Evidence based recommendations for use of hepatitis A vaccines in immunization services: Background paper for SAGE discussions

SAGE Hepatitis A Working Group

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1. Introduction

Hepatitis A is caused by the hepatitis A virus (HAV), an hepatovirus of the *picornaviridae* family mostly transmitted through the fecal-oral route, either by direct contact with an infectious person or by ingestion of contaminated food or water. The proportion of HAV infections that are symptomatic increases progressively with age (Hollinger, 1996). Most children experience asymptomatic infections while most adults develop signs and symptoms of acute hepatitis. When HAV infection is symptomatic, in most cases, it causes an acute, self-limited hepatitis. However, relapses occur and some patients may progress to fulminant liver failure that may be fatal. The estimated case-fatality ranges from 0.1% for children less than 15 years old to 0.3% among persons 15 to 39 years of age and 2.1% among adults 40 years of age or older (Hollinger, 1996). Endemicity levels are higher when socio-economic status and hygienic conditions are low (Jacobsen, Koopman 2004).

In 1992, inactivated hepatitis A vaccines were first licensed for use. In 2000, WHO published its first position paper to formulate recommendations for the public health use of hepatitis A vaccine (WHO 2000). This position paper called for conducting epidemiological and economic studies before deciding on national policies about immunization against hepatitis A. WHO also recommended that the national decision to introduce hepatitis A vaccine as part of the routine immunization programme be weighed against competing priorities in terms of burden of disease and the capacity of immunization systems to integrate new and underutilized vaccines, including hepatitis B, *Haemophilus influenzae* type B, rubella and yellow fever. In terms of recommendations, the position paper differentiated high, intermediate and low endemicity settings. In high endemicity settings, WHO did not recommend large-scale vaccination as almost all persons are asymptomatically infected with HAV during childhood. In intermediate endemicity settings, WHO recommended that large-scale childhood vaccination may be considered as a supplement to health education and improved sanitation as a relatively large proportion of the adult population remains susceptible leading to a substantial hepatitis A public health burden. In low endemicity settings, WHO only recommended vaccination against hepatitis A for individuals with increased risk of infection (e.g., travellers to areas of intermediate or high endemicity).

Since WHO published the 2000 position paper, a number of developments occurred. First, the epidemiology of hepatitis A evolved, with more countries experiencing a reduction of the annual risk of infection. As a result, more countries shifted from high to intermediate endemicity with more susceptibility in the older population and higher reported rates (Jacobsen, Wiersma 2010). Second, new evidence became available on the public health benefit associated with the use of hepatitis A vaccines in immunization services, including for universal vaccination of toddlers and outbreak control (Dagan et al. 2005, Belmaker

et al. 2007). Third, immunization systems have become stronger, as indicated by increasing vaccine coverage. This led to improved capacity to integrate new and underutilized vaccines. Fourth, more information became available regarding the efficacy of hepatitis A vaccine, including in terms of post-exposure prophylaxis situation (Victor et al. 2007) and long-term protection (Van Damme et al. 2003). Further, more evidence is available regarding population impact (Dagan et al. 2005) provided by use of hepatitis A vaccines. Fifth, recently more hepatitis A vaccines have became available, leading to a broader offer to potential buyers and a reduction in prices. Sixth, in 2010, the 63th World Health Assembly (WHA) passed a resolution on viral hepatitis calling for countries to implement integrated programmes for the prevention and control of viral hepatitis, including hepatitis A (WHA63.18). To reflect these new developments, in 2011, WHO published "The immunological basis for immunization series: module 18: hepatitis A." (WHO 2011) which summarized information available on hepatitis A vaccines.

2. Methodology

To prepare for an updated WHO position paper, members of the working group formulated four key questions about the public health use of hepatitis A vaccines (Box 1). To answer these questions, the working group requested the WHO Secretariat to systematically review the literature and prepare evidence summaries using the GRADE approach (www.gradeworkinggroup.org).

To address the first question, the WHO Secretariat collaborated with investigators (Irving G, Holden J) who were finalizing a Cochrane review (Irving et al., 2011). This body of work was supplemented by a systematic review to further address question 2. The WHO Secretariat conducted its own systematic reviews to address questions 3 and 4. Finally, the working group reviewed all available relevant evidence using the GRADE approach.

