

Hepatitis A vaccines: WHO position paper – October 2022

References with abstracts cited in the position paper in the order of appearance.

WHO. WHO position paper on hepatitis A vaccines - June 2012. Wkly Epidemiol Rec. 2012;87(28/29):261–76.

[no abstract]

Jacobsen KH et al. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653–7.

Objective: To estimate current age-specific rates of immunity to hepatitis A virus (HAV) in world regions by conducting a systematic review and meta-analysis of published data. The estimation of the global burden of hepatitis A and policies for public health control are dependent on an understanding of the changing epidemiology of this viral infection. **Methods:** Age-specific IgG anti-HAV seroprevalence data from more than 500 published articles were pooled and used to fit estimated age-seroprevalence curves in 1990 and 2005 for each of 21 world regions (as defined by the Global Burden of Disease 2010 Study). **Findings:** High-income regions (Western Europe, Australia, New Zealand, Canada, the United States, Japan, the Republic of Korea, and Singapore) have very low HAV endemicity levels and a high proportion of susceptible adults, low-income regions (sub-Saharan Africa and parts of South Asia) have high endemicity levels and almost no susceptible adolescents and adults, and most middle-income regions have a mix of intermediate and low endemicity levels. **Conclusion:** Anti-HAV prevalence estimates in this analysis suggest that middle-income regions in Asia, Latin America, Eastern Europe, and the Middle East currently have an intermediate or low level of endemicity. The countries in these regions may have an increasing burden of disease from hepatitis A, and may benefit from new or expanded vaccination programs.

Lemon SM et al. Type A viral hepatitis: A summary and update on the molecular virology, epidemiology, pathogenesis and prevention. J Hepatol. 2017;68(1):167–84.

Although epidemic jaundice was well known to physicians of antiquity, it is only in recent years that medical science has begun to unravel the origins of hepatitis A virus (HAV) and the unique pathobiology underlying acute hepatitis A in humans. Improvements in sanitation and the successful development of highly efficacious vaccines have markedly reduced the worldwide prevalence and incidence of this enterically-transmitted infection over the past quarter century, yet the virus persists in vulnerable populations and remains a common cause of food-borne disease outbreaks in economically-advantaged societies. Reductions in the prevalence of HAV have led to increases in the median age at which infection occurs, often resulting in more severe disease in affected persons and paradoxical increases in disease burden in some developing nations. Here, we summarize recent advances in the molecular virology of HAV, an atypical member of the Picornaviridae family, survey what is known of the pathogenesis of hepatitis A in humans and the host-pathogen interactions that typify the infection, and review medical and public health aspects of immunisation and disease prevention.

Nainan OV et al. Diagnosis of hepatitis a virus infection: a molecular approach. Clin Microbiol Rev. 2006;19(1):63–79.

Current serologic tests provide the foundation for diagnosis of hepatitis A and hepatitis A virus (HAV) infection. Recent advances in methods to identify and characterize nucleic acid markers of viral infections have provided the foundation for the field of molecular epidemiology and increased our knowledge of the molecular biology

and epidemiology of HAV. Although HAV is primarily shed in feces, there is a strong viremic phase during infection which has allowed easy access to virus isolates and the use of molecular markers to determine their genetic relatedness. Molecular epidemiologic studies have provided new information on the types and extent of HAV infection and transmission in the United States. In addition, these new diagnostic methods have provided tools for the rapid detection of food-borne HAV transmission and identification of the potential source of the food contamination.

Martin A et al. Hepatitis A virus: from discovery to vaccines. *Hepatology*. 2006;43(2 Suppl 1):S164–72.

Hepatitis A virus (HAV), the causative agent of type A viral hepatitis, is an ancient human virus that was first identified almost 35 years ago. It has several characteristics that make it unique among the Picornaviridae, particularly in terms of its mechanisms of polyprotein processing and virion morphogenesis, and which likely contribute to its pathobiology. Although efficacious vaccines containing formalin-inactivated virus produced in cell culture have been licensed in multiple countries, their use has been limited by cost considerations. Changes in public health sanitation and generally increasing standards of living are leading to a decreasing incidence of acute hepatitis A worldwide, with the result that the prevalence of preexisting immunity among adults is declining in many regions. These changes in the epidemiology of HAV may paradoxically enhance the disease burden, as greater numbers of individuals become infected at older ages when disease is more likely to be clinically evident, thus providing greater incentives for vaccine utilization.

Immunological basis for immunization series: module 18: hepatitis A. Update 2019 ed. Geneva: World Health Organization; 2019.

[no abstract]

Hollinger FB et al. Hepatitis A and B vaccination and public health. *J Viral Hepat*. 2007;14 Suppl 1:1–5.

The introduction and implementation of hepatitis B vaccination programmes in areas of high endemicity has been very stressful. However, this initial accomplishment has led to the reassessment of priorities in some countries which could undermine these early successes. Work still remains to be done to support and implement interventions that will bring us closer to the WHO goal and to the control of hepatitis B in the community at large. Hepatitis A vaccine strategy for immunizing toddlers is shifting to those countries with intermediate endemicity where increasing morbidity in adults is being observed. Accumulating evidence indicates that such programmes can result in impressive reductions in the incidence of hepatitis A by herd immunity. Monitoring of these populations to determine durability of protection will be important to avoid shifting the infection to the older age population, when symptoms are more likely to occur. National policies need to consider hepatitis A vaccination in the context of other public health priorities.

Zamir C et al. Control of a community-wide outbreak of hepatitis A by mass vaccination with inactivated hepatitis A vaccine. *Eur J Clin Microbiol Infect Dis*. 2001;20(3):185–7.

The epidemiology and control of hepatitis A virus was investigated during an outbreak of hepatitis A in a village in Israel. Postexposure administration of immune globulin to contacts was ineffective in controlling the outbreak. However, within 2 weeks of starting a mass immunization campaign with hepatitis A vaccine, the incidence of hepatitis A declined dramatically; the last case occurred 6 weeks after the immunization program began. The study demonstrated that while postexposure administration of immune globulin may diminish but

not entirely arrest transmission of hepatitis A virus, active hepatitis A vaccination is a safe and effective intervention that can be used safely in hepatitis A virus antibody-positive children.

Glikson M et al. Relapsing hepatitis A. Review of 14 cases and literature survey. *Medicine (Baltimore)*. 1992;71(1):14–23.

We have reviewed our experience with 14 cases of relapsing hepatitis A (RH-A), as well as 68 cases reported in the literature. Relapse occurs in 3 to 20% of patients with acute hepatitis A, and rarely takes the form of a polyphasic disease (multiple relapses). After a stage of typical hepatitis A, remission phase ensues, with partial or complete resolution of clinical and biochemical manifestations. Relapse usually occurs after a short period (usually less than 3 weeks). Relapse is usually clinically milder than the first phase, with variable liver function abnormalities and a tendency toward more marked cholestatic features. Not uncommonly, immune manifestations occur during this phase, including purpura, nephritis, and arthralgia, with common laboratory findings of rheumatoid factor as well as false-positive reaction to HCV-EIA tests. The clinical course in relapsing hepatitis A is almost always benign, and uneventful recovery is the rule with few exceptions. Steroid treatment, first reported in the present series, resulted in marked clinical improvement. Preliminary results suggest that R-HA is associated with a continuing viremia as well as shedding of virus in stools during the relapse phase. The pathogenesis of R-HA probably involves an interaction between persistent viral infection and immune mechanisms responding to the continuing antigenic stimulation.

Sjogren MH. The success of hepatitis A vaccine. *Gastroenterology*. 1993;104(4):1214–6.

[no abstract available]

Hollinger F et al. Hepatitis A virus. In: Fields B, Knipe D, Howley P, editors. *Fields Virology*. Sixth edition ed. Philadelphia: Lippincott Williams and Wilkins; 2013. p. 550-81.

[no abstract available]

Elinav E et al. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology*. 2006;130(4):1129–34.

Background & Aims: Hepatitis A virus (HAV) infection is the most common cause of acute hepatitis but is rarely reported during pregnancy. Our aim was to evaluate the impact of acute HAV infection on pregnancy outcome. **Methods:** Consecutive admissions of 79,458 pregnant females during a 25-year period were retrospectively reviewed. **Results:** Thirteen cases of second and third trimester HAV infection were found and evaluated. Nine of the 13 patients (69%) developed gestational complications, including premature contractions (n = 4), placental separation (n = 2), premature rupture of membranes (n = 2), and vaginal bleeding (n = 1). In 8 of these patients, complications led to preterm labor, at a median of 34 gestational weeks (range, 31–37 weeks). Delivery was vaginal in 12 of the 13 cases; fetal distress was noted in a single case, and meconium in amniotic fluid in 2 cases. Median birth weight was 1778 grams and 3040 grams in preterm and term deliveries, respectively (P < .05). Child outcome was favorable in all cases. In 4 cases, neonatal serum HAV RNA levels were measured and found negative. The presence of fever and hypoalbuminemia were associated with delivery at an earlier gestational week. There was a positive relation between gestational week at diagnosis of HAV infection and birth week (r = 0.68, P = .02), suggesting a causality relationship. All mothers featured full recovery from HAV infection. **Conclusions:** Acute HAV infection during pregnancy is associated with high risk of maternal

complications and preterm labor. HAV serology and maternal vaccination during prepregnancy evaluation should be considered in areas of the world in which susceptible adult populations exist.

Chaudhry SA et al. Hepatitis A infection during pregnancy. Can Fam Physician. 2015;61(11):963–4.

Question: Many of my patients are from Southeast Asia, where hepatitis A virus (HAV) infection is quite common. What precautions can I suggest my pregnant patients take before traveling to these areas and what is the risk of contracting HAV during pregnancy? **Answer:** Hepatitis A virus is a water-borne pathogen transmitted by the fecal-oral route. To reduce the risk of contracting HAV while traveling to endemic areas, it is important to maintain hygienic practices such as hand washing with safe water, particularly before handling food, avoiding drinking water or using ice cubes of unknown purity, and avoiding eating unpeeled fruits and vegetables. An HAV vaccine is available and can be administered before traveling to endemic countries. Hepatitis A virus infection has a largely favourable expected outcome even during pregnancy. Infection occurring in the second or third trimester has been reported to be associated with preterm labour.

Mohd Hanafiah K et al. Challenges to mapping the health risk of hepatitis A virus infection. Int J Health Geogr. 2011;10:57.

Background: World maps are among the most effective ways to convey public health messages such as recommended vaccinations, but creating a useful and valid map requires careful deliberation. The changing epidemiology of hepatitis A virus (HAV) in many world regions heightens the need for up-to-date risk maps. HAV infection is usually asymptomatic in children, so low-income areas with high incidence rates usually have a low burden of disease. In higher-income areas, many adults remain susceptible to the virus and, if infected, often experience severe disease. **Results:** Several challenges associated with presenting hepatitis A risk using maps were identified, including the need to decide whether prior infection or continued susceptibility more aptly indicates risk, whether to display incidence or prevalence, how to distinguish between different levels of risk, how to display changes in risk over time, how to present complex information to target audiences, and how to handle missing or obsolete data. **Conclusion:** For future maps to be comparable across place and time, we propose the use of the age at midpoint of population susceptibility as a standard indicator for the level of hepatitis A endemicity within a world region. We also call for the creation of an accessible active database for population-based age-specific HAV seroprevalence and incidence studies. Health risk maps for other conditions with rapidly changing epidemiology would benefit from similar strategies.

IHME. Global Burden of Disease Study 2019. Dataset. (<http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/8f4e502fb3985c0fc186c6f27ef14a79>, accessed 29 August 2022).

[no abstract available]

IHME. Acute hepatitis A — Level 4 cause.

(https://www.healthdata.org/results/gbd_summaries/2019/acute-hepatitis-a-level-4-cause, accessed 28 June 2022).

[no abstract available]

Jacobsen KH. Globalization and the Changing Epidemiology of Hepatitis A Virus. Cold Spring Harb Perspect Med. 2018.

Increased economic interdependence, social integration, and other aspects of globalization are contributing to significant changes in hepatitis A epidemiology. Globally, the incidence of hepatitis A virus (HAV) infection is decreasing, the age at midpoint of population immunity (AMPI) is increasing, and the proportion of symptomatic cases is increasing as the average age at infection increases. In low-income countries, HAV remains endemic but improved water and sanitation systems are reducing transmission rates among young children. In high-income countries, most adults remain susceptible to HAV and foodborne outbreaks are becoming more frequent. Middle-income countries have diverse epidemiological profiles, and they play important roles in the global spread of HAV through international trade and travel. Future changes in the epidemiology of hepatitis A will be heavily influenced by globalization processes.

Munné MS et al. Molecular characterization of hepatitis A virus in children with fulminant hepatic failure in Argentina. *Liver Int.* 2008;28(1):47–53.

Background: Hepatitis A infection, a vaccine-preventable disease, is an important cause of fulminant hepatic failure (FHF) in children in Argentina. Universal vaccination in 1-year-old children was implemented in June 2005. The limited studies about the correlation between the characteristics of the hepatitis A virus (HAV) and FHF have been carried out in adults. **Methods:** Samples from 41 children with FHF were studied from September 2003 to January 2006 and HAV RNA was detected, sequenced and analysed in the 5' non-coding region and VP1/2A region. **Results:** Eighteen HAV strains were characterized and found to be different at the nucleotide level from the self-limited acute infection strains that have been circulating in Argentina with no temporal or geographical pattern. They did not form a genetic cluster, but some of them were identical in the largest fragment characterized and some of them seemed to be more closely related in time and/or geographically. **Conclusion:** Our results suggest that viral factors could be involved in the severity of the clinical presentation of HAV infection in children in Argentina.

Santos DC et al. Fulminant hepatitis failure in adults and children from a Public Hospital in Rio de Janeiro, Brazil. *Braz J Infect Dis.* 2009;13(5):323–9.

Fulminant hepatic failure (FHF) is characterized by massive hepatocellular injury, whose physiopathology is still unclear. Hepatitis B (HBV) is probably the most common viral cause of FHF, while hepatitis A (HAV) virus seem occurs less frequently. However, the host and viral factors that determine the outcome of these infections are poorly understood. In the present study, viral load and genotyping determining regions of HAV and HBV genomes were sequenced. Eight FHF patients and one patient with severe acute hepatitis (SAH) were included. Liver and blood samples were collected during liver transplantation or necropsy procedures. HAV-RNA and HBV-DNA were extracted from serum, biopsy and paraffin liver. Nucleotide sequencing of HAV-RNA was performed from VP1/2A and HBV-DNA from PreS/S region. The amplified samples were quantified by Real-Time PCR. The cases of HAV infection were due to subgenotype IA. The cases of HBV infection were due to genotype A2 and D4. The case of HAV/HBV coinfection was infected by genotype IA and D3. Hepatitis A and B infection were associated with genotypes most prevalent in Brazil. In hepatitis A infection the mean of period evolution was 13 days. In hepatitis B, FHF patients infected by genotype D have a shorter period of evolution than FHF patients infected by genotype A (mean 15 v. 53 days). There was no association with genotype-determining region with the severity of hepatitis, however nucleotide differences and high viral load could be observed among FHF.

