety of the inactivated HepA vaccine in

individuals aged ≥40 years were compared with those aged 20–30 years in a retrospective pooled analysis of four 2-dose immunization studies. (Mannucci *et al.,* 2018).

At one month following the first dosage (91%–99.7%) and second dose (95.3%–100%), the immune response ranged similarly throughout the age groups. However, adults aged 20–30 years had a greater seroconversion rate at 15 days (92.3%; 95% CI: 84–97) than those aged ≥40 years (79.7%; 95% CI: 68.8–88.2) (Grifols *et al.,* 2019). Using the usual Twinrix regimen, the percentage of those who experienced hepatitis A seroconversion was 93.8% after one dose, 98.8% after two doses, and 99.9% one month after three doses; further details are available in the Twinrix box insert, (Grifols *et al.,* 2019).

Vaccine Efficacy

About 40,000 children between the ages of 1 and 16 participated in a double-blind, randomized controlled clinical trial in Thailand to assess Havrix's effectiveness. Active surveillance in 1989–1991 showed that the children lived in communities with 119 instances of HAV infection per 100,000 people. The vaccine's effectiveness in preventing clinical hepatitis A was 94% (95% CI: 79%–99%) following two doses (360 ELISA units per dose) given one month apart. About 1,000 children between the ages of 2 and 16 who lived in a town in New York where 68% of adults over the age of 19 had measurable antibody levels participated in a double-blind, place-be-controlled, randomized clinical study employing Vaqta (Werzberger *et al.,* 2021). Following the administration of one dose (25 units) of the vaccine, the protective effectiveness against clinical hepatitis A was 100% (lower bound of the 95% CI: 87%). Twinrix's effectiveness should be comparable to that of each of the monovalent HepA and HepB vaccine ingredients; more details are available in the Twinrix package insert, (Grifols *et al.,* 2019).

Long-Term Protection

Although the precise length of protection against HAV infection following vaccination is uncertain, lifetime protection happens following a spontaneous HAV infection and may also exist following immunization. Studies on the long-term immunogenicity of children who received vaccinations as children, adults who received vaccinations as children, and adults who received vaccinations as adults have all been conducted. (Ezeanolue *et al*., 2018).

Children vaccinated at age, Adults vaccinated as adults.

Two randomized double-blind studies of people who received Havrix 1440 ELISA units with a 2-dose schedule of 0–6 months or 0–12 months in 1992–1993 were conducted to evaluate antibody persistence every year (Hens *et al.,* 2014; Theeten *et al.,* 2015). More than 97% of persons tested positive for anti-HAV antibodies 20 years following immunization. 34 out of 36 participants who received the initial vaccination on a two-dose regimen between 0 and 6 months had GMCs of 312 mIU/ml, whereas 85 out of 86 patients who received the vaccination between 0 and 12 months had GMCs of 317 mIU/ml, (Ezeanolue *et al*., 2018).

Following the delivery of the HepA vaccination booster, six out of seven subjects who had lost circulating anti-HAV antibodies developed a robust response over the course of a 20-year follow-up. According to Theeten *et al*. (2015), mathematical modeling indicated that seropositive anti-HAV levels will remain in ≥90% of vaccinations at ion-a r 40 and ≥95% at year 30. Regular evaluations of the length of protection are still carried out. (Ezeanolue *et al*., 2018). Anamnestic response to HepA booster doses suggests ongoing immunological memory and protection against HAV infection, despite signs of declining anti-HAV, (Theeten *et al*., 2015). Long-term protection may also be facilitated by cellular immunity.

Protection from a Single-Dose Hepatitis A Vaccine According to research evaluating long-term protection up to 10.67 years after a single dose of the inactivated HepA vaccine,

protective anti-HAV antibody levels can last for nearly 11 years and rise or return after booster vaccination, (Grifols *et al.,* 2019). Furthermore, it has been demonstrated that a single dose of the HepA vaccine can produce HAV-specific cellular immunity that is comparable to that produced by a natural infection. It has also been demonstrated that a single dose of the single-antigen HepA vaccination can contain hepatitis A epidemics, (McMahon *et al.,* 2023). In certain South American nations, universal single-dose kid vaccination programs have been started. Brazil's National Immunization Program implemented a single-dose universal immunization for children ages 15 to 24 months in 2014, (Brito *et al.,* 2018).