Box 1: Questions addressed by the SAGE hepatitis A vaccine working group, 2010-2011

1. The efficacy and safety of available hepatitis A vaccines, i.e. Does hepatitis A vaccine prevent HAV-related disease?
2. The use of hepatitis A vaccines in post-exposure prophylaxis and outbreak control, i.e. Does hepatitis A vaccine prevent HAV-related disease when given post-exposure?
3. Experience regarding the public health impact of the use of hepatitis A vaccine in mass immunization programs, i.e. Does universal hepatitis A vaccination reduce the disease burden of hepatitis A in the population?
4. Evidence on the duration of protection achieved by hepatitis A vaccine, i.e. Do hepatitis A vaccines provide long-term protection?

3. Burden of disease

Sources of information available to estimate the HAV-related disease burden are heterogeneous. There are two main sources of information that can be used to estimate the burden of disease associated with HAV infection. First, serological surveys estimate the *prevalence* of serological evidence of past infections,

pointing to endemicity and susceptibility levels that are associated with specific patterns of transmission and disease (Jacobsen, Wiersma 2010). However, up-to date seroprevalence information is sparse. Second, reporting systems measure the *incidence* of morbidity or mortality. Mathematical models have been proposed to project available data into burden estimates formulated in terms sequelae, including deaths, which can be used to calculate Disability Adjusted Life Years (DALYs). However, the epidemiology of HAV infection is a dynamic phenomenon that must be analyzed over decades. Prolonged community-wide outbreaks may occur after few years of lower rates. Accumulation of susceptible individuals over decades may lead to large-scale outbreaks. Finally, the risk of infection may vary over time because of changes in risk factors related to socio-economic conditions or because of use of immunization.

With respect to serological prevalence surveys, profiles vary geographically (Jacobsen, Wiersma 2010). In high-income regions (Western Europe, Australia, New Zealand, Canada, the United States, Japan, the Republic of Korea, and Singapore) the prevalence of anti-HAV is very low (<50% immunity among persons > 30 years of age). In these regions, the high proportion of susceptible individuals among adults could theoretically allow transmission, but there is almost no circulation of the virus. A few cases are reported among high-risk groups (e.g., travellers). In low-income regions (sub-Saharan Africa and parts of South Asia) the prevalence of anti-HAV is high (> 90% immunity by the age of 10). As a result, there are few susceptible adolescents and adults and little symptomatic disease. Most middle-income regions in Asia, Latin America, Eastern Europe, and the Middle East have a mix of intermediate (>50% immunity by the age of 15) and low (>50% immunity by the age of 30) prevalence of anti-HAV. In these regions where substantial proportion of adolescents and adults are susceptible, HAV may circulate, often through regular community-wide outbreaks, leading to higher levels of morbidity and mortality. Hence, countries in these regions may most benefit the most from new or expanded universal vaccination programmes.

With respect to methods to estimate hepatitis A incidence and mortality, the quality of data is heterogeneous. Surveillance for detection of events (i.e., outbreak) is relatively easier to implement. However, surveillance of hepatitis A for the estimation of rates is technically difficult in resource-constrained settings. Clinical criteria are insufficient to confirm the diagnosis of acute hepatitis A and serological testing (IgM anti-HAV) is required. Methods to estimate mortality are also limited by the need of laboratory diagnosis and difficulties associated with cause of death attribution. Other methods that reflect HAV-associated disease burden include reports of cases of HAV-associated fulminant hepatitis. However, information on the causes of fulminant hepatitis, including on the causes of liver transplant are usually available in the form of ad hoc reports while systematic exhaustive registries would be needed to monitor trends.

In 2010, WHO conducted a burden model using prevalence data to generate burden of disease expressed in terms of sequelae, including deaths (Table ES-1). Preliminary results obtained from this model suggest that in 2005, 212 million HAV infections caused 35,245 HAV-related deaths. This compares with 177 millions infections causing 30,283 HAV-related deaths in 1990. This model is undergoing further review and modification but presents a view of the potential global burden associated with HAV infection.