Kim YJ et al. Increasing incidence of hepatitis A in Korean adults. *Intervirol.* 2010;53(1):10–4.

Hepatitis A infection is caused by the hepatitis A virus (HAV), which is transmitted through the fecal-oral route. Lifelong protective antibodies are present after infection. The number of cases of adult hepatitis A has

progressively been increasing during the last several decades in Korea. In addition, the pattern of age-specific seroprevalence of anti-HAV has changed with economic growth. The prevalence of anti-HAV in the 10-50-year age range has declined rapidly during the last 3 decades. As a result, this age group has a high risk for HAV infection and clinically overt hepatitis A is increasing in adolescents and adults. It is well established that the severity of the disease is related to the age of the patients. The development of more cases of adult hepatitis A with severe presentation is expected in the near future. The clinical features and the epidemiological shift of HAV underscore the importance in Korea, as well as in other countries with similar issues, of childhood vaccination and consideration of catch-up vaccination for adolescents and adults as well as of targeted vaccination for individuals at increased risk for infection or its complications. There is a need to extensively evaluate the nationwide epidemiology of HAV infection, make cost-benefit analyses of HAV vaccination, and establish guidelines for HAV vaccination.

Bendre SV et al. Fulminant hepatic failure: etiology, viral markers and outcome. Indian Pediatr. 1999;36(11):1107–12.

Objective: To investigate the etiology and outcome of fulminant hepatic failure (FHF) in children. **SETTING:** Hospital based descriptive. **Methods:** 36 children (22 males and 14 females) presenting with FHF over a period of one year were investigated. The ages ranged from 1.5 to 9 years. FHF was defined as occurrence of encephalopathy within eight weeks of onset of jaundice with no evidence of pre-existing liver disease. Detailed history, clinical examination, routine biochemical parameters and relevant diagnostic tests were carried out. Viral markers studied were anti HAV-IgM, HBsAg, anti HBc-IgM, anti-HCV and anti HEV-IgM. **RESULTS:** A viral etiology could be established in 22 children (61.1%). Hepatitis A (n = 12), Hepatitis B (n = 3), Hepatitis A and B (n = 2), and Hepatitis A and E (n = 4). Two children had enteric fever (1 with associated HEV), 2 children had Wilson's disease, 1 child had Indian Childhood Cirrhosis (ICC) and 2 children had drug induced hepatitis. Etiological diagnosis was not possible in 8 children (22%). Fourteen children (39%) died. Poor outcome was associated with spontaneous bleeding, raised prothrombin time, lower transaminases and higher bilirubin on admission. **Conclusion:** Viral hepatitis is the commonest cause of FHF in children. HAV alone or in combination is responsible for upto 50% of all FHF in children. Chronic liver disease can also present as FHF. Etiological diagnosis is not possible to upto one-fourth of all cases.

Lemon SM. Immunologic approaches to assessing the response to inactivated hepatitis A vaccine. J Hepatol. 1993;18 Suppl 2:S15–9.

Natural immunity to hepatitis A virus (HAV) is complex and likely to involve several distinct arms of the immune system. There is evidence that natural killer cells, human leukocyte antigen (HLA)-restricted cytotoxic T cells, and antibody-secreting cells of B-cell lineage all play roles in the immune response to infection with HAV. However, antibody alone is sufficient to provide a high level of protection against clinical disease. A comparison of the serum levels of antibody to HAV (anti-HAV) following administration of immune serum globulin and hepatitis A vaccine may provide a useful estimate of vaccine efficacy. Such comparisons may be accomplished using solid-phase immunoassays for detection of anti-HAV. However, tests which measure antibody capable of neutralizing virus in vitro are generally more sensitive than solid-phase immunoassays. The use of endogenously labelled virus in radioimmunoprecipitation assays shows promise of providing an equally sensitive means of measuring antibodies which are reactive with HAV particles.

Fiore AE et al. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(Rr-7):1–23.

Routine vaccination of children is an effective way to reduce hepatitis A incidence in the United States. Since licensure of hepatitis A vaccine during 1995-1996, the hepatitis A childhood immunization strategy has been implemented incrementally, starting with the recommendation of the Advisory Committee on Immunization Practices (ACIP) in 1996 to vaccinate children living in communities with the highest disease rates and continuing in 1999 with ACIP's recommendations for vaccination of children living in states, counties, and communities with consistently elevated hepatitis A rates. These updated recommendations represent the final step in the childhood hepatitis A immunization strategy, routine hepatitis A vaccination of children nationwide. Implementation of these recommendations will reinforce existing vaccination programs, extend the benefits associated with hepatitis A vaccination to the rest of the country, and create the foundation for eventual consideration of elimination of indigenous hepatitis A virus transmission. This report updates ACIP's 1999 recommendations concerning the prevention of hepatitis A through immunization (CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1999;48[No. RR-12]:1-37) and includes 1) new data on the epidemiology of hepatitis A in the era of hepatitis A vaccination of children in selected U.S. areas, 2) results of analyses of the economics of nationwide routine vaccination of children, and 3) recommendations for the routine vaccination of children in the United States. Previous recommendations for vaccination of persons in groups at increased risk for hepatitis A or its adverse consequences and recommendations regarding the use of immune globulin for protection against hepatitis A are unchanged from the 1999 recommendations.

Requirements for Hepatitis A vaccines (inactivated), Annex 2, TRS No 858. Geneva: World Health Organization; 1995.

WHO International Standards/Reference Reagents: Submission to ECBS of post-establishment stability evaluation: 1st IS for Inactivated Hepatitis A Vaccine / by Gillian Cooper and Javier Martin. Geneva: World Health Organization; 2011. (<https://apps.who.int/iris/handle/10665/70856>, accessed 29 August 2022).

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

Hepatitis A and B are two of the most common vaccine-preventable liver diseases and continue to be a significant cause of morbidity and mortality worldwide, with their severity related to the individual's age upon initial infection. Twinrix (GlaxoSmithKline), a combined vaccine providing protection against both hepatitis A and B, has been available in more than 72 countries worldwide since 1997. This paper provides a critical review of clinical data on the efficacy, immunogenicity and tolerability of the combined vaccine, with particular focus on the clinical benefits of dual vaccination.

Beran J et al. A combined dual-chamber typhoid/hepatitis A vaccine as a booster dose in hepatitis A primed adults. Vaccine. 2003;21(32):4650–4.

Vivaxim™ is a combined hepatitis A/typhoid fever vaccine (HA/Vi) licensed for vaccination of travellers, but long-term protection against hepatitis A requires two immunisations at least 6 months apart. A randomised, controlled study was performed in 116 healthy adults primed with hepatitis A vaccine (Avaxim™) to compare immune responses to HA/Vi and Avaxim™ given as booster doses 6 months later. Both vaccines elicited marked booster responses achieving antibody geometric mean titres (GMTs) of 4576 and 3760mIU/ml in the HA/Vi and Avaxim™ groups, respectively. Although twice as frequent in the HA/Vi group, local reactions (mostly pain) were mainly mild and transient, probably reflecting the larger volume injected (1ml). Vivaxim™ offers a convenient means of administering both HA and typhoid fever vaccines in subjects already primed for hepatitis A.

Bovier PA et al. Interchangeability and tolerability of a virosomal and an aluminum-adsorbed hepatitis A vaccine. *Vaccine*. 2005;23(19):2424–9.

The interchangeability of virosomal (Epaxal) and aluminum-adsorbed (Havrix 1440) hepatitis A virus (HAV) vaccines was studied in 111 healthy adults who were vaccinated in a randomized, single-blind, crossover clinical trial. Anti-HAV antibody titers were measured at days 0 (first dose), 14, and 28, and months 3, 6, 12 (second dose), 13, 24, 36, 48, 60 and 72. Most subjects (>95%) had sero-converted 14 days after the first dose of either vaccine. The second dose with either vaccine induced a high antibody response in all vaccines, irrespective of the type of vaccine administered as the first dose. Although both vaccines were well tolerated, the incidence of local adverse events (in particular pain) was significantly lower in subjects receiving the virosomal vaccine. Six-year follow-up data did not reveal any significant differences between the vaccination groups.

Ekwall E et al. Interchangeability of Hepatitis A boosters, Avaxim and Vaqta, in healthy adults following a primary dose of the combined typhoid/Hepatitis A vaccine Viatim. *Vaccine*. 2006;24(20):4450–7.

This study investigated the suitability of Avaxim and Vaqta as Hepatitis A booster vaccines 6 months after priming with the combined Hepatitis A/typhoid vaccine, Viatim. One hundred and twenty adults were randomly assigned to one of the three groups. Group A (reference group) received Avaxim then Avaxim (n = 40), Group B received Viatim then Avaxim (n = 41) and Group C received Viatim then Vaqta (n = 39). One month after booster vaccination, anti-Hepatitis A virus (anti-HAV) antibodies geometric mean concentrations (GMC) of subjects primed with Viatim were non-inferior to the group primed and boosted with the monovalent Hepatitis A vaccine Avaxim. Anti-Salmonella typhi capsular polysaccharide virulence antigen (anti-Vi) GMCs in groups primed with Viatim were protective and all vaccines were well-tolerated. Therefore, Viatim may be used as a primary HAV vaccine with either Avaxim or Vaqta as Hepatitis A boosters and it will provide the same protection as two doses of Avaxim.

Letson GW et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. *J Pediatr*. 2004;144(3):327–32.

Objective: To determine the effect of maternal antibody on hepatitis A vaccine immunogenicity in infants. Study design Infants of mothers negative for antibody to hepatitis A virus (anti-HAV; group 1) were administered hepatitis A vaccine at 2, 4, and 6 months of age, and infants of anti-HAV-positive mothers were randomized to receive either hepatitis A vaccine (group 2) or hepatitis B vaccine (group 3) on the same schedule. Group 3 infants subsequently received hepatitis A vaccine at 8 and 10 months of age. RESULTS: At 15 months of age, 100% of infants in group 1, 93% in group 2, and 92% in group 3 had protective levels of antibody. However, there were significant differences in the geometric mean concentration (GMC) of anti-HAV between groups. Group 1 GMC was 231 mIU/mL, compared with 85 mIU/mL for group 2 and 84 mIU/mL for group 3 (P<.001, group 1 vs group 3). **Conclusions:** Passively acquired maternal anti-HAV resulted in a significantly lower final antibody response when infants were administered hepatitis A vaccine at 2, 4, and 6 months of age or at 8 and 10 months of age.

Dagan R 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(11):1045–52.

Background: Maternal antibodies interfere with hepatitis A vaccination in young infants. We examined the response to a high dose hepatitis A vaccine administered concomitantly with a combination of diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus vaccine/Haemophilus influenzae type b vaccine to

initially seropositive vs. initially seronegative infants. **Methods:** Three hundred subjects were originally planned to be enrolled at age 6 to 10 weeks and received hepatitis A vaccine (formalin-inactivated vaccine, SB-Bio, 720 enzyme-linked immunosorbent assay units) at 2, 4 and 6 months concomitantly with a diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus vaccine/H. influenzae type b vaccine. Children initially seropositive received a booster dose at 12 months of age. An additional 100 twelve-month-old infants previously not vaccinated with hepatitis A vaccine were given 1 dose, to observe the primary response at that age. Reactogenicity was recorded on diary cards for the 3 subsequent days. Immunogenicity was measured at Months 2, 4, 5, 10 and 11 after administration of the first vaccine dose. For the subjects enrolled at 12 months, blood was drawn before and 1 month after the first vaccination. **Results:** Of 297 initially enrolled infants 36% were seronegative before vaccination (Group A). The geometric mean concentration (GMC) (milli-International Units/ml) of the seropositive infants (Group B) before immunization was 2587. The GMCs of Group A infants 1 month after each dose and at 12 months of age were 93, 518, 1656 and 786, respectively. For Group B infants, the respective GMCs were 1165, 460, 508 and 167. One hundred subjects of Group B received a booster dose at age 12 months; at Month 13 all were seropositive with a GMC of 1902. For comparison, a third group of 100 not previously immunized 12-month-old infants (Group C) were enrolled and received 1 dose of hepatitis A vaccine with pre- and postimmunization GMCs of 52 and 120, respectively. **Conclusions:** Our results suggest that the initially seropositive infants were primed despite maternal antibody interference. The hepatitis A vaccine was well-tolerated in this population of young infants.

Usonis V et al. Immunogenicity and safety of a combined hepatitis A and B vaccine administered concomitantly with either a measles-mumps-rubella or a diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine mixed with a Haemophilus influenzae type b conjugate vaccine in infants aged 12-18 months. Vaccine. 2005;23(20):2602–6.

Two studies were undertaken to investigate the concomitant administration of combined hepatitis A/B vaccine with a diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine mixed with Haemophilus influenzae vaccine (DTPa-IPV/Hib), or with a measles-mumps-rubella vaccine (MMR), during the second year of life. On completion of the vaccination course, all subjects were seropositive or seroprotected against all antigens except for one subject who was seronegative for anti-PT. Seropositivity and seroprotection rates for all other antibodies were comparable to reference values for each vaccine component, indicating that the immunogenicity of MMR, DTPa-IPV/Hib and combined hepatitis A/B vaccines is not impaired by co-administration. All vaccines were well tolerated.

Dagan R et al. Concomitant administration of a virosome-adjuvanted hepatitis a vaccine with routine childhood vaccines at age twelve to fifteen months: a randomized controlled trial. Pediatr Infect Dis J. 2007;26(9):787–93.

Background: The objectives of this trial were to test for noninferiority of a virosomal hepatitis A virus (HAV) vaccine (Epaxal) coadministered with routine childhood vaccines compared with Epaxal given alone and to an alum-adjuvanted HAV vaccine (Havrix Junior) coadministered with routine childhood vaccines. **Methods:** Healthy children 12- to 15-month-old were randomized to receive either a pediatric dose (0.25 mL) of Epaxal coadministered with DTPaHibIPV, oral polio vaccine, and measles-mumps-rubella vaccine (n = 109; group A), or Epaxal given alone (n = 105; group B), or Havrix Junior coadministered with DTPaHibIPV, oral polio vaccine, and measles-mumps-rubella vaccine (n = 108; group C). A booster dose was given 6 months later. Anti-HAV antibodies were tested before and 1 month after each vaccination. Safety was assessed for 1 month after each vaccination. Solicited adverse events were assessed for 4 days after each vaccination. **Results:** : HAV seroprotection rates (> or =20 mIU/mL) at 1 and 6 months after first dose were: A: 94.2% and 87.5%, B: 92.6% and 80.0%, C: 78.2% and 71.3%, respectively (A versus C: P < 0.001 and P = 0.017 at month 1 and 6,

respectively). The respective geometric mean concentrations were: A: 51 and 64 mIU/mL, B: 49 and 59 mIU/mL, C: 33 and 37 mIU/mL (A versus C: $P < 0.001$ at both time points). All groups achieved 100% seroprotection after the booster dose. The geometric mean concentrations after the booster dose were 1758, 1662, and 1414, for groups A, B and C, respectively (A versus C: $P = 0.15$). No clinically significant reduction in immune response to all concomitant vaccine antigens was seen. All vaccines were well tolerated. **Conclusions:** : Coadministration of pediatric Epaxal with routine childhood vaccines showed immunogenicity and safety equal to Epaxal alone as well as to Havrix Junior. After first dose, Epaxal was significantly more immunogenic than Havrix Junior.