Regardless of the mother's anti-HAV status, there was a notable drop in HAV cases among infant's ages 1 year, (Bell *et al.,* 2022; Dagan *et al.,* 2023). Immune Globulin and Hepatitis A Vaccine Administration at the Same Time The percentage of people who later had protective antibody levels did not change, despite the fact that the GMCs of adults who got IG and vaccine were lower one month after the vaccine series was finished than the GMCs of adults who had received HepA vaccine alone, (Wagner *et al.,* 1993; Walter *et al*., 2018). Therefore, it is unknown how lower GMCs will affect long-term protection. Immunocompromising Conditions Immunocompromised children and adults (such as recipients of hematopoietic cell transplants [HCT], patients on chemotherapy, and individuals infected with HIV) may have a decreased humoral response to the HepA vaccine, (Garcia *et al*., 2015; *Rubin et al.,* 2019; Fritzsche *et al*., 2019). Modified dosing regimens, such as doubling the usual antigen dose or administering extra doses, may improve response rates, according to the limited data. Furthermore, regardless of the source of the transplanted stem cells, ACIP best practice guidelines urge that recipients of HCT who had vaccinations prior to their HCT be routinely immunized or revaccinated following HCT; HepA vaccine revaccination doses are advised following HCT, (Rubin *et al.,* 2019).

The Infectious Disease Society of America has guidance for vaccination of the immunocompromised host.

According to the guidelines, a series of HepA vaccinations should be administered to solid organ transplant candidates who are unvaccinated, under vaccinated, or seronegative for hepatitis A. This is especially true for liver transplant candidates who are between the ages of 12 and 23 months (strong recommendation, moderate-quality evidence) and ≥2 years (strong recommendation, moderate-quality evidence), (Rubin *et al.,* 2019).

People with HIV Infection Have Lower CD4 Counts and Other Factors

For both adults and children with HIV infection, the HepA vaccination is immunogenic when administered according to a prescribed dosage and timing. Adults with lower CD4 counts are less likely to develop protective antibody levels, even while individuals with higher CD4 counts (>200–300 cells/mm3) react almost as effectively as those without immunocompromised conditions, (Huang *et al.,* 2019; Armstrng *et al*., 2002-2007). According to Rubin *et al.,* (2019), this finding implies that immune reconstitution with antivirals may restore the capacity to respond to vaccination. Up to 6–10 years following HepA vaccination, the majority of persons with HIV infections under control had persistent seropositive responses. Protective, according to one study (Rubin *et al.,* 2019). Higher weight (overweight and obese), lower CD4 count or HIV viremia at the time of HepA vaccination, or lower or delayed seroresponse to vaccination are factors linked to seroreversion (loss of seroresponse) among HIV-positive individuals who had an initial seroconversion, (Rubin *et al.,* 2019).

Chronic Liver Disease

When children or adults with viral or nonviral chronic liver disease were vaccinated, seroprotection proportions were comparable to those seen in healthy adults, (Huang *et al.,* 2019); Lee *et al.,* (2018). Seroprotection varies greatly among liver transplant recipients. In one study, six (26%) out of 23 liver transplant recipients responded to the HepA immunization, whereas in another, none of the eight patients who received the vaccination after receiving a liver transplant responded, (Rubin *et al.,* 2019). In a different trial, however, the HepA vaccination proved immunogenic for the majority of liver transplant recipients, with 38 (97%) reacting to a typical dosage and regimen, (*Rubin et al.,* 2019), (Older Age (Being over 40). There is little evidence to support the idea that older recipients of the HepA vaccine may not have as strong of an immune response as younger recipients. In other trials, those over 40 who received the vaccination had lower seroprotection rates than people under 40, especially when levels were tested within 15 days of the first dose, although they also had similar lower CD4 counts and other factors. Among Individuals Infected with HIV For both adults and children with HIV infection, the HepA vaccination is immunogenic when administered according to a prescribed dosage and timing, (*Rubin et al.,* 2019). Adults with lower CD4 counts are less likely to develop protective antibody levels, even while individuals with higher CD4 counts (>200–300 cells/mm3) react almost as effectively as those who are not immunocompromised, (Garcia *et al.,* 2019). The ability to respond to vaccination may be restored by immunologic reconstitution using antivirals, according to this finding, (Rubin *et al.,* 2019). After receiving HepA vaccine, the majority of persons with well-managed HIV infections showed persistent seropositive responses for six to ten years, (Garcia *et al*., 2019). The 32 children with HIV infection (mean age: 5.5 years) developed protective antibodies in 100% of them in one study, (Garcia *et al.,* 2019). Higher weight (overweight and obese), lower CD4 count or HIV viremia at the time of HepA vaccination, or lower or delayed seroresponse to vaccination are factors linked to seroreversion (loss of seroresponse) in persons with HIV infection who had an initial seroconversion, (Huang *et al.,* 2019).

