Hepatitis A vaccines

Summary of WHO Position Paper

WHO position paper on hepatitis A vaccines – October 2022
Weekly Epidemiological Record
7 October 2022

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Executive summary

1. Hepatitis A infection causes inflammatory liver disease disease that may progress in rare instances to fulminant liver failure

   A. Clinical outcome and mortality strongly correlated with age: while young children generally have asymptomatic infection, older children and adults commonly experience symptomatic disease which may lead to severe illness and sometimes death.

   B. Disease burden is estimated at 160 million cases and 40000 deaths annually

2. Available hepatitis A vaccines are safe and highly effective and provide long-term protection against symptomatic and severe disease.

3. WHO recommends inclusion of hepatitis A in childhood immunization programmes if indicated on the basis of: i) an increasing trend over time of acute hepatitis A disease, including severe disease, among older children, adolescents or adults; ii) changes in the endemicity from high to intermediate; and iii) considerations of cost–effectiveness.

   A. Single or two doses of inactivated vaccines administered starting respectively at >12 months of age.

   B. Single dose of live attenuated vaccine administered at >18 months of age.
Background of hepatitis A infection

- Hepatitis A virus infections causes inflammatory liver disease that may progress in rare instance to fulminant liver failure.

- Transmission primarily via the faecal/oral route through ingestion of contaminated food and water, or through direct contact with an infectious person.

- Transmission associated with extensive shedding of the virus in faeces, up to 6 months or longer (for example, contact with a case within a household).

- The incidence of hepatitis A infection correlates with socioeconomic indicators, decreasing with increasing income, and access to clean water and adequate sanitation.

- Clinical outcome strongly correlated with age: while young children generally have asymptomatic infection, older children and adults commonly experience symptomatic disease.

- Estimated 40 000 deaths per year. Mortality increases with age (0.23% in under 30, to 2.1% in those aged >49 years).

Key take-aways

Hepatitis A infections, may in rare instance lead to fulminant liver failure, mainly in adults.
### 1A Background of hepatitis A infection

**Profiles of seroprevalence by age vary geographically**

<table>
<thead>
<tr>
<th></th>
<th>Most low-income regions</th>
<th>Most high-income regions</th>
<th>Most middle-income regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong> of anti-HAV antibodies</td>
<td>High &gt;90% by the age of 10 years</td>
<td>Low &lt;50% by the age of 30 years</td>
<td>Mix of Intermediate or Low</td>
</tr>
<tr>
<td><strong>Circulation</strong> of HAV/ risk of outbreaks</td>
<td>Low*</td>
<td>Low**</td>
<td>Increased***</td>
</tr>
<tr>
<td><strong>Incidence</strong> of clinical significant disease, including severe disease</td>
<td>Low*</td>
<td>Low**</td>
<td>Increased***</td>
</tr>
</tbody>
</table>

*Due to few susceptible adolescents and adults left, and hence little symptomatic disease

**Due to favourable socioeconomic conditions and hygienic practices

***Due to substantial proportion of adolescents and adults are susceptible

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### Key take-aways

Hepatitis A severe infections **increase** with when countries move from **high to intermediate** endemicity
• HAV is transmitted primarily via the faecal/oral route. Incubation period of acute hepatitis A is usually 14–28 days,

• Symptoms include malaise, fatigue, anorexia, vomiting, abdominal discomfort, diarrhoea.

• Elevated levels of liver enzymes, dark urine and clay-coloured stools and jaundice are characteristic manifestations of acute viral hepatitis.

• Hepatitis A resolves completely in >99% of cases, and does not cause chronic liver disease. Immunity is assumed to persist for life.

• Serological testing for IgM anti-HAV is required to establish the etiological diagnosis of acute hepatitis A. HAV RNA can be detected in body fluids and faeces and can persist for several months

• Treatment of hepatitis A is mainly symptomatic. In very rare instances of life-threatening liver failure, hepatic transplant might be required.

• Incidence of hepatitis A infection correlates with socioeconomic indicators, decreasing with increasing income, and access to clean water and adequate sanitation.
Hepatitis A vaccines

- Two different vaccines types: Inactivated and Live attenuated vaccines
- Both vaccine types shown to be safe and highly effective to protect against symptomatic infection
- Inactivated vaccines administered intramuscularly can be used in a single- (off label) or two-dose schedule from 12 months onwards
  - Both schedules demonstrated long-term protection (for up to 12 years), albeit the two-dose schedules resulting in higher GMCs compared to single-dose schedule
  - 2 WHO prequalified products
- Life attenuated vaccines, licensed as single-dose products and administered subcutaneously from 18 months onwards, are mainly used in China
- Vaccines can be used effectively in hepatitis A outbreak response

Key take-aways
Currently available hepatitis A vaccines are safe and effective to prevent symptomatic disease in children and adults
WHO Position along 5 dimensions

A. Product choice & schedule

B. Vaccine introduction strategy

C. Coadministration & special contexts

D. Vaccination of Special Populations

E. Surveillance & Research
2 Summary of WHO Position

• Vaccination against hepatitis A should be part of a comprehensive plan for the prevention and control of viral hepatitis, including measures to improve safe drinking-water, sanitation and hygiene (such as hand washing) and measures for outbreak control.
• WHO recommends that vaccination against hepatitis A virus be introduced into national immunization schedules for individuals aged ≥12 months, if indicated on the basis of:
  i) an increasing trend over time of acute hepatitis A disease, including severe disease, among older children, adolescents or adults;
  ii) changes in the endemicity from high to intermediate; and iii) considerations of cost–effectiveness.
• Both inactivated and live attenuated hepatitis A vaccines are safe and highly immunogenic, and vaccination with either generates long-lasting, possibly life-long, immunization against hepatitis A in children, as well as in adults.
• For children, inactivated vaccines can be given as a single- (off-label) or two-dose schedule.
WHO Position- Product Choice and schedule