Yetman RJ et al. Concomitant administration of hepatitis A vaccine with measles/mumps/rubella/varicella and pneumococcal vaccines in healthy 12- to 23-month-old children. Hum Vaccin Immunother. 2013;9(8):1691–7.

This open-label, multicenter, randomized, comparative study evaluated immunogenicity, safety and tolerability of concomitant (Group 1; $n=330$) vs. non-concomitant (Group 2; $n=323$) VAQTA™ (25U/0.5 mL) (hepatitis A vaccine; HAV) with ProQuad™ (measles/mumps/rubella/varicella; MMRV) and Prevnar™ (7-valent pneumococcal; PCV-7) in healthy, 12-23 mo old children. Group 1 received HAV/MMRV/PCV-7 concomitantly on Day 1 and second doses of HAV/MMRV at Week 24. Group 2 received MMRV/PCV-7 on Day 1, HAV at Weeks 6 and 30 and MMRV at Week 34. Hepatitis A seropositivity rate (SPR: ≥ 10 mIU/mL; 4 weeks postdose 2), varicella zoster-virus (VZV) SPR (≥ 5 gpELISA units/mL) and geometric mean titers (GMT) to *S. pneumoniae* were examined. Injection-site and systemic adverse experiences (AEs) and daily temperatures were collected. Hepatitis A SPR were 100% for Group 1 and 99.4% for Group 2 after two HAV doses; risk difference=0.7 (95%CI: -1.4,3.8, non-inferior) regardless of initial serostatus. VZV SPR was 93.3% for Group 1 and 98.3% for Group 2; risk difference=-5.1 (95%CI: -9.3, -1.4; non-inferior). *S. pneumoniae* GMT fold-difference (7 serotypes) ranged from 0.9 to 1.1; non-inferior. No statistically significant differences in the incidence of individual AEs were seen when HAV was administered concomitantly vs. non-concomitantly. Three (all Group 2 post-administration of MMRV/PCV-7) of 11 serious AEs were considered possibly vaccine-related: dehydration and gastroenteritis (same subject) on Day 52; febrile seizure on Day 9. No deaths were reported. Antibody responses to each vaccine given concomitantly were non-inferior to HAV given non-concomitantly with MMRV and PCV-7. Administration of HAV with PCV-7 and MMRV had an acceptable safety profile in 12- to 23-mo-old children.

Fangcheng Z et al. Era of vaccination heralds a decline in incidence of hepatitis A in high-risk groups in China. Hepat Mon. 2012;12(2):100–5.

Background: Hepatitis A was ranked first among all of the different types of viral hepatitis in China, which occurred an average of 500,000 cases annually during the 1980's. A live attenuated hepatitis A vaccine was applied in preventing of the disease in 1992, large scale used in vaccination program in 1995, and incorporated in the Expanded Program of Immunization in 2008 in China. **Objective:** The objective of this study was to determine whether, and to what extent, the decline in the incidence of hepatitis A in China was the result of hepatitis A (HA) vaccination. **Materials and methods:** Official documents and longitudinal serological follow-up studies were reviewed to compare the incidence of HA before and after the introduction of the vaccine. **RESULTS:** National trends in the incidence of HA in China saw rates decrease by 92.7% in 2009, compared to the levels seen in 1992. A mass vaccination program was carried out in 3-18 year old children (Wuhan City, China), and its protective efficacy was 85.4%. In a mass vaccination program of an entire population (Shenshi County, China), the annual HA incidence decreased from 359.7/100,000 to 17.7/100,000 (almost 20.3 times). There was a significant relationship found between vaccine coverage and the incidence of HA, the correlation of the negative regression was significant at the 1% (Kendall rank correlation, significant level $P < 0.05$). **Conclusions:** In summary, this study highlights the important role of implementing a vaccination program in decreasing the incidence of HA, and the large protective efficacy of such a strategy, as demonstrated in China.

André FE. Universal mass vaccination against hepatitis A. *Curr Top Microbiol Immunol.* 2006;304:95–114.

When first introduced in 1992 the hepatitis A vaccine was recommended for individuals at high risk of exposure. This policy was not expected to have a significant impact on disease incidence at population level in view of the epidemiology of the hepatitis A virus (HAV). More recently two countries, Israel and Bahrain, and regions or subpopulations in others (Australia, China, Byelorussia, Italy, Spain, US) have embarked upon more ambitious vaccination programmes that aim to immunize whole birth cohorts. After a brief survey of the virology and epidemiology of HAV, the disease burden it inflicts and a short history of the development of HAV vaccines--both live (in China) and killed vaccines are available--the vaccination programmes introduced in the countries mentioned above are described. The results have been spectacular: disease incidence, not only in the vaccinated cohorts but also in the whole population, have plummeted within a few years of the start of mass vaccination. There is now convincing evidence that the vaccine confers herd immunity if the main spreaders of the virus are targeted for immunization. This finding should encourage other countries to start mass vaccination programmes against HAV, particularly as pharmaco-economic studies are beginning to show that such a strategy could be a cost-effective way of controlling the disease. It is now even conceivable to eradicate HAV. In fact, this should be easier to achieve than polio eradication as HAV vaccines confer more durable immunity than polio vaccines. However, the global disease burden of HAV is generally thought not to be high enough to justify such an undertaking in the foreseeable future.

Innis BL et al. Protection against hepatitis A by an inactivated vaccine. *Jama.* 1994;271(17):1328–34.

Objective: To evaluate the safety and efficacy of a new inactivated hepatitis A vaccine. **DESIGN:** Double-blind randomized controlled trial stratified by community. **SETTING:** Community-based in Thailand. **STUDY participants:** A total of 40,119 children, aged 1 to 16 years, attending 148 primary schools: 38,157 (95%) entered surveillance a mean of 138 days after receiving vaccine dose 1; 33,586 (84%) completed the controlled trial of 532 days; and 31,075 (81%) received crossover vaccine and remained under surveillance until day 844. **Intervention:** Participants received hepatitis A vaccine or control hepatitis B vaccine starting January 7, 1991 (doses in months 0, 1, and 12), and crossed over to the alternate vaccine 18 months later. **Main outcome measure:** Cases of hepatitis A (symptoms, alanine aminotransferase levels of 45 U/L or higher, and IgM to hepatitis A virus) were identified by evaluating school absences of 2 or more days. **Results:** There were no serious adverse reactions despite administration of more than 109,000 doses of hepatitis A vaccine. Among initially seronegative recipients of two doses of hepatitis A vaccine, the proportion with 20 mIU/mL or more of antibody to hepatitis A virus before and 5 months after a 1-year booster was 94% and 99%, respectively. Of 6976 episodes of illness during the controlled trial, there were 40 cases of hepatitis A; 38 were in the control group. Of the 40 cases, six, all in controls, occurred after the 1-year booster dose. Following two doses of hepatitis A vaccine (days 138 through 386), protective efficacy was 94% (95% confidence interval, 79% to 99%); cumulative efficacy including the postbooster period (days 138 to 532) was 95% (95% confidence interval, 82% to 99%). The two hepatitis A vaccine recipients who had symptomatic infections (257 and 267 days after dose 1) appeared to have been partially protected since their illnesses were brief and associated with only slight increases in alanine aminotransferase. **Conclusions:** Inactivated hepatitis A vaccine is safe; when administered in two doses, it protects against hepatitis A for at least 1 year.

Background document for the SAGE April 2022 session on hepatitis A vaccines. Geneva: World Health Organization; 2022. (<https://who.int/publications/m/item/sage-april-2022-background-hepatitis-a-vaccines>, accessed 29 August 2022).

[no abstract available]

Shaw FE, Jr. et al. Hepatitis transmission among the Sioux Indians of South Dakota. *Am J Public Health.* 1990;80(9):1091–4.

Hepatitis A continues to occur in cyclical community-wide epidemics on the Indian reservations of South Dakota. In June 1985 a population-based serosurvey for viral hepatitis involving 120 households was conducted at the Pine Ridge and Rosebud Sioux Indian reservations in South Dakota. The serosurvey was performed shortly after a large hepatitis A epidemic on the Pine Ridge reservation in 1983-84, and immediately before a large hepatitis A epidemic on the Rosebud reservation in 1985-86. The overall seroprevalence for antibodies to hepatitis A virus (anti-HAV) was 76.2 percent (Pine Ridge reservation 80.5 percent, Rosebud reservation 72.0 percent, relative risk = 1.12, 95 percent confidence interval = 1.01, 1.24). For age groups 0 to 4 years, 54.2 percent and 36.1 percent of children were seropositive at Pine Ridge and Rosebud, respectively. Seropositivity rose rapidly with age; by age 40, more than 90 percent of persons at both Pine Ridge and Rosebud were anti-HAV positive. Only 1.1 percent of persons tested were positive for hepatitis B markers. Anti-HAV seroprevalence rates in both communities are similar to rates observed in developing countries. The surprisingly high anti-HAV seroprevalence among young children at Rosebud, where clinical hepatitis A had been virtually absent in the previous seven years, indicates that high-grade silent transmission was taking place during the interepidemic period.

Peach D et al. Impact of recurrent epidemics of hepatitis a virus infection on population immunity levels: Bristol Bay, Alaska. *J Infect Dis.* 2002;186(8):1081–5.

The dynamics of population-based immunity were examined by using serologic surveys of 7 villages in rural Alaska between 2 epidemics of hepatitis A virus (HAV) and after the second epidemic (1988-1990). Among persons aged 2-30 years, the overall age-adjusted prevalence of antibody to HAV (anti-HAV) was 51% in 1983 and 49% in 1993 (P=.506). In children aged <5 years, prevalence rates were 0% and 11% in 1983 and 1993, respectively. The prevalence of HAV infection increased with age in both surveys. When examined by 5-year birth cohorts, anti-HAV prevalence increased in children born between 1979 and 1983 (P<.001). Between the 2 survey periods, 43 clinical cases of HAV infection were reported in these villages; all occurred from 1988 to 1990. Despite high overall prevalence of immunity, transmission during epidemics was facilitated by children aged <15 years susceptible to HAV. Little transmission occurred between epidemics. Vaccination of children against HAV should prevent future epidemics.

Mayorga Perez O et al. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. *J Infect Dis.* 2003;188(5):671–7.

Immunization of young children could control hepatitis A virus (HAV) infection, but the efficacy of hepatitis A vaccines in early childhood is unknown. In a randomized, double-blind trial of a single dose of a virosome-formulated, aluminum-free inactivated HAV vaccine in Nicaragua, 274 children (age range, 1.5-6 years) received vaccine or placebo injections; 239 children seronegative for hepatitis A were included in the primary efficacy analysis. HAV infection documented by immunoglobulin M antibodies was the primary end point. Among children seronegative for hepatitis A, infection was diagnosed in 4 children in the vaccine group and 22 children in the placebo group (protective efficacy, 84.6%; 95% confidence interval, 54.7%-96.1%). All infections in children in the vaccine group occurred within 6 weeks. After 6 weeks, protective efficacy was 100% (79.8%-100%). In children in the placebo group, the incidence of HAV infection was 17.6 and that of icteric illness was 1.6 cases/100 person-years. Adverse effects were rare in both children in the vaccine group and children in the placebo group. A single dose of a hepatitis A virosome vaccine is safe and protects young children against HAV infection.

Espul C et al. Persistence of immunity from 1 year of age after one or two doses of hepatitis A vaccine given to children in Argentina. *Hepat Med.* 2012;4:53–60.

Background: This study was done to determine the immunogenicity of a single dose of hepatitis A vaccine in children, providing needed clinical data on the flexibility of booster administration. **Methods:** Participants had received one dose of inactivated hepatitis A vaccine (Avaxim™ 80 U Pediatric) at 12–23 months of age or two doses of the same vaccine at 12 and 18 months of age prior to enrolment. Anti-hepatitis A antibody concentrations were measured at the first, second, and third year after vaccination. Suspected cases of hepatitis A in participant families were assessed and family socioeconomic data were collected. **Results:** A series of 546 participants were enrolled. Of 467 (85.5%) participants completing 3 years of follow-up, 365 had received a single vaccine dose and 94 had received two vaccine doses. Seropositivity (anti-HAV \geq 10 mIU/mL) at 3 years was 99.7% after one dose and 100% after two doses. At one year, geometric mean concentrations were higher after two doses (1433.9 mIU/mL, 95% confidence interval [CI] 1108–1855) than one (209.7 mIU/mL, 95% CI 190.6–230.6). Geometric mean concentrations decreased in both groups during the study, but remained well above 10 mIU/mL through the third year. The geometric mean of 3-year to one-year anti-hepatitis A concentration ratios was 0.74 (95% CI 0.70–0.79) following one dose and 0.57 (95% CI 0.47–0.70) following two doses. The greatest decrease in geometric mean concentrations occurred during the third year, ie, 21.2% in the one-dose group and 40.8% in the two-dose group. Six participants became seronegative during follow-up and responded strongly to a booster dose. Anti-hepatitis A concentrations increased in 135 children (34.9%) in the second year and 50 (13.7%) in the third year; none lived in a family with a case of hepatitis A. Three confirmed cases of hepatitis A occurred in family members. Participants belonged to a middle-income, urban/suburban population with good sanitation facilities and water supplies. **Conclusion:** A single dose of hepatitis A vaccine at 12–23 months of age resulted in hepatitis A seropositivity in all but one vaccinee after 3 years. Increased anti-hepatitis A serum concentrations suggested exposure to wild-type hepatitis A virus in this middle-class socioeconomic environment. Continuing surveillance is required to confirm the effectiveness of a single-dose hepatitis A vaccination; however, the results of the first three years are encouraging.

Ott JJ et al. Long-term protective effects of hepatitis A vaccines. A systematic review. *Vaccine.* 2012;31(1):3–11.

