Hepatitis A Vaccines

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12.1 The Disease

Hepatitis A is a liver disease caused by the hepatitis A virus (HAV). The incubation period of hepatitis A is usually 14–28 days. Symptoms of hepatitis A range from mild to severe and can include fever, malaise, loss of appetite, diarrhea, nausea, abdominal discomfort, dark-colored urine, and jaundice (a yellowing of the skin and whites of the eyes). Infected children under 6 years of age do not usually experience noticeable symptoms, and only 10% develop jaundice. Among older children and adults, infection usually causes more severe symptoms, with jaundice occurring in more than 70% of cases. Because of the often asymptomatic or subclinical course of hepatitis A infection, incidence rates are often underestimated. Review data from 1990 to 2005 suggest a global increase from 117 million HAV infections in 1990 to 121 million infections in 2005.

Hepatitis A sometimes relapses. The person who just recovered falls sick again with another acute episode. This is, however, followed by recovery. Unlike hepatitis B and C, hepatitis A infection does not cause chronic liver disease and is rarely fatal.

The estimated case–fatality ratio of hepatitis A varies with age and ranges from 0.1% among children <15 years of age to 0.3% among persons 15–39 years of age and is 2.1% among adults aged ≥40 years. In Argentina, 0.4% of pediatric patients developed fulminant hepatitis, 60% of which were fatal. Reports from South America and the Republic of Korea have raised concerns that the incidence of fulminant hepatitis A might be rising, particularly in children.

There is no specific treatment for hepatitis A. Recovery from symptoms following infection may be slow and may take several weeks or months.

12.2 Epidemiology

Hepatitis A occurs sporadically and in epidemics worldwide, with a tendency toward cyclic recurrences. The hepatitis A virus is one of the most frequent causes of foodborne infection. The HAV persists in the environment and can withstand food production processes routinely used to inactivate and/or control bacterial pathogens.

The HAV is transmitted primarily via the fecal–oral route, that is, when an uninfected person ingests food or water that has been contaminated with the feces of an infected person. In families, this may happen when an infected person prepares food for family members with dirty hands. Waterborne outbreaks, though infrequent, are usually associated with sewage-contaminated or inadequately treated water. The virus can also be transmitted through close physical contact with an infectious person, although casual contact among people does not spread the virus.

In developing countries with poor sanitary conditions and hygienic practices, most children (90%) are infected with the HAV before the age of 10 years, mostly with no noticeable symptoms. Epidemics are uncommon because older children and adults are generally immune. Symptomatic disease rates in these areas are low and outbreaks are rare.

In middle-income countries, often developing countries with transitional economies, and regions where sanitary conditions are variable, children often escape infection in early childhood and reach adolescence or adulthood without immunity. Ironically, these improved economic and sanitary conditions may lead to accumulation of adolescence and adults who have never been infected and who have no immunity. This higher susceptibility in older age groups may lead to higher disease rates, and large outbreaks can occur in these communities.

In industrialized countries with good sanitary and hygienic conditions, infection rates are low. Disease may occur among adolescents and adults in high-risk groups, such as injecting drug users, men who have sex with men (MSM), people travelling to areas of high endemicity, and isolated populations, such as closed communities. Seroprevalence and surveillance in Europe illustrate the large variability in hepatitis A endemicity across the WHO-EURO region, ranging from very