Hepatitis A Single-Antigen and Combination Vaccine Safety Administration

In prelicensure clinical trials, injection site reactions (such as pain and erythema) and mild systemic reactions (such as fever, irritability, and loss of appetite, drowsiness, and headache) were the most frequent adverse events after vaccination with Havrix and Vaqta (HepA) and Twinrix (combination HepA and HepB), (Havrix*,* 2024). Adverse event rates after Twinrix immunization were comparable to those seen with HepA and HepB vaccinations given separately. Post-licensure safety monitoring of U.S. vaccinations is carried out through VAERS, a spontaneous reporting (passive surveillance) system run by the FDA and CDC, (Shimabukuro *et al.,* 2015). Five percent of the 25,079 U.S. reports of HepA vaccines that VAERS received between 2006 and 2018 were categorized as serious, meaning that at least one of the following occurred: death, life-threatening illness, hospitalization or prolongation of an existing hospitalization, or permanent disability (Post marketing reporting of adverse experiences, 2010), of all the reports, 48.6% involved people between the ages of 2 and 18; 29.5% involved children between the ages of 12 and 23 months; and 13.3% involved adults over the age of 19. HepA vaccinations were given concurrently with additional vaccinations at the same medical visit in the majority of studies (80.3%). Fever (16.2%), injection site erythema (14.8%), injection site edema (9.9%), rash (9.0%), and erythema (8.9%) were the most commonly reported side effects, out of 2,117 U.S. reports concerning the combined HepA and HepB vaccine that VAERS received throughout the same time period (2006–2018), 8.6% were deemed serious. People ≥18 years old (the legal age for the licensed vaccine) accounted

for 92.9% of all reports. In the majority of complaints (60.3%), the Twinrix vaccine was given concurrently with other vaccinations during the same medical appointment, (CDC, 2018).

The following side effects were most commonly reported: dizziness (9.4%), injection site pain (9.8%), fever (13.6%), headache (11.5%), and pain (11.5). VAERS does not evaluate whether a vaccination caused an adverse event, and thus is susceptible to the limitations of spontaneous reporting systems in general. These VAERS results for the HepA and Twinrix combination vaccinations, however, are comparable to those for other inactivated vaccines that are often given to these age groups, (Ciccullo *et al.,* 2018).

There is little information available about HepA vaccination during pregnancy

No alarming trends of adverse events in the pregnant women or their unborn children were found in a published safety evaluation of 139 reports submitted to VAERS between 1996 and 2013 about women who got the HepA vaccine or the combo Twinrix vaccine during pregnancy, (Moro *et al*., 2014). A multisite study, (Groom *et al*., 2019). HepA vaccine administration during pregnancy was not linked to an increased risk for a variety of adverse events examined among pregnancies that resulted in live births, according to CDC's Vaccine Safety Data link (VSD), a population-based research and surveillance data system of maternal HepA vaccination. Nonetheless, a correlation was discovered between infants that were tiny for gestational age and the mother's HepA immunization. Although researchers think this link was probably caused by unmeasured confounding, it may nevertheless merit further investigation, (Groom *et al*., 2019).

The HepA vaccine should not be administered to those who have experienced a severe allergic reaction (such as anaphylaxis) following a prior dose or who have a severe allergy to a component of the vaccine, (Groom *et al*., 2019). When a person has a moderate to severe acute sickness, whether or not they have a fever, they may choose to postpone getting vaccinated, (Groom *et al.,* 2019).

Administration of Additional Vaccines at the Same Time

Additional information can be found in the manufacturer's package inserts, although the data currently available do not show a decreased response when the HepA vaccine is given with other vaccines to both adults and children, (Perrecz *et al.,* 2019). The HepA vaccine does not reduce the immune response to either vaccine or increase the frequency of adverse events when administered concurrently with the diphtheria, poliovirus (oral and inactivated), tetanus, typhoid (oral and intramuscular), cholera, Japanese encephalitis, rabies, or yellow fever vaccines, according to limited data from adult studies, (Perrecz *et al*., 2019). Prior to Twinrix being licensed in the US, research showed that the HepB and HepA vaccines may be given concurrently without lowering vaccination immunogenicity or raising the incidence of side effects, (Perrecz *et al.,* 2019). The immunogenicity and reactogenicity of these vaccinations are unaffected by research done on newborns and young children, (Perrecz *et al*., 2019). About 4,300 children between the ages of 12 and 23 months responded favorably to receiving one or two doses of Vaqta, either by alone or in combination with other vaccines (M-M-RII, Varivax, Tripedia, Prevnar, ProQuad, PedvaxHIB, and Infanrix) in the United States, (Petrecz *et al*., 2019).