Objective: Data on duration and long-term protective effects of hepatitis A vaccines (HepA) have not been reviewed using a systematic approach. Our objective is to provide a comprehensive review of evidence on the duration of protection achieved by HepA, which is needed for revising existing vaccine policies. Limitations in data availability and implications for future research in this area are discussed. **Methods:** A systematic literature review was conducted including all studies published between 1997 and 2011 reporting on long-term protection of HepA. The outcomes considered were hepatitis A virus (HAV) infection and sero-protection measured by anti-HAV antibodies after follow-up times of over 5 years post-vaccination. **Results:** 299 studies were identified from MEDLINE and 51 studies from EMBASE. 13 manuscripts met our inclusion criteria. The maximum observation times and reported persistence levels of sero-protective anti-HAV antibodies was 15 years for live attenuated HepA and 14 years for inactivated HepA. All data were from observational studies and showed that higher number of doses of live attenuated vaccine led to higher seropositivity and GMT, but dosage and schedule did not significantly impact the long-term protection following inactivated vaccine. Few comparisons were made between the two vaccine types indicating highest levels of antibody titers achieved by multiple doses of live attenuated vaccines 7 years post-vaccination. **Conclusion:** Available data indicate that both inactivated and live attenuated HepA are capable of providing protection up to 15 years as defined by currently accepted, conservative correlates of protection. Further investigations are needed to continue to

monitor the long-term protection afforded by these vaccines. Standardized methods are required for vaccine-follow-up studies including assessment of co-variables potentially affecting long-term protection.

Vizzotti C et al. Impact of the Single-dose Immunization Strategy Against Hepatitis A in Argentina. *Pediatric Infectious Disease Journal*. 2014;33(1):84–8.

Background: After a country wide outbreak occurred during 2003-2004, 1 dose of hepatitis A vaccine was introduced into Argentinian regular immunization schedule for all children aged 12 months in June 2005. The aim of this study was to assess the impact of this novel intervention. **Methods:** A longitudinal analysis was done of hepatitis A virus (HAV) infection rates reported to the National Epidemiological Surveillance System from 2000 to 2011. Occurrence of fulminant hepatic failure (FHF) and liver transplantation cases up to 2011 were also assessed. Incidence rates and clinical impact were compared between pre- and postvaccination periods (2000-2002 vs. 2006-2011). Notification rates were also compared by age groups and geographical regions. **Results:** Since 2006, an abrupt decline was observed in HAV infection rates, as well as in FHF and liver transplantation cases. The mean incidence rate of 7.9/100,000 in the postvaccination period represents a reduction of 88.1% ($P < 0.001$) when compared with the prevaccination period. Neither FHF nor liver transplantation due to HAV infection were observed since March 2007. Decline in incidence rates was evident in all geographical regions and all age groups but was higher in the prevaccination most affected areas and in young children. Although an absolute decrease was observed for cases and rates in all age groups, since 2006, a higher proportion of cases was observed in people >14 years of age. **Conclusions:** The single-dose vaccination strategy has been highly effective for controlling HAV infection in all age groups till now in Argentina. Long-term surveillance will be critical to document the sustained success of this unique intervention.

Urueña A et al. Single-dose universal Hepatitis A immunization in 1-year-old infants in Argentina: high prevalence of protective antibodies up to 11 years following vaccination. *Open Forum Infect Dis*. 2017;4(suppl_1):S320–S.

Single-dose Hepatitis A Virus (HAV) vaccination was implemented for all Argentinean children aged 12 months in 2005, instead of the standard two-dose schedule. Previous studies demonstrated a dramatic decline in HAV infection rates, fulminant hepatitis, and liver transplantation along with low viral circulation and high prevalence of protective antibody response 8 years following the intervention. This study assessed long-term seroprotection against HAV after vaccination with this novel scheme. Children who received one dose of HAV vaccine at 1 year of age, at least nine years before enrollment, were included at three centers in Argentina between May 2015 and April 2016. Demographic and socio-economic characteristics of the child, mother and house were collected through a questionnaire after informed consent signature. Blood samples were tested for anti-HAV antibodies. Antibody titers ≥ 10 mIU/mL were considered seroprotective. Logistic regression analysis was done to evaluate associations between different variables and seroprotection. Of 1119 children included, 97.0% lived in urban areas, 92.7% had safe water access and 57.8% had sewers at home. Mean age was 10.7 years, and the mean post-vaccination interval was 9.7 years (Range: 9.0–11.3 years). Of the total, 87.6% had protective antibodies against HAV. Higher seroprotection rates were observed in Santa Fe compared with the global rate (91.9% vs. 87.6%; OR 1.94 (95% CI: 1.27–2.95); $P = 0.002$). In contrast, lowest rates resulted in San Justo, Buenos Aires (81.4% vs. 87.6% OR 0.45 (95% CI: 0.32–0.65); $P < 0.001$). No association between socio-economic variables and seroprotection was found. Geometric mean concentration (GMC) of HAV Ab titers was 28.0 mIU/mL (95% CI: 26.8–29.3 mIU/mL). Single-dose universal hepatitis A immunization in infants resulted in sustained immunologic protection up to 11 years in Argentina. Lower seroprevalence rates in San Justo have no clear reason and were not associated with an increase in HAV cases in that area. These findings,

along with the low current disease burden confirm the success of the intervention. All authors: No reported disclosures.

Brito WI et al. Universal hepatitis A vaccination in Brazil: analysis of vaccination coverage and incidence five years after program implementation. Rev Bras Epidemiol. 2020;23:e200073.

INTRODUCTION: In 2014, Brazil introduced a universal immunization program against the hepatitis A virus (HAV) for children in the second year of life, using a single dose of inactivated virus vaccine. The objective of this study was to evaluate the vaccination coverage (VC) against HAV in Brazil, against the incidence of cases reported five years after the implementation of the program. **METHODOLOGY:** Secondary data were obtained by searching free access electronic sites of the Ministry of Health, Department of Informatics of the Unified Health System (Departamento de Informática do Sistema Único de Saúde - DATASUS), for incidence analysis and VC from 2014 to 2018. **RESULTS:** VC ranged from 60.13 to 97.07%. The homogeneity of VC against hepatitis A did not reach the established goal throughout all states but for a few exceptions. After 2015, CV decreased in all regions of the country. Despite insufficient coverage, a concomitant reduction in the incidence of Hepatitis A took place throughout the country. The incidence rate fell from 3.29 to 0.80/100,000 between 2014 and 2018. However, there was an interruption in the pace of incidence fall between 2017 and 2018, which may be a consequence of insufficient VC. This phenomenon seems to be part of a widespread downward trend in vaccination effort across the country, also verified for other vaccines, such as poliomyelitis and measles, mumps and rubella vaccine. **CONCLUSION:** These figures suggest the need for implementing efforts to improve hepatitis A VC rates in the country.

Mikhailov MI et al. Universal single-dose vaccination against hepatitis a in children in a region of high endemicity. Vaccines. 2020;8(4):1–11.

Since August 2012, universal single-dose vaccination in children aged at least three years has been implemented in the Republic of Tuva, which was previously the region most affected by hepatitis A in Russia. The objective of this cross-sectional study was the assessment of the immunological and epidemiological effectiveness of vaccination program five years following its implementation. In the pre-vaccination period, anti-HAV antibody detection rates in Tuva was 66.0% [95% CI: 56.3-74.6%] in children aged 10-14 years and reached a plateau (>95%) by age 20-29 years. Annual incidence rates in children under 18 years of age peaked at 450-860 per 100,000 in pre-vaccination years but dropped to 7.5 per 100,000 in this age group and to 3.2 per 100,000 in the total population one year after the start of vaccination. Since 2016, no cases of hepatitis A has been reported in Tuva. Serum anti-HAV antibodies were quantified in samples from healthy children following single-dose vaccination. Protective anti-HAV antibody concentrations (≥ 10 mIU/mL) were detected in 98.0% (95% CI: 96.2-99.0% (442/451)) of children tested one month after single-dose immunization, in 93.5% (95% CI: 91.0-95.4% (477/510)) and in 91.1% (95% CI: 88.2-93.4% (422/463)) of children one year and five years after single-dose immunization, respectively. Anti-HAV antibody geometric mean concentrations were similar in sera collected one month, one year, and five years following single-dose vaccination: 40.24 mIU/mL, 44.96 mIU/mL, and 57.73 mIU/mL, respectively ($p > 0.05$). These data confirm that single-dose vaccination is an effective method of bringing hepatitis A under control in a short period of time in a highly endemic region.

Werzberger A et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med. 1992;327(7):453–7.

BACKGROUND: Although inactivated hepatitis A vaccine is known to be well tolerated and immunogenic in healthy children and adults, its efficacy has yet to be established. **METHODS:** To evaluate the efficacy of the hepatitis A vaccine in protecting against clinically apparent disease, we conducted a double-blind, placebo-

controlled trial in an Hasidic Jewish community in upstate New York that has had recurrent outbreaks of hepatitis A. At the beginning of a summer outbreak, 1037 healthy seronegative children 2 to 16 years of age were randomly assigned to receive one intramuscular injection of a highly purified, formalin-inactivated hepatitis A vaccine or placebo. A case was defined by the presence of typical signs and symptoms, a diagnostic increase in IgM antibody to hepatitis A, and a serum concentration of alanine aminotransferase at least twice the upper limit of normal. Cases occurring greater than or equal to 50 days after the injection were included in the evaluation of efficacy. The children were followed for a mean of 103 days. **RESULTS:** A total of 519 children received vaccine, and 518 received placebo. The vaccine was well tolerated, with no serious adverse reactions. From day 50 after the injection, 25 cases of clinically apparent hepatitis A occurred in the placebo group and none in the vaccine group (P less than 0.001), confirming that the vaccine had 100 percent protective efficacy. Before day 21, seven cases occurred in the vaccine group and three cases in the placebo group. After that time, there were no cases among vaccine recipients and 34 cases among placebo recipients. **CONCLUSIONS:** The inactivated purified hepatitis A vaccine that we tested is well tolerated, and a single dose is highly protective against clinically apparent hepatitis A.

Victor JC et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med. 2007;357(17):1685–94.

Background: Hepatitis A vaccine administered to persons after exposure to the hepatitis A virus has not been compared directly with immune globulin, which is known to be highly effective in preventing hepatitis A when given within 2 weeks after exposure to the virus. **Methods:** We randomly assigned household and day-care contacts, 2 to 40 years of age, in Almaty, Kazakhstan, to receive one standard age-appropriate dose of hepatitis A vaccine or immune globulin within 14 days after exposure to patients with hepatitis A. Instances of laboratory-confirmed, symptomatic hepatitis A infection occurring between 15 and 56 days after exposure were then assessed during active follow-up of all susceptible contacts. **Results:** Of 4524 contacts who underwent randomization, 1414 (31%) were susceptible to hepatitis A virus and 1090 were eligible for the per-protocol analysis. Among these contacts, 568 received hepatitis A vaccine and 522 received immune globulin. Most contacts were children (average age, 12 years), and most received prophylaxis during the second week after exposure (average interval after exposure, 10 days). The baseline characteristics of the contacts were similar in the two groups. Symptomatic infection with hepatitis A virus was confirmed in 25 contacts receiving vaccine (4.4%) and in 17 contacts receiving immune globulin (3.3%) (relative risk, 1.35; 95% confidence interval, 0.70 to 2.67). **Conclusions:** Low rates of hepatitis A in both groups indicate that hepatitis A vaccine and immune globulin provided good protection after exposure. Although the study's prespecified criterion for noninferiority was met, the slightly higher rates of hepatitis A among vaccine recipients may indicate a true modest difference in efficacy and might be clinically meaningful in some settings. Vaccine has other advantages, including long-term protection, and it may be a reasonable alternative to immune globulin for postexposure prophylaxis in many situations. (ClinicalTrials.gov number, NCT00139139 [ClinicalTrials.gov].).

GRADE Hepatitis A vaccine for post-exposure prophylaxis in adults >40 years of age. United States Centers for Disease Control and Prevention. (<https://www.cdc.gov/vaccines/acip/recs/grade/hav-grade-tables.html>, accessed 25 August 2022).

[no abstract available]

Shouval D et al. Safety, tolerability, and immunogenicity of an inactivated hepatitis A vaccine: effects of single and booster injections, and comparison to administration of immune globulin. J Hepatol. 1993;18 Suppl 2:S32–7.

Hepatitis A virus (HAV) infection in adults is often symptomatic and disabling. The present article summarizes our experience with phase 2 studies of an inactivated hepatitis A virus vaccine. Pre- and post-exposure prophylaxis with immune globulin (IG) is only effective for 4-6 months. We compared the safety, tolerability, and immunogenicity of a single i.m. injection of IG with single and booster doses of an inactivated hepatitis A virus vaccine (iHAV) in adults. A total of 75 healthy volunteers (aged 18-50 years) were evaluated in two separate studies. The first included 15 volunteers who received 25 units iHAV i.m. at 0 and 24 weeks. The second, a randomly controlled study, consisted of three groups receiving 25 units iHAV i.m. at 0, 1, and 6 months, or at 0, 2, and 6 months, or 0.06 ml/kg IG i.m. given once. Anti-HAV seroconversion was measured by radioimmunoassay (RIA). After IG injection, anti-HAV seroconversion occurred in 100% of recipients at week 1, declining to 10% at week 12, and 0% by week 20. In contrast, after a single 25-unit dose, RIA seropositivity in iHAV vaccines was 73% by week 2, reaching 100% by week 5, and persisted in all up to week 24, at which time anti-HAV geometric mean titers (GMT) were 2-fold higher than those seen at week 1 after IG. Administration of a booster dose given 1 or 2 months after primary immunization did not significantly improve the quantitative anti-HAV response at 6 months as compared to the effect of the primary dose.(ABSTRACT TRUNCATED AT 250 WORDS)

Ramaswamy M et al. Hepatitis A vaccine immunogenicity 25 years after vaccination in Alaska. J Med Virol. 2021 Jun;93(6):3991-3994. doi: 10.1002/jmv.26327. Epub 2020 Aug 25.

The hepatitis A vaccine is recommended for all children greater than or equal to 1 year of age, however, the duration of vaccine protection is unknown and protection through adulthood is crucial to prevent symptomatic hepatitis later in life. We report on 25 years of follow-up of a cohort of Alaska Native individuals who were vaccinated in early childhood. We assessed the duration of vaccine protection by calculating the geometric mean concentration and proportion of participants with protective levels of IgG antibody to hepatitis A virus (anti-HAV) (≥ 20 mIU/mL) every 2 to 3 years. We estimated the amount of time until the anti-HAV dropped below protective levels using survival analyses. At 25 years, 43 of the original 144 participants were available, mean anti-HAV levels were 91.5 mIU/mL, and 35 (81.4%) had protective levels of anti-HAV. Using data from all persons and all time points, a survival analysis estimated 78.7% of participants had protective levels of anti-HAV at 25 years. The high level of protective antibodies in this cohort indicate that supplemental doses of hepatitis A vaccine are not needed 25 years after completion of the vaccine series.