Inactivated vaccines
- For children, can be given as a single- or two-dose schedule, and administered intramuscularly. With a two-dose schedule,
- the first dose should be given starting from age ≥12 months.
- The interval between doses is flexible, from 6 months up to 4–5 years or more, but is usually 6–18 months.
- Data on vaccine effectiveness, antibody persistence, and modelling on long-term seroprotection indicate that an off-label, single-dose schedule is equivalent to the two-dose schedule in children, in addition to being less costly and easier to implement.
- For adults aged >40 years, vaccination with inactivated vaccines using the two-dose schedule is preferred since there is insufficient evidence on the immunogenicity and long-term protection from a single dose in this age group.
- Inactivated hepatitis A vaccines produced by different manufacturers, including combined hepatitis A vaccines, are interchangeable.
- Apart from severe allergic reaction to the previous dose, there are no contraindications to the use of inactivated hepatitis A vaccines.

Live attenuated vaccines
- are licensed for individuals aged ≥18 months and are administered as a single subcutaneous dose.
- Severe allergy to components included in the live attenuated hepatitis A vaccines is a contraindication to their use. Live attenuated vaccines may pose a theoretical risk to the developing foetus and therefore should not be used during pregnancy, nor should they be used in severely immunocompromised patients.
WHO Position- Vaccine introduction strategy

- **Choice of vaccination strategy** guided by
  - estimation of **country burden** of hepatitis A.
  - **age-specific prevalence of anti-HAV IgG antibodies** surveys,
  - hepatitis A incidence, associated **morbidity** and mortality.
  - These analyses need to be tailored to be able to detect geographical variations.
  - **Economic evaluation**, including cost–effectiveness of relevant immunization strategies, is a useful additional element for decision-making.
- **In highly endemic countries,**
  - most individuals are **asymptomatically infected** with HAV in childhood, which prevents clinical hepatitis A in adolescence and adulthood.
  - In these countries, **large-scale hepatitis A vaccination programmes are not routinely recommended**, because they carry a risk of a paradoxical increase in disease incidence in unvaccinated people.
- Countries with **improving socioeconomic status**
  - may rapidly move from high to intermediate hepatitis A endemicity, rendering a larger proportion of the adolescent and/or young adult population susceptible to HAV infection.
  - In such countries, **large-scale hepatitis A vaccination in early childhood** is likely to be cost–effective and is therefore **recommended**.
  - When introducing the vaccine, these countries should based on **age-specific seroprevalence rates** or other markers of susceptibility.
- **In low and very low endemicity settings**
  - **Targeted vaccination** of high-risk groups should be considered to provide individual health benefits

Key take-aways

Hepatitis A vaccine recommended in countries moving from high to intermediate hepatitis A endemicity
WHO Position- Coadministration and special contexts

• Co-administration
  • Hepatitis A vaccines can be administered simultaneously with any of the vaccines routinely used in childhood immunization programmes.

• Special contexts
  • Outbreaks
    • In outbreak situations, single-dose hepatitis A vaccination is recommended, taking into account the epidemiology and feasibility of rapidly implementing a well targeted vaccination programme. The use of hepatitis A vaccine to control outbreaks is most likely to be successful when the outbreak involves a small self-contained community or a well-defined population; when vaccination is started early in the course of the outbreak; and when high coverage of those likely to be affected can be achieved.
  
• Pre and post exposure prophylaxis
  • Hepatitis A vaccine has largely replaced immune globulin for pre- and post-exposure prophylaxis due to having a similar efficacy and better safety profile, lower cost, wider availability and accessibility, and the advantage of providing longer persistent protection.

Key take-aways

Hepatitis A vaccines are efficacious in outbreaks, and pre and post exposure prophylaxis
WHO Position- Vaccination of Special Populations

Key take-aways

High risk groups should be vaccinated in particular in low endemicity settings.

- Groups at higher risk of hepatitis A should be vaccinated, including *travellers* from low-endemic countries to areas of intermediate or high endemicity, *men who have sex with men*, at-risk *occupational groups*, people who *inject drugs*, people who experience *homelessness, migrants, refugees, incarcerated* persons; and patients with *chronic liver disease* or *HIV*, particularly in *countries with low and very low endemicity*.

- For *immunocompromised individuals*, until further experience has been obtained with a single-dose schedule, a *two-dose schedule of inactivated vaccine is recommended*.

- Inactivated hepatitis A vaccines should also be considered for use in *pregnant women at risk of HAV infection*.

- *Health workers* are generally *not at special risk* of contracting hepatitis A and should follow the vaccine recommendations for the general population.
WHO Position- Surveillance and Research Priorities

- Following the introduction of hepatitis A vaccines, it is important to monitor
  - Impact using morbidity and mortality surveillance data.
  - Seroprotection, and the duration of protection induced by single- and two-dose schedules
- Modelling studies are needed to
  - Characterize relationship between levels of endemicity over time, mean age at infection, and increased risk of symptomatic and severe disease
  - Guide countries on determining the right timing for childhood vaccination introduction.
- Data are needed on individuals who received a single dose of inactivated vaccine during adult age (rather than as children), particularly at >40 years, to confirm long-term protection.

Key take-aways

Monitoring and research is needed to fully understand duration of protection and characterise thresholds for introduction.
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In case of additional questions, please reach out to the SAGE Secretariat at sageexecsec@who.int