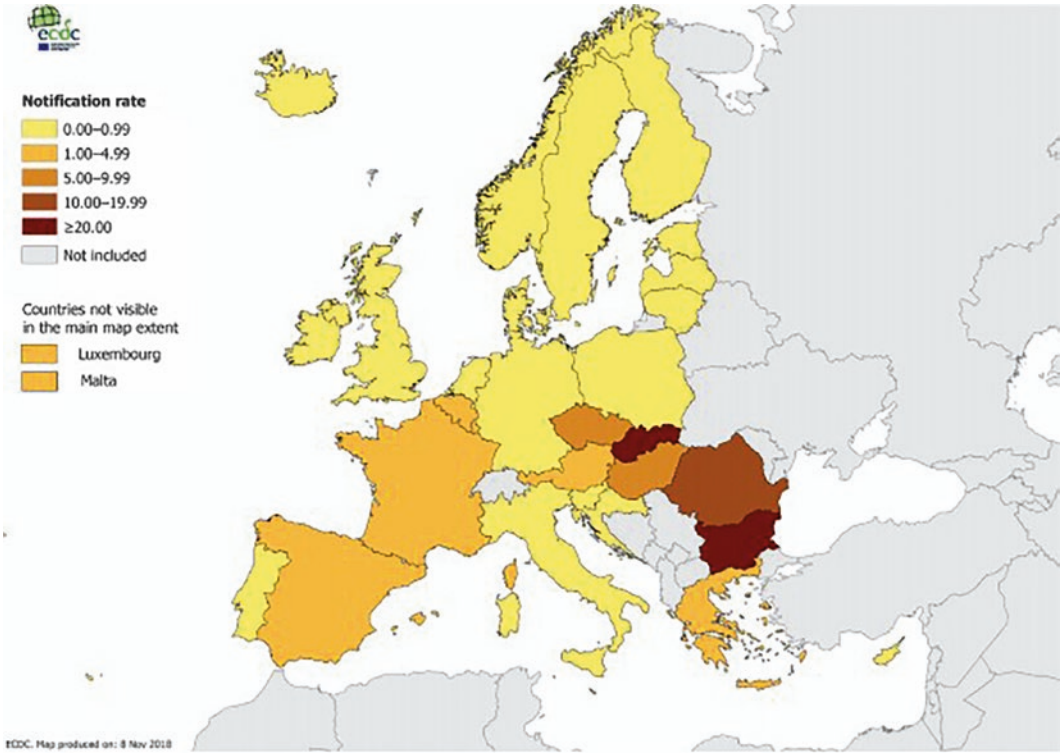

Fig. 12.1 Distribution of confirmed hepatitis A cases per 100,000 population by country in EU/EEA countries, 2016 (► https://www.ecdc.europa.eu/sites/default/files/documents/AER-2016-hepatitis-A.pdf)

low in Scandinavian countries (15%) and low in Western Europe (reaching 40–70% somewhere between 35 and 70 years) to intermediate and high in Central Europe and the Newly Independent States[1] (with 50% seropositivity reached during childhood or by the age of 20). Data from 2005 show a further overall trend of decreasing incidence, with seroprevalence rates in Europe still increasing from west to east. ECDC data based on notification from 1997 to 2011 mention a decrease from 10.0 to 2.5/100,000 population, with 21 of the 28 countries reporting rates less than or equal to 1/100,000. Since the end of 2016, several EU countries have been reporting an increase of hepatitis A cases, both in the general population and in specific risk groups, predominantly in men who have sex with men. Since the beginning of 2017, 14 countries, i.e., Austria, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Latvia, Lithuania, the Netherlands, Poland, Portugal, Slovenia, and Spain, reported 5983 cases of hepatitis A according to online publicly available information (Fig. 12.1). This is higher than the average annual number of cases reported by this group of countries to The European Surveillance System (TESSy) between 2007 and 2016 (2506 cases).

1 Newly Independent States (NIS): The NIS is a collective reference to 12 republics of the former Soviet Union: Russia, Ukraine, Belarus (formerly Byelorussia), Moldova (formerly Moldavia), Armenia, Azerbaijan, Uzbekistan, Turkmenistan, Tajikistan, Kazakhstan, Kirgizstan (formerly Kirghizia), and Georgia. Following dissolution of the Soviet Union, the distinction between the NIS and the Commonwealth of Independent States (CIS) was that Georgia was not a member of the CIS. That distinction dissolved when Georgia joined the CIS in November 1993.

12.3 Prevention

Improved sanitation, food safety, and immunization are the most effective ways of combating hepatitis A. The spread of hepatitis A can be reduced by adequate supplies of safe drinking water; proper disposal of sewage within communities; and personal hygiene practices such as regular hand-washing with safe water.

12.4 HAV Vaccines

Several inactivated and live attenuated vaccines against hepatitis A were developed in the 1980s and licensed for use in the early 1990s. These vaccines are safe and well-tolerated, they are highly immunogenic, and they provide long-lasting protection against hepatitis A disease in children and adults. Four formalin-inactivated, cell culture-produced, whole-virus vaccines have been available internationally: Havrix (HM 175 strain, GlaxoSmithKline Biologicals, Rixensart, Belgium), Vaqta (CR326F strain, Merck, West Point, PA, USA), Epaxal (RG SB strain, Crucell [Janssen vaccines], Leiden, Netherlands), and Avaxim (GBM strain, Sanofi Pasteur, Lyon, France) are licensed in most parts of the world. Epaxal is no longer available.