Racznik GA et al. Duration of protection against hepatitis A for the current two-dose vaccine compared to a three-dose vaccine schedule in children. Vaccine. 2013;31(17):2152-5.

Background: Hepatitis A is mostly a self-limiting disease but causes substantial economic burden. Consequently, United States Advisory Committee for Immunization Practices recommends inactivated hepatitis A vaccination for all children beginning at age 1 year and for high risk adults. The hepatitis A vaccine is highly effective but the duration of protection is unknown. **Methods:** We examined the proportion of children with protective hepatitis A antibody levels (anti-HAV ≥ 20 mIU/mL) as well as the geometric mean concentration (GMC) of anti-HAV in a cross sectional convenience sample of individuals aged 12-24 years, who had been vaccinated with a two-dose schedule in childhood, with the initial dose at least 5 years ago. We compared a subset of data from persons vaccinated with two-doses (720 EL.U.) at age 3-6 years with a demographically similar prospective cohort that received a three-dose (360 EL.U.) schedule and have been followed for 17 years. **Results:** No significant differences were observed when comparing GMC between the two cohorts at 10 ($P=0.467$), 12 ($P=0.496$), and 14 ($P=0.175$) years post-immunization. For the three-dose cohort, protective antibody levels remain for 17 years and have leveled-off over the past 7 years. **Conclusion:** The two- and three-dose schedules provide similar protection >14 years after vaccination, indicating a booster

dose is not needed at this time. Plateauing anti-HAV GMC levels suggest protective antibody levels may persist long-term.

Lopez EL et al. Modeling the long-term persistence of hepatitis A antibody after a two-dose vaccination schedule in Argentinean children. *Pediatr Infect Dis J.* 2015;34(4):417–25.

Background: Long-term seroprotection data are essential for decision-making on the need and timing of vaccine boosters. Based on data from longitudinal serological studies, modeling can provide estimates on long-term antibody persistence and inform such decision-making. **Methods:** We examined long-term anti-hepatitis A virus (anti-HAV) antibody persistence in Argentinean children ≤ 15 years after the initial study where they completed a 2-dose course of inactivated hepatitis A vaccine (Avaxim 80U Pediatric, Sanofi Pasteur, Lyon, France). Blood serum samples were taken at baseline, 2 weeks (post first dose), 6 months (pre-booster), 6.5 months (post-booster), 10 years and 14-15 years after first vaccine dose. We fitted 8 statistical model types, predominantly mixed effects models, to anti-HAV persistence data, to identify the most appropriate and best fitting models for our data set and to predict individuals' anti-HAV levels and seroprotection rates up to 30 years post vaccination. **Results:** Fifty-four children (mean age at enrollment 30.4 months) were enrolled up to 15 years post first vaccine dose. There were 3 distinct periods of antibody concentration: rapid rise up to peak concentration post-booster, rapid decay from post-booster to 10 years, followed by slower decay. A 3-segmented linear mixed effects model was the most appropriate for the data set. Extrapolating based on the available 14-15-year follow-up, the analysis predicted that 88% of individuals anti-HAV seronegative prior to vaccination would remain seroprotected at 30 years post vaccination and lifelong seroprotection for vaccinees seropositive prior to vaccination. **Conclusions:** Currently available data demonstrate that Avaxim 80U Pediatric confers to most vaccinees a high level of seroprotection against hepatitis A infection for at least 20-30 years.

Mosites E et al. Immunogenicity of the hepatitis A vaccine 20 years after infant immunization. *Vaccine.* 2020;38(32):4940–3.

To determine the duration of immunity provided by the Hepatitis A vaccination (HepA), we evaluated a cohort of participants in Alaska 20 years after being immunized as infants. At recruitment, participants received two doses of inactivated HepA vaccine on one of three schedules. We conducted hepatitis A antibody (anti-HAV) testing for participants at the 20-year time-point. Seventy-five of the original 183 participants (41%) were available for follow-up. The overall anti-HAV geometric mean concentration was 29.9 mIU/mL (95% CI 22.4 mIU/mL, 39.7 mIU/mL) and 50 participants (68%) remained seropositive (titer ≥ 20 mIU/mL). Using a fractional polynomial model, the predicted percent seropositive at 25 years was 55.3%, 49.8% at 30 years and 45.7% at 35 years, suggesting that the percent sero-positive could drop below 50% earlier than previously expected. Further research is necessary to understand if protection continues after seropositivity diminishes or if a HepA booster dose may become necessary.

Van Herck K et al. Antibody persistence and immune memory in healthy adults following vaccination with a two-dose inactivated hepatitis A vaccine: long-term follow-up at 15 years. *J Med Virol.* 2011;83(11):1885–91.

Long-term persistence of vaccine-induced immune response in adults was assessed annually for 15 years following primary immunization with a two-dose inactivated hepatitis A vaccine. In 1992, 119 and 194 subjects aged 17-40 years and naïve for hepatitis A virus (HAV) were enrolled in two studies to receive 1,440 ELISA units (El.U) of inactivated hepatitis A vaccine (Havrix™, GlaxoSmithKline Biologicals, Belgium) according to a standard 0, 6 or an extended 0, 12 months schedule, respectively. Serum samples were taken 1 month after the second vaccine dose and every consecutive year up to 15 years after primary vaccination for measurement of anti-

HAV antibody concentrations (NCT00291876 and NCT00289757). At year 15, 100% (48/48) and 97.3% (108/111) of subjects vaccinated at 0, 6 or 0, 12 months remained seropositive for anti-HAV antibodies, with geometric mean concentrations (GMCs) of 289.2 and 367.4 mIU/ml, respectively. An additional dose of HAV vaccine (1,440 EI.U) was administered to the six subjects who had become seronegative for anti-HAV antibodies since year 11. All subjects mounted a humoral immune response to the additional HAV challenge dose, although post-challenge anti-HAV antibody levels remained low in one subject. These studies represent the longest annual follow-up of hepatitis A vaccine in healthy adults. The immune response induced by two doses of this inactivated HAV vaccine was shown to persist for at least 15 years. No difference in long-term antibody persistence was observed between the two primary vaccination schedules, reinforcing the potential for flexibility in the timing of the second primary vaccine dose.

Agrawal A et al. Long-term persistence of antibody response with two doses of inactivated hepatitis A vaccine in children. *Infect Dis Ther.* 2020;9(4):785–96.

Introduction: Hepatitis A virus infection is more severe in adults than children. Although vaccination can protect adults, current childhood programs cover a large population more successfully. Childhood vaccination is, therefore, a solution to protecting adults if it induces lasting immunity. Fifteen-year protection has been demonstrated in children, but longer-term data are only available for adults. We aimed to predict long term persistence of antibody in children beyond 15 years and assess if immunological mechanisms triggered by vaccination support longer-term protection. **Methods:** Long-term clinical studies using hepatitis A (HAV) or A/B vaccines (HAB) containing 720 or 1440 Enzyme-linked immunosorbent assay Units (EU) of hepatitis A virus antigen were identified. Duration of persistence of antibodies and possible protection was determined by descriptively comparing antibody geometric mean concentration (GMC) kinetics, as well as GMC (95% confidence interval) at 15 years post-vaccination across studies. Immunological mechanism studies describing hepatitis A vaccination were identified. **Results:** One study in children 12-15 years (2-dose HAB 720) and four in adults (2-dose HAV 1440 and 3-dose HAB 720) showed comparable GMC kinetics and per year rates of change up to 15 years. At 15 years, the GMC in children [414.7 mEU/ml (336.9; 510.5)] was in the same range as in adults [range 282.6 (217.6; 367.0) to 550.1 (416.0; 727.4)]. Based on these data, mathematical model predictions from adult studies (showing >85% protected at 50 years) were deemed likely to also apply to children. Studies identified, both humoral and cell-mediated responses are induced following vaccination. **Conclusion:** Based on comparable antibody data in adults and children up to 15 years, similar longer-term antibody persistence is expected in children with 2-dose inactivated hepatitis A 720 containing vaccine at least up to 50 years. Accordingly, improving routine childhood hepatitis A vaccination coverage could protect against more severe disease in adulthood. Fig. 1 Plain language summary TRIAL REGISTRATION: ClinicalTrials.gov identifiers, NCT00875485, NCT01000324, NCT01037114, NCT00289757, NCT00291876.

Yu YP et al. Modeling the long-term antibody response and duration of immune protection induced by an inactivated, preservative-free hepatitis A vaccine (Healive) in children. *Biomed Environ Sci.* 2020;33(7):484–92.

Objective: Long-term seroprotection via the hepatitis A vaccine is essential for the prevention of disease from the hepatitis A virus (HAV). Due to documented difficulties during decade-long follow-ups after receiving vaccines, statistical-modeling approaches have been applied to predict the duration of immune protection. **Methods:** Based on five-year follow-up data from a randomized positive-controlled trial among Chinese children (1-8 years old) following a 0, 6 months vaccination schedule, a power-law model accounting for the kinetics of B-cell turnover, as well as a modified power-law model considering a memory-B-cell subpopulation, were fitted to predict the long-term immune responses induced by HAV vaccination (Healive or Havrix). Anti-HAV levels of each individual and seroconversion rates up to 30 years after vaccination were predicted. **Results:**

A total of 375 participants who completed the two-dose vaccination were included in the analysis. Both models predicted that, over a life-long period, participants vaccinated with Healive would have close but slightly higher antibody titers than those of participants vaccinated with Havrix. Additionally, consistent with previous studies, more than 90% of participants were predicted to maintain seroconversion for at least 30 years. Moreover, the modified power-law model predicted that the antibody titers would reach a plateau level after nearly 15 years post-vaccination. **Conclusions:** Based on the results of our modeling, Healive may adequately induce long-term immune responses following a 0, 6 months vaccination schedule in children via induction of memory B cells to provide stable and durable immune protection.

Urueña A et al. Humoral and cellular immune memory response 12 years following single dose vaccination against hepatitis A in Argentinian children. Vaccine. 2022;40(1):114–21.

Infants' universal hepatitis A virus (HAV) single-dose vaccination has been highly effective for controlling HAV infection in Argentina, and in other Latin-American countries that adopted that strategy. Although antibodies wane over time, this has not been associated with HAV outbreaks or breakthrough infections, suggesting a relevant role for memory immunity. This study assessed long term humoral and cellular immune memory response after an average of 12 years follow-up of HAV single-dose vaccination. We selected 81 HAV-single dose vaccinated individuals from a 2015 study, including 54 with unprotective (UAL) and 27 with protective antibody levels (PAL) against HAV. Humoral memory response was assessed by measuring anti-HAV antibody titers at admission in both groups, and 30 days after a booster dose in the UAL group. Flow cytometry analysis of peripheral blood mononuclear cell samples stimulated with HAV antigen was performed in 47/81 individuals (21 with PAL, 26 with UAL) to identify activated CD4 + memory T cells or CD8 + memory T cells. The results showed that 48/52 (92%) individuals from UAL group who completed follow up reached protective levels after booster dose. In the PAL group, anti-HAV Abs waned in 2/27 (7%) individuals lacking seroprotection, while in 25/27 (93%) Abs remained >10 mUI/mL. HAV-specific memory CD4 + T cells were detected in 25/47 (53.2%) subjects while HAV-specific memory CD8 + T cells were observed in 16/47 (34.04%) individuals. HAV-specific memory CD4(+) and CD8(+) T cell responses were detected in 11/21 (52.4%) and in 9/21 (42.9%) subjects with PAL and in 14/26 (53.8%) and in 7/26 (26.9%) individuals with UAL, showing that the presence of memory T-cells was independent of the level or presence of anti-HAV antibodies. Long-term immunity demonstrated in the present work, including or not antibody persistence, suggests that individuals with waned Ab titers may still be protected and supports the single-dose HAV strategy.

Irving GJ et al. Hepatitis A immunisation in persons not previously exposed to hepatitis A. Cochrane Database Syst Rev. 2012;2012(7):Cd009051.

Background: In many parts of the world, hepatitis A infection represents a significant cause of morbidity and socio-economic loss. Whilst hepatitis A vaccines have the potential to prevent disease, the degree of protection afforded against clinical outcomes and within different populations remains uncertain. There are two types of hepatitis A virus (HAV) vaccine, inactivated and live attenuated. It is important to determine the efficacy and safety for both vaccine types. **Objectives:** To determine the clinical protective efficacy, sero-protective efficacy, and safety and harms of hepatitis A vaccination in persons not previously exposed to hepatitis A. **SEARCH methods:** We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and China National Knowledge Infrastructure (CNKI) up to November 2011. **Selection criteria:** Randomised clinical trials comparing HAV vaccine with placebo, no intervention, or appropriate control vaccines in participants of all ages. **Data collection and analysis:** Data extraction and risk of bias assessment were undertaken by two authors and verified by a third author. Where required, authors contacted investigators to obtain missing data. The primary outcome was the occurrence of clinically apparent hepatitis

A (infectious hepatitis). The secondary outcomes were lack of sero-protective anti-HAV immunoglobulin G (IgG), and number and types of adverse events. Results were presented as relative risks (RR) with 95% confidence intervals (CI). Dichotomous outcomes were reported as risk ratio (RR) with 95% confidence interval (CI), using intention-to-treat analysis. We conducted assessment of risk of bias to evaluate the risk of systematic errors (bias) and trial sequential analyses to estimate the risk of random errors (the play of chance). **Main results:** We included a total of 11 clinical studies, of which only three were considered to have low risk of bias; two were quasi-randomised studies in which we only addressed harms. Nine randomised trials with 732,380 participants addressed the primary outcome of clinically confirmed hepatitis A. Of these, four trials assessed the inactivated hepatitis A vaccine (41,690 participants) and five trials assessed the live attenuated hepatitis A vaccine (690,690 participants). In the three randomised trials with low risk of bias (all assessing inactivated vaccine), clinically apparent hepatitis A occurred in 9/20,684 (0.04%) versus 92/20,746 (0.44%) participants in the HAV vaccine and control groups respectively (RR 0.09, 95% CI 0.03 to 0.30). In all nine randomised trials, clinically apparent hepatitis A occurred in 31/375,726 (0.01%) versus 505/356,654 (0.18%) participants in the HAV vaccine and control groups respectively (RR 0.09, 95% CI 0.05 to 0.17). These results were supported by trial sequential analyses. Subgroup analyses confirmed the clinical effectiveness of both inactivated hepatitis A vaccines (RR 0.09, 95% CI 0.03 to 0.30) and live attenuated hepatitis A vaccines (RR 0.07, 95% CI 0.03 to 0.17) on clinically confirmed hepatitis A. Inactivated hepatitis A vaccines had a significant effect on reducing the lack of sero-protection (less than 20 mIU/L) (RR 0.01, 95% CI 0.00 to 0.03). No trial reported on a sero-protective threshold less than 10 mIU/L. The risk of both non-serious local and systemic adverse events was comparable to placebo for the inactivated HAV vaccines. There were insufficient data to draw conclusions on adverse events for the live attenuated HAV vaccine. **Authors' conclusions:** Hepatitis A vaccines are effective for pre-exposure prophylaxis of hepatitis A in susceptible individuals. This review demonstrated significant protection for at least two years with the inactivated HAV vaccine and at least five years with the live attenuated HAV vaccine. There was evidence to support the safety of the inactivated hepatitis A vaccine. More high quality evidence is required to determine the safety of live attenuated vaccines.