Table ES-1. Overall Global Estimate of Hepatitis A, 1990 and 2005

Outcome	Year	Total Infec-tions	Asymp-tomatic	Mild Symp-tomatic Illness	Moderate Symp-tomatic Illness	Severe Non-Fulminant Illness	Fulminant Cases Resulting in Death	Other Fulminant Cases
Total Cases (Thousands)	1990	117,292,997	86,832,211	23,343,781	5,903,602	1,015,515	97,686	101,307
Total Cases (Thousands)	2005	126,114,572	86,995,185	27,635,349	6,189,342	1,270,586	111,350	114,383
Per 100,000 People	1990	2,114	1,565	421	106	18	2	2
Per 100,000 People	2005	1,844	1,272	404	91	19	2	2

Source: Rein et al. 2010

While low and high endemicity settings are less prone to year-to-year variations in incidence, intermediate endemicity settings are typically characterized by the regular occurrence of community-wide outbreaks. In addition, communities in which persons from different endemicity profile come in contact with each other (e.g., migrations, population sub-groups with higher endemicity profile) may face higher rates. With hepatitis A incidence decreases among children, there is an increased risk of hepatitis A outbreaks among susceptible older children, adolescents and adults. Such hepatitis A outbreaks can affect a high number of individuals (Wheeler et al. 2005). Shifts from high endemicity to intermediate endemicity have been reported from many countries worldwide (Jacobsen, Wiersma 2010). In such countries, a decrease in the annual risk of infection because of improvement in socio-economic status and hygienic conditions in the absence of routine hepatitis A immunization may lead to accumulation of susceptible and large-scale outbreaks. For example, the Republic of Korea experienced a dramatic reduction of transmission in the second half of the 20th century (Kang et al. 2004). In the early 2000s, the endemicity profile became low and a large proportion of adolescents and adults were susceptible. In 2008-9, a large outbreak affected the country. The 1980s hepatitis A outbreak in Shanghai associated with shellfish consumption also represented an example of transmission facilitated by the accumulation of susceptible individuals through improvement of hygienic conditions before the era of immunization (Xu et a. 1992).

4. Vaccines available

A number of inactivated vaccines are available on the international market that vary in terms of strains used, adjuvants and titration method to measure potency (WHO 2000). Formaldehyde inactivated vaccines include the monovalent HAVRIX®[33], VAQTA®[34], EPAXAL®[36], AVAXIM®, and two other inactivated vaccines which are available in China – TZ 84 HEALIVE® and Lv-8 Weisairuian (Table 1, adapted from WHO 2011).

Table 1: Monovalent inactivated hepatitis A vaccines available worldwide.

Trade name	Attenuated HAV strain	Adjuvant	HAV antigen dose/injection		Manufacturers
			Pediatric	Adult	
HAVRIX®	HM-5	Alum hydroxide	720 EU	1440 EU	GSK
VAQTA®	CR-326	Alum hydroxide	25 U	50 U	MSD
AVAXIM®	GBM	Alum hydroxide	80 U	160 U	Sanofi Pasteur
EPAXAL®	RG-SB	Virosome	12 U	24 U	Crucell

Source: Adapted from WHO 2011

In addition to monovalent HAV vaccines, formaldehyde inactivated combination vaccines have been developed in Europe including TWINRIX® and AMBIRIX® (hepatitis A and B), VIATIM®/VIVAXIM® and HEPATYRIX® (hepatitis A and typhoid).

Inactivated hepatitis A vaccines are licensed for use in a two-dose schedule, with a first dose that leads to the development of protective levels of antibody in nearly 100% of immune competent individuals (WHO 2011). This high level of immunogenicity allows a flexible time interval between the first and second dose. When the second dose is administered after six months, it leads to an anamnestic antibody response that ensures long-term protection. In studies evaluating the duration of protection of two or more doses of hepatitis A vaccine, 99%-100% of vaccinated individuals had levels of antibody indicative of protection 5-8 years after vaccination (WHO 2000). However, there is no evidence that these lower levels of antibody few years after vaccination would be associated with reduced protection. Mathematical models predicting the kinetics of decrease of antibody levels suggest that protection can last at least 20 years and possibly for a lifetime (Van Herck et al. 2000, Van Herck, Van Damme 2001). Presence of maternal antibodies may affect the level of antibody response following vaccination, but there is no evidence that this reduction could have an effect on the protective efficacy and the second booster dose leads to a sufficiently high level of antibodies. Clinical trials and field investigations have documented a protective efficacy above 90% (Irving et al. 2011, WHO 2000). The safety profile of the vaccine is excellent, with Adverse Events Following Immunization (AEFI) that are rare and benign (e.g., local indurations and headaches, Irving et al. 2011). The vaccine may be used during pregnancy. Various vaccines allow for various co-administration options (diphtheria, tetanus, acellular pertussis, polio, *Haemophilus influenzae*, MMR typhoid, hepatitis B, cholera, Japanese encephalitis, rabies and yellow fever vaccines) and various hepatitis A vaccines may be inter-changed for the first and second dose (WHO 2011). However, unlike most other EPI vaccines, hepatitis A vaccines are not licensed for the use in children aged < 1 year (WHO 2000).

