WHO position paper on Hepatitis A vaccines

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Transmission and incidence

- Hepatitis A virus (HAV) is transmitted primarily via the faecal/oral route
- The incidence of hepatitis A strongly correlated with access to clean water and adequate sanitation
- WHO estimates that 212 million cases of acute hepatitis A occurred in 2005

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Levels of hepatitis A-endemicity

- The level of hepatitis A-endemicity can be classified according to prevalence of hepatitis A - antibodies in different age groups
- *High*: ≥90% seropositive by age 10 years
- *intermediate:* ≥50% seropositive by age 15 years (<90% by 10 years)
- *low:* ≥50% seropositive by age 30 years (<50% by 15years)
- *very low:* <50% seropositive by age 30 years

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Socioeconomic impact on incidence of hepatitis A

- *In low-income regions:* exposure to HAV occurs mostly before 5 years of age (mainly asymptomatic infections)
- *In high-income regions:* low risk of HAV infection
- *In middle-income regions:* often a mix of intermediate and low prevalences. A large proportion of adolescents and adults may be susceptible
- HAV infection in older children and adults is associated with a higher rate of severe clinical manifestations
- Paradoxically, transition from high to intermediate endemicity may result in an increased incidence of clinically significant cases of hepatitis A.

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Risk groups for hepatitis A

- Groups at high risk of HAV exposure include health care workers, travellers to areas of high endemicity, men who have sex with men, and injection drug users
- Groups at risk of serious clinical outcome, once infected, include elderly and/or immuno–compromised individuals

Clinical features of HAV infection

- Typical manifestations of acute viral hepatitis include malaise, fatigue, anorexia, vomiting, abdominal discomfort, and diarrhoea.
- Also characteristic are elevated levels of liver enzymes, appearance of dark urine and sometimes clay–coloured stools and jaundice
- Hepatitis A resolves completely in >99% of the cases.
- Fatality (0.1% in children <15 years of age and 2.1% in adults ≥40 years of age) associated mainly with fulminant hepatitis.

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Vaccine types, safety, and correlate of protection

- Two types of hepatitis A vaccines are currently used
- (a) formaldehyde inac) vated vaccines; manufactured in many countries, used worldwide
- (b) live attenuated vaccines; manufactured in China, used in several countries
- The excellent safety record of inactivated hepatitis A vaccines is well documented
- No substantial safety concerns have been identified in trials using live attenuated vaccines (not recommended in pregnant women and immune compromised patients)
- For both vaccine types, a positive test for total anti-HAV antibodies signifies immunity to hepatitis A

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Inactivated hepatitis A vaccines

- Inactivated hepatitis A vaccines, alone or in fixed combinations, are widely used internationally
- Licensed for intramuscular use in persons aged ≥12 months
- Manufacturers recommend a 2-dose schedule with 6–12 (up to 18–36) months interval between the 2 doses
- These vaccines are interchangeable and can be given simultaneously with any other routinely used vaccine
- In general, 2 doses of inactivated hepatitis A vaccine induce protective efficacies of 90–95%, or more
- Long-lasting, possibly life-long, protection

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A single dose schedule of inactivated vaccine

- Annual, country-wide, single dose, immunization of 12-months old children was implemented in Argentina in 2005. Dramatic reduction in national incidence. So far, (2012) no hepatits A cases in vaccinated individuals.
- In adult travellers, 1 dose of hepatitis A vaccine induces immunological memory and in most cases, anti-HAV antibodies that persist throughout 4–11 year periods of observation
- High efficacy (~80%) of post-exposure prophylaxis given as one dose of inactivated vaccine within 2 weeks of HAV exposure

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Live vaccines

- Live attenuated hepatitis A vaccines are based on the viral H–2 and the LA–1 strains of HAV
- One dose is used in children aged ≥1 year in several national immunization programmes
- Large controlled trials conducted among children aged 1–15 years have shown up to 100% pre–exposure and 95% post-exposure efficacy
- Long-lasting protection: Anti-HAV antibodies were detected in 72–88% of the vaccinees 15 years after vaccination

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Cost-effectiveness (C–E)

- Data mainly from high/middle income countries
- Lower C–E ratios for universal vaccination than for more targeted vaccination
- Universal vaccination found to be particularly cost–effective in children in high incidence areas
- For targeted vaccination, C–E highly dependent on risk of infection in targeted groups
- Incidence of hepatitis A disease, vaccine cost, and discount rate were the most influential parameters in sensitivity analyses

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- Both inactivated and live attenuated hepatitis A vaccines are safe and induce long-lasting, possibly life-long, protection against hepatitis A in all age groups
- Vaccination should be part of a comprehensive plan for preven) on/control of viral hepatitis
- If indicated (considering assessment i.a. of local epidemiology and cost–effectiness), hepatitis A vaccination for children aged ≥1 year should be integrated into the national immunization programme

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- In *high* endemicity areas, where most children acquire natural immunity, large-scale vaccination programmes are not recommended
- In areas of *intermediate* endemicity repeated outbreaks of clinically significant hepatitis A can occur and hence, large-scale hepatitis A vaccination is encouraged. Community-wide outbreaks may be interrupted if vaccination is started early and with high coverage.
- In *low/very low* endemicity areas, targeted vaccination of high-risk groups should be considered

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WHO position

- Inactivated HAV vaccines are licensed for intramuscular use in a 2-dose schedule. May be co–administered with other vaccines. No contraindication, except severe allergy to vaccine components. Should be considered also in pregnancy if high risk of HAV infection
- Compared to a 2-dose schedule, one dose of inactivated vaccine is similarly efficacious, less expensive and easier to implement. Therefore, countries may consider using a single-dose schedule of inactivated vaccine. (In risk groups for hepatitis A, a two dose vaccination schedule is preferred)

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- Live attenuated vaccine is given as one single subcutaneous dose. As a rule, this vaccine should not be used in pregnancy or in severely immuno–compromised patients
- Following introduction, the impact of hepatitis A vaccination should be assessed regularly, including duration of protection following 1 versus 2 doses of inactivated vaccine
- Normally, hepatitis A vaccines rather than passive prophylaxis with immune globulin should be considered for both pre–and post–exposure prophylaxis against hepatitis A