Demicheli V et al. The effectiveness and safety of hepatitis A vaccine: a systematic review. *Vaccine*. 2003;21(19-20):2242–5.

We report on the conduct of a systematic review to assess the efficacy and the safety of hepatitis A vaccines in adults and children. We identified, retrieved, and assessed all trials evaluating the effects of hepatitis A vaccines on prevention of cases of hepatitis A, death from hepatitis A, and assessing nature and frequency of adverse events. We included eight randomised trials, four containing efficacy outcomes, three containing only safety outcomes and a single study containing efficacy and adverse events outcomes. Combined inactivated vaccine effectiveness was 86% (95% CI: 63-95%). Combined attenuated vaccine effectiveness was 95% (95% CI: 81-99%). Inactivated vaccine effectiveness in the prevention of HAV secondary cases, compared to non-intervention was 82% (95% CI: 23-96%). Safety profile of vaccines was similar to that of their comparators. Despite poor design and reporting of trials, we found convincing evidence of the effectiveness and safety of inactivated HAV vaccines.

Black S et al. A post-licensure evaluation of the safety of inactivated hepatitis A vaccine (VAQTA, Merck) in children and adults. *Vaccine*. 2004;22(5-6):766–72.

Background: Hepatitis A is a major cause of epidemic hepatitis in the US. In pre-licensure trials, inactivated hepatitis A vaccine (HAV, VAQTA, Merck) was shown to be generally well-tolerated and effective in inducing immunity to hepatitis A infection in adults and children over 2 years of age. Following the licensure of this vaccine, we began a Phase IV safety evaluation in adults and in children over 2 years of age. **Methods:** Safety was assessed by comparing the rates of diagnoses in clinic, emergency and hospital utilization. From April 1997

to December 1998, rates of diagnoses within 30 days for the clinic and emergency setting and 60 days for hospitalization were compared with unexposed follow-up time in the same individuals both before receipt of vaccine and after the 60 days interval post-vaccination. **Results:** There were a total of approximately 2000 comparisons between the risk and "before" or "after" period. Among them, 106 were found to have statistically significant differences in rates (30 elevated, 76 lowered). Among children/adolescents (2-17 year-old), in the hospitalization category, the only statistically significant elevated risk found was "elective procedures", as compared with both "before" and "after" periods. In the outpatient visit category for children and adolescents, elevated risks were found for consultation/general medicine/exam when compared with both "before" and "after" periods, and ganglion and viral warts when compared with either "before" or "after" period. Among adults (> or =18 year-old), in the outpatient visit category, a statistically significant elevated relative risk was seen for diarrhea/gastroenteritis for both "before" and "after" periods. There were additionally 17 diagnostic categories that showed a statistically significantly elevated relative risk compared with either "before" or "after" period. Except for diarrhea/gastroenteritis, the other eight events were elevated only in one comparison (either "before" or "after"). These eight elevated relative risks might be explained by chance resulting from multiple comparison or seasonal variations. There were no serious adverse events judged by the investigator to be associated with HAV. **Conclusion:** In this large Phase IV evaluation of the safety of HAV, the vaccine appeared to be generally well-tolerated. These data support the continued routine use of HAV for vaccination in children and adults.

Nelson NP et al. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep. 2020;69(5):1–38.

Hepatitis a is a vaccine-preventable, communicable disease of the liver caused by the hepatitis a virus (hav). the infection is transmitted via the fecal-oral route, usually from direct person-to-person contact or consumption of contaminated food or water. hepatitis a is an acute, self-limited disease that does not result in chronic infection. hav antibodies (immunoglobulin g [igg] anti-hav) produced in response to hav infection persist for life and protect against reinfection; igg anti-hav produced after vaccination confer long-term immunity. this report supplants and summarizes previously published recommendations from the advisory committee on immunization practices (acip) regarding the prevention of hav infection in the united states. acip recommends routine vaccination of children aged 12-23 months and catch-up vaccination for children and adolescents aged 2-18 years who have not previously received hepatitis a (hepa) vaccine at any age. acip recommends hepa vaccination for adults at risk for hav infection or severe disease from hav infection and for adults requesting protection against hav without acknowledgment of a risk factor. these recommendations also provide guidance for vaccination before travel, for postexposure prophylaxis, in settings providing services to adults, and during outbreaks.

Jiang R et al. Adverse Events Induced by Immunization of Concomitant Inoculation of Freeze-dried Hepatitis A (Live) Vaccine with Vaccines for National Immunization Program from Surveillance Data. Chinese Journal of Pharmacovigilance. 2020;17(10):5.

[no abstract available]

Zhu Q et al. Immunogenicity of hepatitis A attenuated live vaccine, and measles, rubella and mumps combined attenuated live vaccine for standalone and simultaneous vaccination in 18-23-month-old children Chinese Journal of Vaccines and Immunization. 2019;25(6):5.

[no abstract available]

Wang XY et al. Long-term immunogenicity after single and booster dose of a live attenuated hepatitis A vaccine: results from 8-year follow-up. *Vaccine*. 2007;25(3):446–9.

Live, attenuated hepatitis A vaccines are used widely in China but there is uncertainty regarding the persistence of vaccine-induced anti-HAV antibodies after single dose and booster dose administered at month 12. A large scale clinical trial to evaluate the live, attenuated hepatitis A vaccine was conducted in Hebei province between 1996 and 1999. Five years after the trials, children in single dose and booster dose groups were bled and followed. Seventy two percent (61/85) of children who received a single trial dose had detectable anti-HAV antibodies for 96 months (GMC at 96 months: 89.0 mIU/mL). In the booster group 98% (48/49) children remained anti-HAV positive with GMC of 262.8 mIU/mL at month 96. The reinjection with live attenuated HAV vaccine can elicit a booster effect. Results from single dose group seems not to support the need for booster doses of live attenuated hepatitis A vaccine in immunocompetent individuals regarding the persisting anti-HAV and anamnestic response of a single dose vaccine. Continued monitoring of anti-HAV antibodies is needed for a rational hepatitis A immunization strategy in China.

Zhao YL et al. H2 strain attenuated live hepatitis A vaccines: protective efficacy in a hepatitis A outbreak. *World J Gastroenterol*. 2000;6(6):829–32.

Aim: To investigate the protective efficacy of H2 strain attenuated live hepatitis A vaccines (H2-strain vaccines) in hepatitis A (HA) outbreaks. **Methods:** With the permission of their parents, 5551 pre-school and grade 1-3 primary school children were inoculated with 1 dose (10^{6.5} TCID₅₀) of H2 strain vaccines in a nonrandomized, controlled trial conducted in Fucheng County, Hebei Province in May 1997. Another 6485 children in the same grades and compatible in gender and age were enrolled as controls. Epidemiological and serological survey was conducted to evaluate the protective efficacy of the vaccines. ELISA was used to detect serum IgM anti-HAV. **Results:** HA outbreak started in early May 1998, peaked in the middle of the same month, and lasted about 80 days. Overall 302 HA cases were found, 192(63.58%) were 5-9 years old. One vaccinee and 25 control cases were found to have hepatitis A, which account for 0.28% (1/356) and 5.92% (25/422) of all vaccinees and controls in the 14 villages, respectively. The protective efficacy of vaccines was 95.27% (95% CI: 85.83%-104.72%). In subjects tested for anti-HAV IgM from 13 villages, 1(0.40%) overt and 11(4.06%) asymptomatic HAV cases were found in 271 vaccinees but 21(6.69%) of overt and asymptomatic ones were found in 314 controls. **Conclusion:** H2 strain vaccines were excellent in preventing overt hepatitis A, but not so effective in preventing asymptomatic hepatitis A virus infection. A booster dose might be needed to get permanent reliable immunity.

Mao JS et al. Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H2-strain) in humans. *Vaccine*. 1997;15(9):944–7.

A study on the possibility of transmission of live hepatitis A vaccine (H2-strain) from vaccinees to nonvaccinees was conducted. As a result, no seroconversion was found among 87 seronegative nonvaccinees, who had a close contact with their 141 subcutaneously vaccinated classmates nor was it found among 101 seronegative children administered the vaccine orally. The above findings suggest that by losing the ability to be transmitted orally the vaccine virus may result in a decreasing possibility of dissemination among contacts. A 4-year study on the protective efficacy of the H2-strain vaccine was done at 11 primary schools starting at 1991 in Shaoxing County. Since then, there has been no hepatitis A reported among 18102 cumulative person-years in the vaccination group, while 495 cases occurred among 242168 cumulative person-years in the control groups. A large scale vaccination with a cumulative vaccination coverage of 89.45% was carried out in Jiaojiang City among children 1-15 years old. Hepatitis A in this age group in the city, which had 12-87 cases per annum with

an average of 32 for 8 years before vaccination, decreased drastically to 0-1 cases after vaccination. The protective efficacy of H2-strain vaccine proved to be satisfactory.

Wang Z et al. Changing epidemiological characteristics of hepatitis A in Zhejiang Province, China: increased susceptibility in adults. PLoS One. 2016;11(4):e0153804.

Background: Hepatitis A is a common acute hepatitis caused by hepatitis A virus (HAV). Annually, it affects 1.4 million people worldwide. Between 1991 and 1994, HAV infections were highly endemic in Zhejiang Province (China), with 78,720 reported HAV infections per year. Hepatitis A vaccine came on the market in 1995 and was implemented for voluntary immunization. Since 2008, hepatitis A vaccine has been integrated into the national childhood routine immunization program. **Objective:** To understand the current epidemiological profile of hepatitis A in Zhejiang Province since hepatitis A vaccine has been available for nearly two decades. **Methods:** This study used the 2005-2014 National Notifiable Diseases Reporting System data to evaluate the incidence rate of notified hepatitis A cases in Zhejiang Province. **Results:** The overall trend of incidence rate of notified hepatitis A cases significantly decreased from 2005 to 2014 ($P < 0.001$). During the study period, the reported incidence rate in individuals aged ≤ 19 years declined to the historically lowest record in 2014. Compared with individuals aged ≤ 19 years, those aged ≥ 20 years showed the highest incidence rate ($P < 0.001$). Majority of HAV infected cases were Laborers, accounting for approximately 70% of reported cases. **Conclusions:** Childhood immunization strategy with hepatitis A vaccine seemed to be effective in decreasing notified hepatitis A incidence rate in individuals aged ≤ 19 years. Those aged ≥ 20 years were observed to be the most susceptible population. The vast majority of hepatitis A cases were notified among Laborers. Therefore, we strongly suggest that future preventive and control measures should focus more on adults, particularly Laborers, in addition to the current childhood hepatitis A vaccination programme.

Xiaojin S et al. Long-term seropositivity, safety, and impact of inactivated and live, attenuated hepatitis A vaccines in China - A cross-sectional study. Vaccine. 2020;38(52):8302–9.

Background: In 2008, China introduced live, attenuated hepatitis A vaccine (L-HepA, licensed in 1992) and inactivated hepatitis A vaccine (I-HepA, licensed in 2002) nationwide, and is currently the only country using L-HepA in routine immunization. We assessed seropositivity and its duration following vaccination, safety, and association with hepatitis A incidence and population seroprevalence for I-HepA and L-HepA. **Methods:** We obtained seroprevalence data from two nationwide serosurveys (in 1992 and 2014), vaccination status from the 2014 serosurvey, and vaccine safety and disease incidence data from the national surveillance system. We compared long-term HAV seropositivity among vaccine recipients and described safety profiles of both vaccines. We categorized the 31 provinces into those predominately using I-HepA and achieving high coverage ($n = 4$), those predominately using L-HepA achieving high coverage ($n = 4$), and those predominately using L-HepA achieving lower coverage ($n = 23$). We compared population HAV seropositivity, coverage, and disease incidence among the three groups. **Results:** One year after vaccination, seropositivity from I-HepA was significantly higher than from L-HepA (97.8% vs 90.7%), and seropositivity declined to 73.5% for L-HepA and 75.4% for I-HepA after 10 years - not significantly different by vaccine. The annual incidence of serious AEFI was $< 0.5/100\ 000$ for both vaccines. Prior to licensure of either HepA vaccine, provinces that would go on to predominantly use I-HepA had lower incidences of hepatitis A and lower seropositivity levels to HAV than provinces that would go on to use L-HepA. By 2014, these differences were significantly diminished. Regardless of vaccine selection, all three province groups had lower immunity to HAV among individuals born during the 10 years prior to nationwide vaccine introduction - individuals who were 10 to 24 years old in 2014. **Conclusion:** Evidence of good immunogenicity, safety, and impact on incidence supports continued use of both I-HepA and L-HepA in the EPI system. These results may be useful for countries considering integrating HepA vaccines into their routine programs.

Sun X et al. The impact of expanded program on immunization with live attenuated and inactivated Hepatitis A vaccines in China, 2004-2016. *Vaccine*. 2018;36(10):1279–84.

Introduction: Since 2008, two types of hepatitis A (HepA) vaccines were integrated into the expanded program on immunization (EPI) in China. Children were given either one dose of live attenuated HepA (L-HepA) or two doses of inactivated HepA (I-HepA), depending on geographic regions. We sought to evaluate the impact of the EPI on HepA incidence in China. **Methods:** We reviewed the epidemiology of HepA during 2004–2016 from National Notifiable Disease Reporting System (NNDRS). We collected data of L-HepA and I-HepA coverage from Children Immunization Information Management System (CIIMS). Based on the regions where two types of HepA vaccines were used, the coverage and incidence of HepA were compared over time. **Results:** In 2008–2016, the HepA vaccine coverage was 98.8% among target children, with 99.6% in I-HepA region and 98.7% in L-HepA region. HepA incidence declined by 78.0% and 82.3% in L-HepA region and I-HepA region, respectively, without significant difference. Dramatic decline were seen in all age groups of both regions. **Conclusion:** The study suggests that the EPI, with high coverage for both I-HepA and L-HepA, had positive impact on HepA incidence in China.

Bhave S et al. Long term immunogenicity of single dose of live attenuated hepatitis A vaccine in indian children - results of 15-year follow-up. *Indian Pediatr*. 2021;58(8):749–52.