Other hepatitis A vaccines are produced with limited or local distribution. These include, for instance, a Chinese live attenuated vaccine, MEVAC™-A (H2 strain, Zhejiang Academy of Medical Sciences, Hangzhou, People's Republic of China), and a vaccine manufactured by Vaccine and Bio-product Company in Vietnam since 2004.

Several types of combination vaccines containing an inactivated hepatitis A vaccine have been developed to protect individuals against more than one infectious disease when travelling to endemic countries. Such vaccines include Twinrix (GlaxoSmithKline Biologicals, Rixensart, Belgium), the only combined vaccine against both hepatitis A and hepatitis B infections, licensed since 1996; other combined vaccines include Hepatyrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and ViATIM (Sanofi Pasteur, Lyon, France), both protecting against hepatitis A and typhoid fever.

Table 12.1 Dosage and schedule for inactivated monovalent hepatitis A vaccines (in chronological order)

Vaccine	Antigen content (HAV strain)	Volume (ml)	Two-dose schedule (months)
Havrix™720 Junior	720 El.U (HM 175)	0.5	0, 6–12
Havrix™1440 Adult	1440 El.U (HM 175)	1	0, 6–12
Vaqta®	25 U (CR326 F)	0.5	0, 6–18
Vaqta®	50 U (CR326 F)	1	0, 6–18
Avaxim® 80 U Pediatric	80 antigen units (GBM)	0.5	0, 6–12
Avaxim ®160 U	160 antigen units (GBM)	0.5	0, 6–12

HAV hepatitis A virus, *El. U* ELISA units

Inactivated hepatitis A vaccines all contain HAV antigen, but the content per vaccine dose is expressed in different units by various manufacturers (Table 12.1). Recommended vaccination schedules, ages for which the vaccine is licensed, and whether there is a pediatric and adult formulation also vary. All vaccines are licensed from 1 year of age in most countries. The inactivated vaccines are produced according to similar manufacturing processes involving whole-virus preparations of HAV strains growing in human MRC-5 diploid cell cultures, with subsequent virus purification and inactivation with formalde-

hyde. Havrix (HM175 strain), Vaqta (CR326F strain), and Avaxim (GBM strain) are adjuvanted with alum, whereas Epaxal (RG SB strain) contained a liposome adjuvant in the form of immunopotentiating reconstituted influenza virosomes (IRIV). Havrix and Avaxim contain 2-phenoxyethanol as a preservative, whereas the other vaccines are preservative-free formulations. All vaccines are administered via intramuscular injection, according to varying dosages and schedules, as described in ◘ Table 12.1.

If medically indicated, such as in hemophiliacs or in patients under anticoagulation, all four vaccines can be given subcutaneously.

12.5 Vaccine Tolerability

To date, millions of doses of hepatitis A vaccines have been administered to children and adults worldwide, with no serious adverse event ever statistically linked to their use. The safety profile of inactivated hepatitis A vaccines has been extensively reviewed, and results from clinical trials, and those from post-marketing surveillance studies, have demonstrated that the vaccines are all safe and well-tolerated. The most commonly reported adverse events included mild and transient local site reactions, such as pain, swelling, and redness (21% in children and 52% in adults). General reactions such as low fever, fatigue, diarrhea, vomiting, and headache were reported in less than 5% of subjects.

12.6 Vaccine Immunogenicity and Protective Efficacy

The absolute minimum level of HAV antibodies required to prevent HAV infection has not been defined. Experimental studies in chimpanzees have shown that low levels of passively transferred antibody (<10 mIU/mL) obtained from vaccinated persons do not protect against infection, but do prevent clinical hepatitis and virus shedding. In the absence of an absolute lowest protective level of antibody required to prevent HAV infection, the lower limit of detection of the specific assay used in a study is generally considered as an accepted correlate of protection, i.e., 20 mIU/ml or 33 mIU/ml by ELISA in clinical studies with Havrix, 20 mIU/ml for Avaxim and Epaxal, and 10 mIU/ml for Vaqta.