Cost-Effectiveness Considerations

An investigation published in 2007 that followed a single U.S. birth cohort of almost 4 million people from birth in 2005 to age 95 or death employed a Markov model to assess the cost-effectiveness of routine HepA vaccination on a national level, (Perrecz *et al.,* 2019). A regular vaccination at age one year would save 172,000 illnesses compared to not getting one, at a cost of $28,000 per quality-adjusted life year (QALY) saved. Comparatively speaking, the 1996 and 1999 ACIP guidelines' levels of HepA immunization were maintained under the previous regional

strategy. At a cost of $45,000 per QALY saved, (Rein *et al.,* 2007), global regular vaccination at age 1 year would prevent an extra 112,000 illnesses, (Perrecz *et al.,* 2019). Similar findings were obtained by another economic study that took into account the projected decrease in secondary infections among household contacts of infected children, (Williams *et al.,* 2017). Following the adoption of the global HepA children immunization guidelines from 2006, (Fiore *et al*., 2021), Using hepatitis A incidence rates from 2008 to 2012, the original Markov model was modified in

2015 to evaluate the cost-effectiveness of catch-up HepA vaccination among unvaccinated and partially vaccinated children in comparison with unvaccinated children, (Hankin-Wei *et al.,* 2016). During the cohort's lifespan, catch-up HepA vaccination would increase vaccine doses by 556,989 while lowering the overall number of infections compared to the baseline by 741. The net cost of catch-up vaccination would rise by $10.2 million, or $2.38 per person, (Hankin-Wei *et al.*, 2016). The model's findings were extremely susceptible to changes in the adult vaccination rate, the prevalence of HAV infection, and the discount rate (3%). While adult vaccination rates have remained low, (William *et al.,* 2017), the incidence of hepatitis A and the vaccination rates for hildren and adolescents are significantly higher than they were at the time this model was created, (CDC, 2018 and CDC, 2019). As a result, catch-up vaccination's true cost-effectiveness is probably better now than it was initially thought, (Huang *et al.,* 2019).

Treatment and management of HAV

Chronic liver disease is not caused by the hepatitis A virus; rather, it is a self-limited infectious disease, (Mackinney-Novelo *et al*., 2021). Hepatitis A has no known cure; conservative measures are usually sufficient to help most people recover. The goal of treatment is to preserve comfort and proper nutritional balance, which includes replenishing fluids lost due to diarrhea and vomiting (CDC, 2023). The primary method of treating acute hepatitis A is symptomatic. Adequate fluid replacement therapy is recommended for patients who are at risk of dehydration, (CDC, 2021).

HAV infection prevention and management

Hepatitis A Vaccination, sanitation, and proper hygiene can prevent it, (CDC, 2023). Vaccines come in two varieties: live but attenuated and inactivated. For contacts who are more than seven days past the onset of illness and for those who are at risk of experiencing negative consequences from a HAV infection, human normal immunoglobulin may be provided either in addition to or instead of the vaccine. The best way to avoid contracting HAV and lower the prevalence of the disease is by vaccination. It lasts for at least 15 years, and possibly for the rest of a person's life, and is effective in about 95% of cases. Prior to visiting nations with moderate or higher endemicity, the WHO advises getting vaccinated against HAV. The fecal-oral pathway is how the hepatitis A virus is transmitted from person to person. The foundation of prevention is good hygiene, including thorough hand washing before preparing food and after using the restroom. Care should be made to prevent exposure to hepatitis A through contaminated food and water for visitors to countries with high and intermediate endemicity, (WHO, 2023).

Conclusion

This study highlights the proven effectiveness and safety of hepatitis A vaccines in reducing the incidence and severity of hepatitis A virus (HAV) infections worldwide. Inactivated and combination vaccines have demonstrated high seroconversion rates and long-term immunity, with minimal adverse effects, making them powerful tools in global HAV prevention efforts. Despite these advantages, disparities persist in vaccine accessibility, awareness, and integration into national immunization programs—particularly in low- and middle-income countries (LMICs) like Nigeria, where the burden of HAV remains high. The continued occurrence of HAV outbreaks

in endemic regions reveals significant gaps in vaccination coverage, surveillance, and public health infrastructure. These challenges are compounded by socioeconomic and infrastructural barriers, which hinder effective vaccine deployment. Therefore, while the clinical efficacy of HAV vaccines is well-established, a comprehensive global strategy that addresses contextual and systemic obstacles is critical to ensuring equitable vaccine delivery and long-term control of HAV transmission.

Recommendations

1. National governments, particularly in HAV-endemic regions, should formally include the hepatitis A vaccine in their routine immunization schedules, starting with high-risk populations such as children, food handlers, and individuals with chronic liver disease.
2. Ministries of health should work with global health partners (e.g., Gavi, WHO, UNICEF) to secure funding and reduce the cost barrier for hepatitis A vaccines, making them affordable and accessible, especially in resource-limited settings.
3. Governments should establish or reinforce hepatitis A surveillance systems to monitor incidence, detect outbreaks early, and assess the impact of vaccination programs over time.
4. Healthcare providers should routinely screen high-risk individuals (e.g., travelers, MSM, people with liver disease) for hepatitis A immunity and offer timely vaccination in clinical settings, including primary care and travel clinics.
5. Medical personnel should receive updated training on HAV transmission, vaccine schedules, and adverse event monitoring to improve clinical management and patient education.

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