Objectives: To measure anti-HAV antibodies 15 years after a single dose of live attenuated hepatitis A vaccine in Indian children. **Methods:** Of the 143 children vaccinated in 2004, 109 were evaluated in 2019, clinically and for anti-HAV antibodies. These children have been assessed clinically every year, and for anti-HAV antibodies in 2004, 2007, 2010 and 2014. **Results:** Of the 109 children who came for the present assessment, 11 had received additional doses of hepatitis A vaccine in 2004/2007 because of low anti-HAV titre (<20 mIU/mL). In the remaining 98 children, 94 (96%) had seroprotective levels with a geometric mean titre of 79.6 mIU/mL. Seroprotection rate in all 109 children was 86.2%. **Conclusions:** Single dose of live attenuated hepatitis A vaccine in Indian children demonstrated robust immunogenicity at 15 years post vaccination.

Chen Y et al. Immune memory at 17-years of follow-up of a single dose of live attenuated hepatitis A vaccine. *Vaccine*. 2018;36(1):114–21.

Background: In recent years, hepatitis A virus (HAV) infection has declined considerably in China, associated with wide deployment of HAV vaccines and improvement in socio-economic indicators. Towards the elimination of HA in the country, we assessed the duration and characteristics of immunity conferred by the widely used, locally manufactured HAV vaccine. **Methods:** This is a longitudinal cohort study that followed recipients of a live attenuated HAV vaccine 17 years after the initial administration. Blood samples were collected from participants pre- and two-week post-booster HAV vaccine dose. Serum anti-HAV antibody was measured by ELISA method. Memory B and T cells were determined by ELISPOT and Flow Cytometry assays, respectively. **Results:** A robust anamnestic response was observed two-week post-challenge. Both HAV-specific memory B cell and T cells remained, and responded quickly when re-encountering HAV. The magnitude of recall responses was present, regardless of the status of the serum anti-HAV antibody pre-booster. **Conclusions:** We demonstrated long-term immunity from the live attenuated HAV vaccine, including antibody persistence and immunological memory. Considering the conditions that make elimination of infectious diseases feasible, following polio, hepatitis A could be targeted for elimination in China.

Mitra M et al. Long term follow-up study to evaluate immunogenicity and safety of a single dose of live attenuated hepatitis a vaccine in children. *Hum Vaccin Immunother*. 2015;11(5):1147–52.

Worldwide, viral hepatitis continues to be a cause of considerable morbidity and mortality. Mass immunization with a single dose of live attenuated HAV has been shown to significantly reduce disease burden in the community. This was a phase IV, 5-year follow up study carried out at 4 centers (Kolkata, Delhi, Mumbai and Chennai) across India. The subjects with antibody titer <20 mIU/mL at baseline were evaluated for long term immunogenicity. Of the 503 subjects enrolled, 349 subjects were baseline seronegative with an anti-HAV antibody titer <20 mIU/mL. Overall, 343 subjects could be followed up at some point of time during this 5 y post vaccination period. In the last year (60 months) of follow-up, 108 subjects (97.3%) of 111 subjects (who came for follow-up at the end of 5 y) had a protective antibody titer (anti-HAV antibody titer >20 mIU/mL). The seroconversion rates considering seroprotection levels of anti-HAV antibody titer >20 mIU/mL, following vaccination starting from 6 weeks, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months were 95.1%, 97.9%, 98.3%, 96.2%, 97.8%, 92.6% and 97.3%, respectively. The geometric mean concentration (GMC) over the years increased from 64.9 mIU/mL at 6 weeks to 38.1 mIU/mL and 135.2 mIU/mL at 6 months and 12 months, respectively and was maintained at 127.1 mIU/mL at 60 months. In conclusion, the result of this 5-year follow up study showed that the single dose of live attenuated vaccine is well tolerated and provides long-term immunogenicity in healthy Indian children.

Sfetcu O et al. Hepatitis A outbreak predominantly affecting men who have sex with men in Northern Ireland, October 2008 to July 2009. Euro Surveill. 2011;16(9).

We describe an outbreak of hepatitis A which evolved in Northern Ireland between October 2008 and July 2009, against a background of large concurrent hepatitis A outbreaks in various parts of Europe. Thirty-eight cases were defined as outbreak cases using a stratified case definition; 36 were males with a median age of 29 years and of the 28 males whose sexual orientation was known, 26 were men who have sex with men (MSM). Detailed descriptive epidemiology data collected through standardised questionnaires, together with sequencing of a 289 bp fragment of the VP1/2PA region of the virus, significantly aided the understanding of the spread of the outbreak when non-MSM cases occurred. The sequence of the outbreak strain, genotype IA, was indistinguishable from that involved in a large outbreak in the Czech Republic. Although seeded in a generally susceptible Northern Ireland population, the outbreak remained mostly contained in MSM, showing this sub-population to be the most vulnerable despite ongoing hepatitis A vaccination programmes in genito-urinary medicine clinics.

Tortajada C et al. Hepatitis A among men who have sex with men in Barcelona, 1989-2010: insufficient control and need for new approaches. BMC Infect Dis. 2012;12:11.

BACKGROUND: Men who have sex with men (MSM) are a known group at risk for hepatitis A and outbreaks among this group are frequent. In Barcelona, vaccination for MSM has been recommended since 1994. In 1998 a vaccination campaign among preadolescents was implemented and an immunization program in gay bathhouses began in 2004. OBJECTIVE: to assess the incidence of hepatitis A in adults in Barcelona from 1989 to 2010 and to evaluate the outbreaks among MSM including all genotypes involved. METHODS: All cases of acute hepatitis A among young adults notified to the Public Health Agency of Barcelona from 1989 to 2010 were included for analyses. We calculated the annual incidence rate and the incidence ratio male-to-female (M:F) as a marker for MSM. Spearman's coefficient was used to evaluate trends. We also evaluated the outbreaks among MSM and compared their characteristics using Chi-squared and ANOVA test. Fragment amplification of the VP1/P2A region was used for genetic analysis. RESULTS: The median annual incidence for the period of study was 4.7/100000 among females and 11.7/100000 among males. The rate of hepatitis A for adult woman decreased over time (Spearman's coefficient = -0.63, p = 0.002), whereas there was no decrease for adult men (Spearman's coefficient = 0.097, p = 0.67). During the study period the M:F ratio increased (Spearman's coefficient = 0.73, p < 0.001). Three large outbreaks among MSM were detected. When comparing

outbreaks, there was a decrease in the percentage of bathhouse users (from 47% to 19%, $p = 0.0001$) and sex workers (from 6.5% to 0%) while the percentage of HIV infected individuals did not change significantly (range: 21%-28%, $p = 0.36$). The isolated strains were closely related to those circulating in Europe. **CONCLUSIONS:** Annual incidences remain high among MSM without tendency to decrease. More strategies which effectively reach the whole MSM community are needed.

Cotter SM et al. Outbreak of hepatitis A among men who have sex with men: implications for hepatitis A vaccination strategies. J Infect Dis. 2003;187(8):1235–40.

Between November 1998 and May 1999, 136 cases of hepatitis A were reported in Columbus, Ohio. Eighty-nine (65%) case patients were reinterviewed. Of 74 male case patients, 47 (66%) were men who have sex with men (MSM). These 47 MSM were compared with 88 MSM control subjects, to identify risk factors for infection and potential opportunities for vaccination. During the exposure period, 6 (13%) case patients reported contact with a person who had hepatitis A, compared with 2 (2%) control subjects (odds ratio, 6.15; 95% confidence interval, 1.04-48.02); neither number of sex partners nor any sex practice was associated with illness. Most case patients and control subjects (68% and 77%, respectively) saw a health care provider at least annually, and 93% of control subjects reported a willingness to receive hepatitis A vaccine. MSM are accessible and amenable to vaccination; increased efforts are needed to provide vaccination, regardless of reported sex practices.

Ndumbi P et al. Hepatitis A outbreak disproportionately affecting men who have sex with men (MSM) in the European Union and European Economic Area, June 2016 to May 2017. Euro Surveill. 2018;23(33).

Between 1 June 2016 and 31 May 2017, 17 European Union (EU) and European Economic Area countries reported 4,096 cases associated with a multi-country hepatitis A (HA) outbreak. Molecular analysis identified three co-circulating hepatitis A virus (HAV) strains of genotype IA: VRD_521_2016, V16-25801 and RIVM-HAV16-090. We categorised cases as confirmed, probable or possible, according to the EU outbreak case definitions. Confirmed cases were infected with one of the three outbreak strains. We investigated case characteristics and strain-specific risk factors for transmission. A total of 1,400 (34%) cases were confirmed; VRD_521_2016 and RIVM-HAV16-090 accounted for 92% of these. Among confirmed cases with available epidemiological data, 92% (361/393) were unvaccinated, 43% (83/195) travelled to Spain during the incubation period and 84% (565/676) identified as men who have sex with men (MSM). Results depict an HA outbreak of multiple HAV strains, within a cross-European population, that was particularly driven by transmission between non-immune MSM engaging in high-risk sexual behaviour. The most effective preventive measure to curb this outbreak is HAV vaccination of MSM, supplemented by primary prevention campaigns that target the MSM population and promote protective sexual behaviour.

Foster M et al. Hepatitis A virus outbreaks associated with drug use and homelessness - California, Kentucky, Michigan, and Utah, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(43):1208–10.

During 2017, CDC received 1,521 reports of acute hepatitis A virus (HAV) infections from California, Kentucky, Michigan, and Utah; the majority of infections were among persons reporting injection or noninjection drug use or homelessness. Investigations conducted by local and state health departments indicated that direct person-to-person transmission of HAV infections was occurring, differing from other recent, large HAV outbreaks attributed to consumption of contaminated commercial food products. Outbreaks with direct HAV transmission among persons reporting drug use or homelessness signals a shift in HAV infection epidemiology in the United States, and vaccination of these populations at high risk can prevent future outbreaks.

Hernández E et al. Hepatitis A outbreak associated with a food handler in Bizkaia, 2017. *Enfermedades infecciosas y microbiología clínica*. 2019;37(9):569–73.

Introduction: The reporting of one case of hepatitis A in a food handler at a bakery and five cases in employees of a company after consuming products from the same bakery prompted an outbreak investigation. **Methods:** Outbreak cases were defined as individuals with laboratory-confirmed hepatitis A (HAV) infection, with symptoms which started in June and who, during the incubation period, worked with the food handler and/or had close contact with him and/or consumed products from the bakery. Epidemiologic questionnaires were performed and blood samples were obtained to be tested for the presence of anti-hepatitis A antibodies. Molecular characterisation was carried out by PCR, sequencing of the VP1/2A region and phylogenetic analysis with the maximum likelihood estimation method, bootstrap 1000 (MEGA 7.0 software). **Results:** A total of 14 primary hepatitis A cases were identified: eleven cases related to the consumption of products from the bakery, two cases among co-workers of the food handler, and one case was a household contact. All 12 sequenced viruses were genotype IA, matching one of the strains (RIVM-HAV16-090) responsible for the outbreaks occurring at that time in Europe, mostly affecting men who have sex with men. **Conclusions:** HAV vaccination of at-risk groups should be reinforced in order to prevent future outbreaks. Increasing the use of molecular typing in hepatitis A cases could improve the investigation of outbreaks, which can be expected to increase in the future because of decreasing immunity in the population.

Severi E et al. Large and prolonged food-borne multistate hepatitis A outbreak in Europe associated with consumption of frozen berries, 2013 to 2014. *Euro Surveill*. 2015;20(29):21192.

In May 2013, Italy declared a national outbreak of hepatitis A, which also affected several foreign tourists who had recently visited the country. Molecular investigations identified some cases as infected with an identical strain of hepatitis A virus subgenotype IA. After additional European Union/European Economic Area (EU/EEA) countries reported locally acquired and travel-related cases associated with the same outbreak, an international outbreak investigation team was convened, a European outbreak case definition was issued and harmonisation of the national epidemiological and microbiological investigations was encouraged. From January 2013 to August 2014, 1,589 hepatitis A cases were reported associated with the multistate outbreak; 1,102 (70%) of the cases were hospitalised for a median time of six days; two related deaths were reported. Epidemiological and microbiological investigations implicated mixed frozen berries as the vehicle of infection of the outbreak. In order to control the spread of the outbreak, suspected or contaminated food batches were recalled, the public was recommended to heat-treat berries, and post-exposure prophylaxis of contacts was performed. The outbreak highlighted how large food-borne hepatitis A outbreaks may affect the increasingly susceptible EU/EEA general population and how, with the growing international food trade, frozen berries are a potential high-risk food.

Meltzer MI et al. The economics of vaccinating restaurant workers against hepatitis A. *Vaccine*. 2001;19(15-16):2138–45.

The economics of vaccinating restaurant workers against hepatitis A were studied using Monte Carlo simulation models, one with a restaurant-owner perspective, and one with a societal perspective. The restaurant model allowed for a different size, number of employees and employee turnover rate. Benefits were the avoidance of loss of business (including the possibility of bankruptcy) after publicity linking the restaurant to an outbreak associated with a case of hepatitis A in a food handler. Additional benefits in the societal model included reductions in costs of food handler-associated cases of hepatitis A. The outcome used was Net Present Value (NPV), allowing comparison between models. Regardless of the cost of vaccination (\$50-140/employee), for a restaurateur to ensure that all employees were vaccinated at all times substantial costs were involved (i.e. negative NPV). Even a 75% probability of bankruptcy still resulted in negative NPVs at the 95th percentiles. For

society, vaccination was only cost-saving (i.e. positive NPV) if done only during epidemics and if it cost < \$20/employee. Vaccinating restaurant employees is unlikely to be economical from either the restaurant owner or the societal perspective, even during hepatitis A epidemics.

Garcia Garrido HM et al. Response to Hepatitis A Vaccination in Immunocompromised Travelers. J Infect Dis. 2015;212(3):378–85.

Background: Hepatitis A vaccines are highly immunogenic in healthy patients, but there is uncertainty about their immunogenicity in immunocompromised patients. **Methods:** Our study included immunocompromised patients who received 1 or 2 hepatitis A vaccinations between January 2011 and June 2013. We assessed factors that influenced the serologic response to vaccination. We performed a literature review of previous studies on hepatitis A vaccination in immunocompromised patients. **Results:** Of 85 immunocompromised patients, 65 used immunosuppressive drugs, 13 had received stem cell transplants, and 7 were infected with human immunodeficiency virus. After vaccination, 65 of 85 (76.5%) developed antibodies. Tumor necrosis factor α blocker use was associated with better serologic responses than other immunosuppressive drugs. Female patients were more compliant than male patients with postvaccination antibody titer measurements. In 11 relevant studies, antibody responses after the first and second vaccination averaged 37% and 82%, respectively. Factors that negatively influenced serologic response rates were high doses of immunosuppressive drugs, fewer hepatitis A vaccinations, and a short interval between vaccination and antibody measurement. **Conclusions:** Immunocompromised patients showed moderate to good serologic responses to hepatitis A vaccination, but may need more time to develop immunity. Tumor necrosis factor α blocker use was associated with better antibody responses than other drugs. Specifically, male patients should be motivated to return for antibody titer measurements.