Currently licensed inactivated hepatitis A vaccines have proven highly immunogenic in extensive clinical studies, conferring protective immunity against the disease 2–4 weeks after administration of the first dose. Recent data have shown that most individuals seroconvert within 2–4 weeks of vaccination, with rates ranging from 95 to 100% in children and adults. Administration of the second dose of the primary schedule (6–18 months after the first dose) ensures long-term protection. Review of the immunogenicity data for each vaccine and results from several comparative clinical trials demonstrate the equally high immunogenicity and interchangeability of hepatitis A vaccines.

The protective efficacy of inactivated hepatitis A vaccines against clinical disease has been documented in several controlled clinical efficacy trials. The cumulative protective efficacy of the vaccination course with Havrix in more than 40,000 Thai children aged 1–16 years was 95%. The observed protective efficacy of Vaqta was 100% after one vaccine dose in a trial involving more than 1000 children aged 2–16 years from a highly endemic community in the USA. In a trial involving 274 Nicaraguan children aged 1.5–6 years, the protective efficacy of a single dose of Epaxal was also 100%.

The presence of passively transferred antibodies from previous maternal HAV infection has been shown to result in reduced antibody response to hepatitis A vaccination in infants. However, in spite of lower antibody concentrations observed after primary vaccination of infants born to anti-HAV seropositive mothers, several studies have indicated that priming and immune memory were induced, as demonstrated by the anamnestic response at the time of the booster. This was the case after a second vaccine dose administered at 12 months to 300 infants born to either anti-HAV seronegative or seropositive mothers in a study conducted in Israel. Similarly, in a study conducted in Turkey with children who had received pri-

mary vaccination at 2, 4, and 6 months of age, all subjects showed anamnestic response after booster vaccination at 4 years of age. At 15 months of age, protective levels of antibody were also present in 93% of American Indian infants born to anti-HAV-positive mothers, who had received primary immunization at 2, 4, and 6 months or at 8 and 10 months of age.

12.7 Co-administration

Such findings relating to hepatitis A vaccine immunogenicity in children younger than 2 years of age, in addition to studies showing that hepatitis A vaccine may be effectively and safely co-administered with other pediatric vaccines, such as diphtheria–tetanus–acellular pertussis, inactivated and oral polio, *Haemophilus influenzae* type b, and hepatitis B vaccines, are of particular importance in the implementation of prevention strategies involving routine childhood vaccination programs. Other studies in adults have demonstrated effective and safe co-administration of hepatitis A vaccine with traveler vaccines, including hepatitis B, polio, diphtheria, tetanus, typhoid fever, yellow fever, rabies, cholera, and Japanese encephalitis.

12.8 Flexibility of Schedule

Hepatitis A vaccine has a recommended two-dose schedule, with the second dose being administered at 6–12 months in the case of Havrix, Avaxim, and Epaxal, and at 6–18 months in the case of Vaqta. However, timing of the second dose is flexible since an anamnestic response has been shown to be triggered by a second dose when administered several years after the first vaccine dose in children and adults. Flexible two-dose vaccination schedules with a "delayed" second dose are of critical importance because travelers often miss the second dose and present some years later with a new/repeated indication for hepatitis A vaccination. In addition, a flexible schedule may help to introduce hepatitis A vaccines into established childhood routine vaccination programs. For example, a vaccination schedule for infants/children with the first dose administered during the second year of life and a second dose given at school entry at the age of 5–6 seems worth investigating. Also, additional long-term follow-up studies of individuals who have received a single vaccine dose help in formulating future recommendations in terms of dosing schedule: a systematic review of published data from 2000 till 2019 to assess evidence for one-dose and two-dose universal hepatitis A vaccination in children shows rapid and persistent decline in hepatitis A incidence, with vaccine effectiveness above 95%. Because evidence is limited for one-dose universal vaccination programs, long-term monitoring of one-dose programs is essential.

12.9 Early Protection and Duration of Protection

Hepatitis A vaccines confer early protection, as confirmed by recent data showing that most individuals seroconvert within 2 weeks of vaccination, well within the 28-day incubation period of the virus. Travelers receiving the vaccine any time before departure may thus be expected to be protected against the disease.