In addition to the vaccines available on the international market, China developed a number of inactivated and live attenuated vaccines (Table 2) which have been introduced since 1992 in the country and integrated into the Expanded Programme on Immunization (EPI) in 2007 (Zheng, Cui 2009).

Table 2: Monovalent inactivated and live attenuated hepatitis A vaccines available in China.

Trade name	HAV strain	Adjuvant	HAV antigen dose/injection		Manufacturers
			Pediatric	Adult	
Healive®	TZ84	Alum hydroxide	250 U	500 U	Sinovac Biotech Limited, Beijing
Weisairuian	Lv-8	Alum hydroxide	320 EU	640 EU	Institute of Medical Biology of the Chinese Academy of Medical Sciences; Kunming
Weisairuiji	H2	None	6.5lg TCID50	6.5lg TCID50	Institute of Medical Biology of the Chinese Academy of Medical Sciences; Kunming
NA	H2	None	6.5lg TCID50	6.5lg TCID50	Zhejiang Pukang Biotechnology Company Limited, Zhejiang Academy of Medical Sciences, Hangzhou
NA	L-A-1	None	6.5lg TCID50	6.5lg TCID50	Changchun Institute of Biological Products. & Changchun Changsheng Life Sciences Limited
HAVAC	L-A-1	None	6.5lg TCID50	6.5lg TCID50	Changchun Institute of Biological Products

Source: Adapted from WHO 2011

5. Population impact

Following the introduction of hepatitis A vaccine on the market, experience was progressively acquired regarding the impact of immunization in the population. First, use of the vaccine in supplemental immunization activities as an outbreak response method suggested some population impact that depends upon coverage reached. Epidemiological evidence regarding the effect of hepatitis A immunization to control outbreaks is mostly constituted of descriptive time series that are difficult to interpret. However, experience suggests that outbreak response may have limited effect in the longer term in the absence of routine immunization. Second, use of hepatitis A vaccines in mass vaccination programs led to sustained decreased rates of HAV-related disease in a number of countries and regions, including USA, China, Italy, Spain, North Queensland and Israel (e.g. Dagan et al. 2005, Wasley et al. 2005, Lopalco et al. 2005, Hanna et al. 2005). Most studies reported large impacts despite vaccination coverage that was moderately high (Wasley et al. 2005). Herd immunity effects may explain this effect (Question 3, Box 2). Argentina developed a unique, experimental programme of introduction in immunization services at the age of 12 months with a one-dose schedule (Vacchino et al. 2008). The choice of one dose instead of two was made on the basis of economic grounds to reduce the cost of the programme. While surveillance data indicate a major reduction of reported incidence, long term follow up and monitoring is required to better understand the potential impact of a waning immunity in populations who were exposed to such schedules (Vacchino et al. 2008).

6. High-risk groups

A number of population groups are at increased risk of hepatitis A (WHO 2000). These include travellers to areas of high endemicity, recipients of blood and blood products, care takers of non-human primates, men who have sex with men, and injection drug users. In addition, patients with chronic liver diseases are at higher risk of adverse outcomes following HAV infection. Various countries and institutions have recommended targeted immunization of these groups, which offers individual benefits to persons immunized. However, there is limited evidence to suggest that such vaccination efforts are (a) successful at

reaching high coverage among targeted groups and (b) effective at reducing reported rates in the population. Food handlers have been occasionally assessed as a target group for vaccination for immunization to prevent foodborne hepatitis A. This measure may appeal to decision makers as a practical way to prevent common-source foodborne hepatitis A. However, practical constraints, including staff turn over among food handlers may limit the effectiveness of this approach. Further, the cost-effectiveness of such a strategy is questionable (Meltzer et al. 2001).