Godoi ER et al. Loss of hepatitis A virus antibodies after bone marrow transplantation. Bone Marrow Transplant. 2006;38(1):37–40.

Reimmunization guidelines have recommended the inactivated HAV vaccine for hematopoietic stem cell transplant (HSCT) recipients living in or traveling to areas where hepatitis A is endemic. As a shift from high to medium hepatitis A endemicity has been observed in several countries in Latin America, we conducted a retrospective study to evaluate the prevalence of hepatitis A pre-bone marrow transplant (BMT) and the loss of specific antibodies in consecutive stored serum samples from 77 BMT recipients followed up from 82 to 1530 days. The prevalence of HAV antibodies was 92.2% before BMT. As vaccine was not available in Brazil when the samples were taken, it was assumed that this prevalence reflects natural infection. Survival analysis showed that the probability of becoming seronegative was 4.5% (+/-2.6%), 7.9% (+/-3.4%), 10.1% (+/-4.0%), 23.4% (+/-9.6%) at 1, 2, 3 and 4 years after transplant, respectively. The loss of HAV antibodies was significantly associated with longer follow-up (P=0.0015), younger age (P=0.049) and acute graft-versus-host disease (P=0.035). As most reimmunization protocols start around day +365, in developing countries with similar HAV endemicity, BMT recipients should have serological screening before HAV vaccination and the inactivated vaccine should be advised to those seronegative.

Günther M et al. Rapid decline of antibodies after hepatitis A immunization in liver and renal transplant recipients. Transplantation. 2001;71(3):477–9.

Background: Hepatitis A vaccine is safe and achieves good seroconversion rates in liver (LTX) and renal (RTX) transplant recipients. **Methods:** A study was performed to determine the anti-hepatitis A virus (HAV) antibody decline in LTX and RTX patients, and in healthy controls who have been immunized with two doses of hepatitis A vaccine. **Results:** LTX and RTX patients had a satisfactory seroconversion rate after complete immunisation.

However, 2 years later they had experienced a much more rapid antibody decline than controls, and only 59% of LTX and 26% of RTX seroconverters showed titres above the cut-off level defined as protective. **Conclusions:** Patients on immunosuppressive therapy may not be adequately protected against hepatitis A a few years after vaccination and alternative vaccination schemes may have to be considered.

Smallwood GA et al. Can patients awaiting liver transplantation elicit an immune response to the hepatitis A vaccine? *Transplant Proc.* 2002;34(8):3289–90.

[no abstract available]

Majda-Stanislawski E et al. Immunogenicity of inactivated hepatitis A vaccine in children with chronic liver disease. *Pediatr Infect Dis J.* 2004;23(6):571–4.

One and 6 months after vaccination with hepatitis A virus vaccine (HAVRIX 720 Junior), immunologic responses (anti-hepatitis A virus ≥ 20 mIU/ml) in children with chronic hepatitis C infection seroprotection were 92% (23/25) and 75% (9/12) in children with chronic hepatitis B infection 87% (21/24) and 88% (15/17) and in healthy children 91% (20/22) at both times. A booster dose induced seroprotection in all children.

Wallace MR et al. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis.* 2004;39(8):1207–13.

Background: Hepatitis A is a major health risk for many human immunodeficiency virus (HIV)-infected individuals. Vaccination is a potentially attractive measure to reduce the incidence of hepatitis A among this population, but data on its safety and immunogenicity are incomplete. **Methods:** Ninety HIV-uninfected adults received an inactivated hepatitis A vaccine (VAQTA; Merck), and 90 HIV-infected subjects were randomized, in double-blind fashion, to receive either the vaccine or placebo. The HIV-infected subjects were stratified by CD4 cell count, with 45 subjects having CD4 cell counts of ≥ 300 cells/mm³ and 45 subjects having CD4 cell counts of < 300 cells/mm³. Vaccine was given at weeks 0 and 24 of the study. **Results:** Seroconversion rates at week 28 of the study were 94% among the HIV-infected subjects and 100% among the HIV-uninfected control subjects. HIV-infected subjects with CD4 cell counts of < 300 cells/mm³ had a seroconversion rate of 87%, and HIV-infected subjects with CD4 cell counts of ≥ 300 cells/mm³ had a seroconversion rate of 100%. The vaccine was generally well tolerated, and no adverse effect on either HIV load or CD4 cell count was found. **Conclusion:** Hepatitis A vaccine was both immunogenic and safe among HIV-infected subjects.

Crum-Cianflone NF et al. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. *J Infect Dis.* 2011;203(12):1815–23.

Background: Vaccination provides long-term immunity to hepatitis A virus (HAV) among the general population, but there are no such data regarding vaccine durability among human immunodeficiency virus (HIV)-infected adults. **Methods:** We retrospectively studied HIV-infected adults who had received 2 doses of HAV vaccine. We analyzed blood specimens taken at 1 year, 3 years, and, when available, 6-10 years postvaccination. HAV immunoglobulin G (IgG) values of ≥ 10 mIU/mL were considered seropositive. **Results:** We evaluated specimens from 130 HIV-infected adults with a median age of 35 years and a median CD4 cell count of 461 cells/mm³ at or before time of vaccination. Of these, 49% had an HIV RNA load < 1000 copies/mL. Initial vaccine responses were achieved in 89% of HIV-infected adults (95% confidence interval [CI], 83%-94%), compared with 100% (95% CI, 99%-100%) of historical HIV-uninfected adults. Among initial HIV-infected responders with available specimens, 90% (104 of 116; 95% CI, 83%-95%) remained seropositive at 3 years and

85% (63 of 74; 95% CI, 75%-92%) at 6-10 years. Geometric mean concentrations (GMCs) among HIV-infected adults were 154, 111, and 64 mIU/mL at 1, 3, and 6-10 years, respectively, compared with 1734, 687, and 684 mIU/mL among HIV-uninfected persons. Higher GMCs over time among HIV-infected adults were associated with lower log₁₀ HIV RNA levels ($\beta = -.12$, $P = .04$). **Conclusions:** Most adults with well-controlled HIV infections had durable seropositive responses up to 6-10 years after HAV vaccination. Suppressed HIV RNA levels are associated with durable HAV responses.

D'Acromont V et al. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal) in the elderly. J Travel Med. 2006;13(2):78–83.

Background: Protection against hepatitis A virus (HAV) in the elderly is becoming more important as more senior travelers visit areas of high HAV endemicity, and less have protective antibodies acquired after natural infection during childhood. This study assessed the immunogenicity and safety of hepatitis A vaccine in elderly compared to young adults. **Methods:** In this open, uncontrolled study, subjects of 18 to 45 years or ≤ 50 years of age received two doses of aluminum-free, virosomal HAV vaccine, Epaxal (Berna Biotech Ltd, formerly Swiss Serum and Vaccine Institute, Bern, Switzerland) 12 months apart. **Results:** After both the basic and the booster doses, geometric mean titers (GMT) for anti-HAV antibodies were 1.7-fold higher in subjects younger than 45 years compared with those ≤ 50 years of age. The proportional increase in GMT after the booster dose, however, was similar in younger and older subjects. Seroprotection (≤ 20 mIU/mL) rates in the younger and older subjects were 100 and 65%, respectively, after the first vaccination and 100 and 97%, respectively, after the booster dose. Systemic and local adverse events were mainly mild and short-lived. **Conclusion:** These data show that HAV virosomal vaccine (Epaxal) is well tolerated and immunogenic in elderly subjects. The clinical relevance of lower seroconversion rates after the primary dose is unknown in this population of travelers.

Carlos F et al. Health economic assessment of universal immunization of toddlers against Hepatitis A Virus (HAV) in Mexico. Human vaccines & immunotherapeutics. 2016;12(1):52–63.

Hepatitis A virus (HAV) has shifted from high to intermediate endemicity in Mexico, which may increase the risk of clinically significant HAV infections in older children, adolescents and adults. The objective of this study was to evaluate the cost-utility of single-dose or 2-dose universal infant HAV vaccination strategy in Mexico, compared with no vaccination. A previously published dynamic model estimated the expected number of HAV cases with each strategy, and a decision model was used to estimate the costs and quality-adjusted life-years (QALYs) expected with each strategy. The time horizon was 25 years (2012-2036) and the base case analysis was conducted from the perspective of the Mexican public health system. Costs and QALYs after the first year were discounted at 5% annually. Input data were taken from national databases and published sources where available. The single-dose HAV vaccination strategy had an incremental cost-utility ratio (ICUR) of Mexican peso (MXN) 2,270 per QALY gained, compared with no vaccination. The two-dose strategy had an ICUR of MXN 14,961/QALY compared with no vaccination, and an ICUR of MXN 78,280/QALY compared with the single-dose strategy. The estimated ICURs were below the threshold of 1 x Mexican gross domestic product per capita. When indirect costs were included (societal perspective), the single-dose HAV vaccination strategy would be expected to improve health outcomes and to be cost-saving. This analysis indicates that routine vaccination of toddlers against HAV would be cost-effective in Mexico using either a single-dose or a 2-dose vaccination strategy. GSK study identifier: HO-12-12877.

Hayajneh WA et al. Public health impact and cost effectiveness of routine childhood vaccination for hepatitis a in Jordan: a dynamic model approach. BMC Infect Dis. 2018;18(1):119.

Background: As the socioeconomic conditions in Jordan have improved over recent decades the disease and economic burden of Hepatitis A has increased. The purpose of this study is to assess the potential health and economic impact of a two-dose hepatitis A vaccine program covering one-year old children in Jordan. **Methods:** We adapted an age-structured population model of hepatitis A transmission dynamics to project the epidemiologic and economic impact of vaccinating one-year old children for 50 years in Jordan. The epidemiologic model was calibrated using local data on hepatitis A in Jordan. These data included seroprevalence and incidence data from the Jordan Ministry of Health as well as hospitalization data from King Abdullah University Hospital in Irbid, Jordan. We assumed 90% of all children would be vaccinated with the two-dose regimen by two years of age. The economic evaluation adopted a societal perspective and measured benefits using the quality-adjusted life-year (QALY). **Results:** The modeled vaccination program reduced the incidence of hepatitis A in Jordan by 99%, 50 years after its introduction. The model projected 4.26 million avoided hepatitis A infections, 1.42 million outpatient visits, 22,475 hospitalizations, 508 fulminant cases, 95 liver transplants, and 76 deaths over a 50 year time horizon. In addition, we found, over a 50 year time horizon, the vaccination program would gain 37,502 QALYs and save over \$42.6 million in total costs. The vaccination program became cost-saving within 6 years of its introduction and was highly cost-effective during the first 5 years. **Conclusion:** A vaccination program covering one-year old children is projected to be a cost-saving intervention that will significantly reduce the public health and economic burden of hepatitis A in Jordan.

Suwantika AA et al. Cost-effectiveness of hepatitis A vaccination in Indonesia. Hum Vaccin Immunother. 2014;10(8):2342–9.

Objective: This study aims to assess the cost-effectiveness of hepatitis A immunization in Indonesia, including an explicit comparison between one-dose and two-dose vaccines. **Methods:** An age-structured cohort model based on a decision tree was developed for the 2012 Indonesia birth cohort. Using the model, we made a comparison on the use of two-dose and one-dose vaccines. The model involved a 70-year time horizon with 1-month cycles for children less than 2 years old and annually thereafter. Monte Carlo simulations were used to examine the economic acceptability and affordability of the hepatitis A vaccination. **Results:** Vaccination would save US\$ 3,795,148 and US\$ 2,892,920 from the societal perspective, for the two-dose and one-dose vaccine schedules, respectively, in the context of hepatitis A treatment. It also would save 8917 and 6614 discounted quality-adjusted-life-years (QALYs), respectively. With the vaccine price of US\$ 3.21 per dose, the implementation of single dose vaccine would yield an incremental cost-effectiveness ratio (ICER) of US\$ 4933 per QALY gained versus no vaccination, whereas the two-dose versus one-dose schedule would cost US\$ 14 568 per QALY gained. Considering the 2012 gross-domestic-product (GDP) per capita in Indonesia of US\$ 3557, the results indicate that hepatitis A vaccination would be a cost-effective intervention, both for the two-dose and one-dose vaccine schedules in isolation, but two-dose vaccination would no longer be cost-effective if one-dose vaccination is a feasible option. Vaccination would be 100% affordable at budgets of US\$ 71,408 000 and US\$ 37,690,000 for the implementation of the two-dose and one-dose vaccine schedules, respectively. **Conclusions:** The implementation of hepatitis A vaccination in Indonesia would be a cost-effective health intervention under the market vaccine price. Given the budget limitations, the use of a one-dose-vaccine schedule would be more realistic to be applied than a two-dose schedule. The vaccine price, mortality rate and discount rate were the most influential parameters impacting the ICERs.

Sartori AM et al. Cost-effectiveness analysis of universal childhood hepatitis A vaccination in Brazil: regional analyses according to the endemic context. Vaccine. 2012;30(52):7489–97.

Objective: To conduct a cost-effectiveness analysis of a universal childhood hepatitis A vaccination program in Brazil. **Methods:** An age and time-dependent dynamic model was developed to estimate the incidence of hepatitis A for 24 years. The analysis was run separately according to the pattern of regional endemicity, one

for South+Southeast (low endemicity) and one for the North+Northeast+Midwest (intermediate endemicity). The decision analysis model compared universal childhood vaccination with current program of vaccinating high risk individuals. Epidemiologic and cost estimates were based on data from a nationwide seroprevalence survey of viral hepatitis, primary data collection, National Health Information Systems and literature. The analysis was conducted from both the health system and societal perspectives. Costs are expressed in 2008 Brazilian currency (Real). **Results:** A universal immunization program would have a significant impact on disease epidemiology in all regions, resulting in 64% reduction in the number of cases of icteric hepatitis, 59% reduction in deaths for the disease and a 62% decrease of life years lost, in a national perspective. With a vaccine price of R\$16.89 (US\$7.23) per dose, vaccination against hepatitis A was a cost-saving strategy in the low and intermediate endemicity regions and in Brazil as a whole from both health system and society perspective. Results were most sensitive to the frequency of icteric hepatitis, ambulatory care and vaccine costs. **Conclusions:** Universal childhood vaccination program against hepatitis A could be a cost-saving strategy in all regions of Brazil. These results are useful for the Brazilian government for vaccine related decisions and for monitoring population impact if the vaccine is included in the National Immunization Program.