With regard to the duration of immunity, long-term follow-up studies have shown persistence of protective anti-HAV antibodies for at least 20 years in children, adolescents, and adults, post-vaccination. Mathematical models using data from vaccinated adults have estimated protective antibodies to persist for at least 25–50 years in 99.4% of vaccinees.

12.10 Field Effectiveness of Routine Vaccination Programs

Hepatitis A routine immunization of young children has proven effective in rapidly reducing disease incidence and maintaining very low incidence levels among vaccine recipients and across all other age groups, thus demonstrating the development of herd immunity, in a number of settings. A national toddler immunization pro-

gram in place in Israel since 1999 has also demonstrated vaccine effectiveness, with a decrease in the annual incidence rate of hepatitis A disease from 50.4 per 100,000 (1993–1998) to 2.2–2.5 per 100,000 (2002–2004), representing more than a 95% reduction. This marked decline was seen in targeted vaccine recipients (85–90% coverage), and in all other age groups, thus demonstrating the effectiveness of hepatitis A vaccination and the development of herd immunity. Mass vaccination programs also proved effective in localized regions of intermediate to high HAV endemicity of industrialized nations with otherwise low endemicity levels, such as the Puglia region of Italy, the Catalonia region of Spain, and North Queensland, Australia.

In 2005, public health authorities in Argentina began a universal immunization program in 12-month-old children based on a single-dose schedule of inactivated HAV vaccine. In 2007, with vaccination coverage of 95%, the incidence of symptomatic viral hepatitis A had dropped by >80% in all age groups. Six years after implementation of this country-wide single-dose program, no hepatitis A cases have been detected among vaccinated individuals, whereas among the unvaccinated a number of cases have occurred, confirming continued circulation of HAV in the Argentinian population. An increasing number of countries in Latin America are currently implementing such a one-dose schedule.

12.11 Field Effectiveness of Post-exposure Administration and in an Outbreak Control Situation

Studies in chimpanzees, further supported by randomized trials in humans, have shown that hepatitis A vaccine is effective in preventing HAV infection when administered post-exposure. The post-exposure window for successful vaccination has been defined as the period within 2 weeks of exposure; there is indeed increasing evidence for the efficacy of hepatitis A vaccine as a valid alternative to passive post-exposure prophylaxis with immune globulin (no longer available in most countries), allowing, in particular, for a better control of outbreak situations. Results from studies conducted in chimpanzees have also shown that vaccinated animals did not shed HAV once exposed to the wild-type virus, thus demonstrating that the use of vaccines is effective at controlling the spread in the case of outbreak.

The effectiveness of hepatitis A vaccination to control outbreak situations has been reported in various settings in the USA, including rural communities from Alaska, and Europe, including Slovakia, Croatia, the UK, and Italy.

12.12 Immunization Programs

12.12.1 Risk Group Approach

Based on the transmission of HAV, several risk groups have been identified, for whom prevention by vaccination is recommended by official institutions such as the World Health Organization (WHO), the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention, and the Viral Hepatitis Prevention Board. These risk groups can either be at increased risk for HAV infection (e.g., travelers to endemic regions) or have a higher probability of developing severe complications if a HAV infection were to occur (e.g., chronic liver disease patients; see ► Box 12.1).

Box 12.1 Summary of Current ACIP, WHO, and VHPB Recommendations for Hepatitis A Vaccination

Persons at increased risk for HAV who should be routinely vaccinated:

- Persons travelling to or working in countries that have high or intermediate endemicity of infection.
- MSM.
- Intravenous drug users.
- Persons who have an occupational risk for infection.
- Persons who have clotting factor disorders.
- Day-care center children and staff.
- Persons in residential institutions.
- Food handlers.
- Healthcare workers.

Vaccination of persons who have chronic liver disease:

- Susceptible persons who have chronic liver disease or who are either awaiting or have received liver transplants should be vaccinated.

Hepatitis A vaccination during outbreaks:

- Vaccination for outbreak control should take into consideration the characteristics of hepatitis A epidemiology in the community and existing hepatitis A vaccination programs.

Sources: CDC US, World Health Organization, Viral Hepatitis Prevention Board.