7. Post-exposure prophylaxis

Immunoglobulin (IG) had been the main strategy for prevention of hepatitis A in pre-exposure prophylaxis in unvaccinated individuals and post- exposure prophylaxis, including outbreak control. IG is up to 90% effective in preventing clinical hepatitis A when administered pre-exposure or within two weeks of last exposure in both, children and adults (Fiore et al. 2006). However, IGs are expensive and in short supply. In addition, in countries evolving towards lower endemicity profile, a reduced content in anti-HAV antibodies because of the high prevalence of susceptibility among donors could affect IG efficacy (Baker 2007). National strategies for the routine use of hepatitis A vaccine in preference to IG for post-exposure prophylaxis have been implemented in some European countries (Baker 2007) and the United States of America (CDC 2007) suggesting hepatitis A vaccine as a valid alternative to post-exposure prophylaxis with IG in humans.

8. Summary of GRADE tables

Question 1a: Should inactivated hepatitis A vaccine versus no intervention, inactive control or placebo be used for hepatitis A?

There was high quality, critically important evidence that inactivated hepatitis A vaccines used in the general population compared to inactive control or placebo were both safe and effective in preventing acute hepatitis A. Acute disease outcomes were assessed with both clinical and laboratory criteria over a 12-18 months follow-up period. Four randomized controlled trials were included in this assessment. The results showed a strong association of the intervention with the outcome (RR=0.12).

Question 1b: Should live attenuated hepatitis A vaccine versus no intervention, inactive control or placebo be used for hepatitis A?

There was very low and low quality, critically important evidence that live attenuated hepatitis A vaccines used in the general population compared to inactive control or placebo were safe and effective in preventing acute hepatitis A. Acute disease outcomes were assessed with both clinical and laboratory criteria over a 1-60 months follow-up period and a very strong association was found resulting an RR of 0.09. 13 randomized controlled trials were included in this assessment. There were quality issues with the studies that resulted in a serious risk of bias and inconsistency for the acute disease outcomes and serious bias, very serious inconsistency, serious indirectness, and serious imprecision for the safety outcomes that let to a reduction in the quality scores.

Question 1c: Should single dose inactivated hepatitis A vaccine versus no intervention, inactive control or placebo be used for hepatitis A?
There was high quality, critically important evidence that single dose inactivated hepatitis A vaccine used in the general population compared to inactive control or placebo was effective in preventing acute hepatitis A. Acute disease outcomes were assessed with both clinical and laboratory criteria over a 15 months mean follow-up period and a very strong association was found resulting an RR of 0.03. One randomized controlled trial was included into this assessment.

Question 1d: Should single dose live attenuated hepatitis A vaccine versus no intervention, inactive control or placebo be used for hepatitis A?
There was low quality, critically important evidence that live attenuated hepatitis A vaccines used in the general population compared to inactive control or placebo was effective in preventing acute hepatitis A. Acute disease outcomes were assessed with both clinical and laboratory criteria over a 1-60 months follow-up period and a very strong association was found resulting an RR of 0.09. There were 13 randomized controlled trials included into this assessment. The quality of these studies was lowered by the same factors noted above (see question 1b).

Question 2a: Should use of inactivated hepatitis A vaccine in family contacts of confirmed cases versus no intervention be used for hepatitis A prevention?
There was moderate quality, critically important evidence that household contact vaccination with hepatitis A vaccine is efficacious in preventing acute hepatitis A as measured by IgM anti-HAV positivity after exposure to hepatitis A compared to no intervention. There was one randomized controlled trial available assessing this question which found that household contact vaccination with hepatitis A vaccine is 79% efficacious in preventing IgM anti-HAV positivity after household exposure to hepatitis A compared to no interventions. The quality of this evidence was decreased because of a serious risk of bias in this study.

Question 2b: Should use of inactivated hepatitis A vaccine in contacts of confirmed cases versus immunoglobulins (IG) be used for post-exposure prevention of hepatitis A?
There was high quality, critically important evidence that inactivated hepatitis A vaccine used in post-exposure situations compared to IG was effective in preventing acute hepatitis A as by clinical and/or laboratory criteria over 4-8 weeks follow-up. One randomized controlled trial was found showing no significant difference between IG and inactivated hepatitis A vaccine in either clinical or subclinical hepatitis A or clinical plus subclinical hepatitis A in both per-protocol and intention-to-treat analyses suggesting hepatitis A vaccine as an alternative to immunoglobulin for post-exposure prophylaxis (RR 1.35 (0.7 to 2.67)).