12.13 Universal Immunization Programs

Vaccination against hepatitis A should be part of a comprehensive plan for the prevention and control of viral hepatitis. Planning for large-scale immunization programs should involve careful economic evaluations and consider alternative or additional prevention methods, such as improved sanitation, and health education for improved hygiene practices.

Whether to include the vaccine in routine childhood immunizations depends on the local context. The proportion of susceptible people in the population and the level of exposure to the virus should be considered. Generally speaking, countries with intermediate endemicity benefit the most from the universal immunization of children. Countries with low endemicity may consider vaccinating high-risk adults. In countries with high endemicity, the use of vaccine is limited as most adults are naturally immune.

As of 2019, at least 20 countries used hepatitis A vaccine in the routine immunization of children nationally including 6 countries with a single-dose program (Argentina, Brazil, Chile, Colombia, Paraguay, and Turkmenistan).

In the WHO-EURO region, Israel started a nationwide universal vaccination program in 1999, thereby offering two doses of HAV vaccine to toddlers at 18 and 24–30 months of age, with coverage rates reaching 85–90%. Italy (Puglia) and Spain (Catalonia) have regional universal HAV vaccination programs. In Puglia, Italy, the HAV vaccine has been offered to children aged 15–18 months since 1997, and the existing hepatitis B vaccination program for 12-year-old adolescents simultaneously started using the combined vaccine against hepatitis A and B; in Catalonia, Spain, 12-year-old adolescents have also been offered the combined hepatitis A and B vaccine since 1998–1999. In addition, Greece and Turkey recently introduced a universal immunization program in toddlers.

Regarding immunization for outbreak response, recommendations for hepatitis A vaccination should also be site-specific. The feasibility of rapidly implementing a widespread immunization campaign needs to be included. Vaccination to control community-wide outbreaks is most successful in small communities, when the campaign is started early and when high coverage of multiple age groups is achieved. Vaccination efforts should be supplemented by health education to improve sanitation, hygiene practices, and food safety.

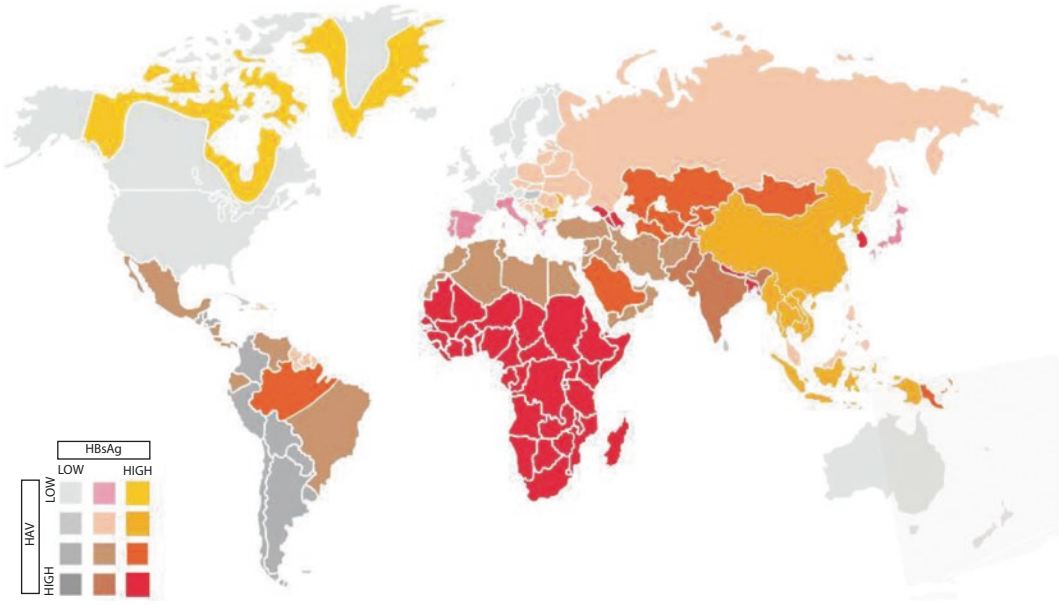

Fig. 12.2 Combined map of hepatitis B surface antigen (HBsAg; date not specified) and estimated prevalence of hepatitis A virus (HAV; 2005). (Adapted from Jacobsen and Wiersma 2010; Plotkin and Orenstein 2013)

12.14 Combined Hepatitis a and B Vaccine

Infections caused by the HAV and hepatitis B virus (HBV), which occur across the globe, are associated with significant morbidity and mortality and inflict a considerable healthcare burden (Fig. 12.2). Vaccination is the most effective method of conferring long-term protection against both viruses and, together with improved sanitation and hygiene, has resulted in a steady reduction in global infection.

Monovalent vaccines against hepatitis A and B are immunogenic and well-tolerated with long-term immunogenic benefits observed in clinical studies with up to 20 years' follow-up. Because of the considerable overlap of risk factors and areas of high endemicity for both diseases, a combined vaccine against both viruses represents a pragmatic approach that reduces the number of vaccine administrations, in particular for travelers, patients with chronic liver disease, patients infected with HCV, or persons at increased risk of sexually transmitted infections (e.g., MSM).

Table 12.2 Three presentations of combined vaccine against hepatitis A and B

Vaccine	Target population	Formulation	Schedule
Twinrix	Adults	1.0 ml–720 El.U HAV–20 µg HBsAg	3 doses
Twinrix pediatric	Children (1–11 years)	0.5 ml–360 El.U HAV–10 µg HBsAg	3 doses
Ambirix	Children and adolescents (1–15 years)	1.0 ml–720 El.U HAV–20 µg HBsAg	2 doses

HBsAg surface antigen of the hepatitis B virus

Three presentations of the combined vaccine against hepatitis A and B are available (Twinrix, Twinrix Pediatric, and Ambirix; GSK Vaccines, Belgium; Table 12.2). These bivalent vaccines are widely available, with a safety and immunogenicity profile demon-

strated as being comparable with that of the respective monovalent vaccines alone. These vaccines confer concurrent protection against the two infections while reducing the number of injections, associated costs, and other logistic issues, offering greater convenience to the vaccinee and healthcare provider.

After complete vaccination with these combined hepatitis A and B vaccines, the rate of anti-HAV seropositivity ranged from 96% to 100% in adults, children, and adolescents. The rate of hepatitis B surface antibody (anti-HBs) ranged from 82% to 100%, with decreasing immunogenicity response with increasing age. Immunogenicity results were equal to or higher for both anti-HAV and anti-HBs following Twinrix and Ambirix vaccination compared with monovalent hepatitis A and B vaccination. Long-term kinetics of the combined vaccine-induced hepatitis A and B antibodies perfectly mimics what was respectively demonstrated with the monovalent hepatitis A and B vaccines, both in terms of long-term persistence of vaccine-induced antibodies (at least 20 years shown in the adult population) and immune memory: the latter was demonstrated by mounting a strong anamnestic response after a challenge dose of HAV or HBV vaccine, indicative of the induction and persistence of immune memory.

Co-administration of Twinrix pediatric or Ambirix with other routine childhood vaccines was immunologically non-inferior to administration of the combined hepatitis A and B vaccine alone and did not significantly alter the safety profile. Safety profiles of the combined versus monovalent hepatitis A and B vaccines were similar.

Further Reading

Andani A, Van Damme P, Bunge EM, Salgado F, van Hoorn RC, Hoet B. One or two doses of hepatitis A vaccine in universal immunization programs in children in 2020: a systematic review. Vaccine. 2021 Jan 29:S0264-410X(21)00054-2. https://doi.org/10.1016/j.vaccine.2021.01.038.

André F, Van Damme P, Safary A, Banatvala J. Inactivated Hepatitis A vaccine: immunogenicity, efficacy, safety and review of official recommendations for use. Expert Rev Vaccines. 2002;1(1):9–23.

Bakker M, Bunge E, Marano C, de Ridder M, De Moerlooze L. Immunogenicity, effectiveness and safety of combined hepatitis A and B vaccine: a systematic literature review. Expert Rev Vaccines. 2016;15:829–51.

Bell BP, Feinstone SM. Hepatitis A vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia: Saunders; 2004. p. 269–97.

Beran J, Beutels M, Levie K, Van Damme P, Dieussaert I, Gillet M, et al. A single dose, combined vaccine against typhoid fever and hepatitis A: consistency, immunogenicity and reactogenicity. J Travel Med. 2001;7(5):246–52.