Question 3: Should mass hepatitis A vaccination be used in population control of hepatitis A?
There was low quality, critically important evidence that mass hepatitis A vaccination in the general

population reduces the incidence of acute hepatitis A and HAV-related mortality. The evidence was based on 14 observational studies which were conducted in different countries and which all showed a reduction in hepatitis A morbidity or mortality. Most of these studies suggested and assessed additional herd effects as indicated by decreases in hepatitis A morbidity and mortality among non-intervention population- and age-groups. Among these studies, one investigation compared pre- and post- hepatitis A-vaccination recommendation cohorts (5 years each) and calculated age-adjusted mortality rates. There was a 32% reduction ($p<0.001$) in HAV-related mortality in the post- hepatitis A vaccine cohort. In addition, there was a 23% reduction of mortality in areas not recommending hepatitis A vaccine which suggests a herd effect.

Question 4a: Should inactivated hepatitis A vaccine be used for long-term protection against hepatitis A?
There was low quality, important evidence that inactivated hepatitis A vaccine provides long-term protection against hepatitis A. Nine observational studies were included into this assessment, all of them showing protective HAV IgG antibody levels (measured as GMC or GMT) up to the end of the follow-up period. The study with the longest follow-up time showed protective GMC to be persistent up to 14 years. Studies of follow-up less than 14 years had a serious risk of bias and imprecision, however, one study with follow-up of 14 years had no quality limitations.

Question 4b: Should single dose live attenuated hepatitis A vaccine be used for long-term protection against hepatitis A?
There was very low quality, important evidence that live attenuated hepatitis A vaccine provides long-term protection (> 5 years) against hepatitis A. Six observational studies were included into this assessment, all of them protective HAV IgG antibody levels (measured as GMC or GMT) up to the end of the follow-up period. The study with the longest follow-up time showed protective GMC to be persistent up to 15 years and sero-protection rates of 86-100%, depending on schedule. Most of the studies included additional modeling of observed data and suggested potential longer protection. These studies had a serious risk of bias and imprecision limiting their quality.

9. Conclusions

In conclusion, use of hepatitis A vaccines in immunization services may be a useful component of national hepatitis prevention and control plans. Consideration of introduction of hepatitis A vaccine into routine childhood immunization in a particular country requires either a national assessment of the endemicity level (seroprevalence by age and year) to estimate burden or reliable surveillance and/or vital statistics data to further quantify morbidity and mortality. Such assessments should also address the potential risks of community-wide outbreaks prospectively. Many inactivated hepatitis A vaccines that are safe and highly effective are currently available for use in national immunization programmes. Integration of these hepatitis A vaccines into universal childhood immunization programmes can reduce morbidity and mortality in the population especially in intermediate endemicity settings.

Persons belonging to high-risk groups may individually benefit from vaccination if targeted vaccination is feasible. Hepatitis A vaccine is also effective in post-exposure prophylaxis situations, which can protect individuals exposed through close contacts with case-patients. Hepatitis A vaccines show good long-term protection that should continue to be monitored in studies of vaccinated cohorts.

10. Recommendations

On the basis of these conclusions, we can formulate a number of recommendations.

1. Integrate hepatitis A vaccine into the national universal childhood immunization schedule if indicated on the basis of burden of disease, changing epidemiology and economic data. Hepatitis A vaccination should be part of comprehensive plan for the prevention and control of viral hepatitis. Countries with improving socioeconomic status may rapidly move from high to intermediate hepatitis A endemicity and are particularly encouraged to consider hepatitis A vaccination.
2. Produce and review information to estimate the national burden of disease associated with hepatitis A and direct use of hepatitis A vaccine in immunization services. This may require examining vital registration systems, acute disease surveillance, surveys estimating age-specific prevalence of antibodies and health information systems capturing fulminant disease and /or causes of liver transplantation. Economic evaluation can serve as a useful additional element for decision-making.
3. Select hepatitis A vaccines on the basis of safety and efficacy data and in conformity with the national regulatory authority. Consideration can be given to the use of single dose inactivated vaccines as an option that is less expensive and easier to implement than the classical two-dose schedule. Single dose use should be accompanied by monitoring and evaluation plans.
4. Following introduction, assessment of the impact of hepatitis A vaccines is important using information on morbidity and mortality generated by surveillance and study data.
5. Consider targeted vaccination of high-risk groups in low endemicity settings to promote individual health benefits.
6. Health systems that have the capacity to offer individual management of reported hepatitis A cases may consider the use of hepatitis A vaccine for post-exposure prophylaxis among close contacts of case-patients.

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