Dagan R, Amir J, Mijalovsky A, Kalmanovitch I, Bar-Yochai A, Thoelen S, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. Pediatr Infect Dis J. 2000;19:1045–52.

Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following Universal Immunization of Toddlers. JAMA. 2005;294:202–10.

Gossner CM, et al. Changing hepatitis A epidemiology in the European Union: new challenges and opportunities. Eurosurveillance. 2015;20(16):1–6.

Herzog C, Van Herck K, Van Damme P. Hepatitis A vaccination and its immunological and epidemiological long-term effects – a review of the evidence. Human Vaccines & Immunotherapeutics 2020; 16: 1−24. https://doi.org/10.1080/21645515.2020.1819742

Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, et al. Protection against hepatitis A by an inactivated vaccine. JAMA. 1994;271:1328–34.

Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. Epidemiol Infect. 2004;132:1005–22.

Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28:6653–7.

Letson GW, Shapiro CN, Kuehn D, Gardea C, Welty TK, Krause DS, et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. J Pediatr. 2004;144:327–32.

Loutan L, Bovier P, Althaus B, Glück R. Inactivated virosome hepatitis A vaccine. Lancet. 1994;343:322–34.

Mayorga O, Bühler S, Jaeger VK, Bally S, Hatz C, Frösner G, Protzer U, Van Damme P, Egger M, Herzog C. Single-dose Hepatitis A immunization: 7.5-year observational pilot study in Nicaraguan children to assess protective effectiveness and humoral immune memory response. J Infect Dis. 2016;214(10):1498–506.

Martin JC, Petrecz ML, Stek JE, Simon JK, Goveia MG, Klopfer SO. Using the power law model to predict the long-term persistence and duration of detectable hepatitis A antibody after receipt of hepatitis A vaccine (VAQTA™). Vaccine. 2021 Apr 15:S0264-

410X(21)00345-5. https://doi.org/10.1016/j.vaccine.2021.03.052.

Ott JJ, Wiersma ST. Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations. Int J Infect Dis. 2013;17(11):e939–44. https://doi.org/10.1016/j.ijid.2013.04.012. Review.

Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine. 2012;31(1):3–11. https://doi.org/10.1016/j.vaccine.2012.04.104. Review.

Plotkin S,Orenstein W, Offit P. Vaccines. 6th (ed). 2013 Saunders. ISBN: 9781455737987. https://www.elsevier.com/books/vaccines/plotkin/978-1-4557-0090-5

Stuurman AL, Marano C, Bunge EM, De Moerlooze L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines – a systematic review. Human Vaccines & Immunotherapeutics 2017; 13 (3): 724−736

Theeten H, Van Herck K, Van Der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. Vaccine. 2015;33(42):5723–7. https://doi.org/10.1016/j.vaccine.2015.07.008.

Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. Expert Rev Vaccines. 2004;3(3):249–67.

Van Damme P, Van Herck K. Effect of hepatitis A vaccination programs. JAMA. 2005;294:246–8.

Van Damme P, Thoelen S, Cramm M, De Groote K, Safary A, Meheus A. Inactivated hepatitis A vaccine: reactogenicity, immunogenicity, and long-term antibody persistence. J Virol Med. 1994;44(4):446–51.

Van Damme P, Banatvala J, Fay O, Iwarson S, McMahon B, Van Herck K, et al. Consensus statement: hepatitis A booster vaccination: is there a need? Lancet. 2003;362:1065–71.

Van Damme P, Leroux-Roels G, Suryakiran P, Folschweiller N, Van Der Meeren O. Persistence of antibodies 20 y after vaccination with a combined hepatitis A and B vaccine. Hum Vaccin Immunother. 2017;13:972–80.

Vidor E, Dumas R, Porteret V, Bailleux F, Veitch K. Aventis Pasteur vaccines containing inactivated hepatitis A virus: a compilation of immunogenicity data. Eur J Clin Microbiol Infect Dis. 2004;23(4):300–9.

Wasley A, Samandari T, Bell B. Incidence of hepatitis A in the United States in the era of vaccination. JAMA. 2005;294:194–201.

Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med. 1992;327(7):453–7.

World Health Organization. Hepatitis A vaccines WHO position paper. Weekly Epidemiology Record. 2012;875:261–76. https://www.who.int/wer/2012/wer8728_29.pdf?ua=1