

# Position Paper on hepatitis A-vaccines

## References with summaries used in the position paper and in the Grading tables

### I References used in the position paper

**André FE. Universal mass vaccination against hepatitis A. *Current Topics in Microbiology and Immunology*, 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.

**Anonychuk, AM, Tricco, AC, Bauch, CT, et al. Cost-Effectiveness Analyses of Hepatitis A Vaccine: A Systematic Review to Explore the Effect of Methodological Quality on the Economic Attractiveness of Vaccination Strategies. *Pharmacoeconomics*, 2008, 26(1):17-32.**

Hepatitis A vaccines have been available for more than a decade. Because the burden of hepatitis A virus has fallen in developed countries, the appropriate role of vaccination programmes, especially universal vaccination strategies, remains unclear. Cost-effectiveness analysis is a useful method of relating the costs of vaccination to its benefits, and may inform policy. This article systematically reviews the evidence on the cost effectiveness of hepatitis A vaccination in varying populations, and explores the effects of methodological quality and key modelling issues on the cost-effectiveness ratios.

Cost-effectiveness/cost-utility studies of hepatitis A vaccine were identified via a series of literature searches (MEDLINE, EMBASE, HSTAR and SSCI). Citations and full-text articles were reviewed independently by two reviewers. Reference searching, author searches and expert consultation ensured literature saturation. Incremental cost-effectiveness ratios (ICERs) were abstracted for base-case analyses, converted to \$US, year 2005 values, and categorised to reflect various levels of cost effectiveness. Quality of reporting, methodological issues and key modelling issues were assessed using frameworks published in the literature.

Thirty-one cost-effectiveness studies (including 12 cost-utility analyses) were included from full-text article review (n = 58) and citation screening (n = 570). These studies evaluated universal mass vaccination (n = 14), targeted vaccination (n = 17) and vaccination of susceptibles (i.e. individuals initially screened for antibody and, if susceptible, vaccinated) [n = 13]. For universal vaccination, 50% of the ICERs were <\$US20 000 per QALY or life-year gained. Analyses evaluating vaccination in children, particularly in high incidence areas, produced the most attractive ICERs. For targeted vaccination, cost effectiveness was highly dependent on the risk of infection.

Incidence, vaccine cost and discount rate were the most influential parameters in sensitivity analyses. Overall, analyses that evaluated the combined hepatitis A/hepatitis B vaccine, adjusted incidence for under-reporting, included societal costs and that came from studies of higher methodological quality tended to have more attractive cost-effectiveness ratios. Methodological quality varied across studies. Major methodological flaws included inappropriate model type, comparator, incidence estimate and inclusion/exclusion of costs.

**Beeching NJ, Clarke PD, Kitchin NR, Pirmohamed J, Veitch K, Weber F. Comparison of two combined vaccines against typhoid fever and hepatitis A in healthy adults. *Vaccine*, 2004, 23:29-35.**

A prospective, randomised, observer-blind, comparative study was performed in healthy adults with a new hepatitis A/typhoid combined vaccine, Viatim, and the marketed Hepatyrix vaccine. Both vaccines induced high levels of protective antibodies, but typhoid responses were higher and hepatitis A responses more rapid with Viatim compared with Hepatyrix. Both vaccines were well tolerated, no serious adverse events (SAEs) occurred, but more Viatim vaccinees had more mild or moderate local reactions (82.7%) than Hepatyrix (53.1%,  $p < 0.001$ ). In this direct comparison Viatim induced more local reactions, but elicited a more rapid and higher immune response to both antigens than Hepatyrix.

**Bendre SV, Bavdekar AR, Bhawe SA, Pandit AN, Chitambar SD, Arankalle VA. Fulminant hepatic failure: etiology, viral markers and outcome. *Indian Pediatr.* 1999 Nov;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 HBe-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.

**Bialek SR, Thoroughman DA, Hu D, Simard EP, Chattin J, Cheek J, Bell BP. Hepatitis A incidence and hepatitis a vaccination among American Indians and Alaska Natives, 1990-2001. *American Journal of Public Health*, 2004, 94:996-1001.**

OBJECTIVES: We assessed the effect on trends in hepatitis A incidence of the 1996 recommendation for routine hepatitis A vaccination of American Indian/Alaska Native (AIAN) children.

METHODS: We examined trends in hepatitis A incidence among AIAN peoples during 1990-2001 and vaccination coverage levels among children on the largest American Indian reservation.

RESULTS: Hepatitis A rates among AIANs declined 20-fold during 1997-2001. Declines in hepatitis A incidence occurred among AIANs in reservation and metropolitan areas. Among 1956 children living on the Navajo Nation whose medical records were reviewed, 1508 (77.1%) had received at least one dose of hepatitis A vaccine, and 1020 (52.1%) had completed the vaccine series.

CONCLUSIONS: Hepatitis A rates among AIAN peoples have declined dramatically coincident with implementation of routine hepatitis A vaccination of AIAN children.

**Bian GL, Ma R, Dong HJ, Ni HX, Hu FJ, Chen YR, Chen JQ, Zhou SY, Lin YX, Xu GZ. Long-term clinical observation of the immunogenicity of inactivated hepatitis A vaccine in children. Vaccine. 2010 Jul 5;28(30):4798-801.**

110 children who were given the complete course of the inactivated hepatitis A vaccine (Havrix) were followed up 10 years later. Age-matched healthy children who were not inoculated served as controls. One month after two primary injections, all children were positive for serum antibody. After 10 years, 99.09% of inoculated children remained positive for serum anti-HAV antibody, with a geometric mean concentration (GMC) of 61.59mIU/mL. GMC values following a secondary immunization in children with antibody levels <20mIU/mL were significantly elevated (567.9mIU/mL), compared with the primary injection alone. Havrix appears to induce persistent immunity and potent immune memory.

**Black S, Shinefield H, Hansen J, Lewis E, Su L, Coplan P. A post-licensure evaluation of the safety of inactivated hepatitis A vaccine (VAQTA, Merck) in children and adults. Vaccine, 2004, 22:766-772.**

**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.

**Bovier PA, Bock J, Ebengo TF, Frösner G, Glaus J, Herzog C, Loutan L. Predicted 30-year protection after vaccination with an aluminum-free virosomal hepatitis A vaccine. Journal of Medical Virology, 2010,82:1629-1634.**

Few studies have examined the duration of protection following vaccination against hepatitis A virus (HAV) with currently licensed HAV vaccines. This study explored the long-term immunogenicity in individuals vaccinated with the virosomal hepatitis A virus, Epaxal. Adult volunteers (N = 130) previously enrolled into four different studies between 1992 and 1994 and who had completed a 0/12-month immunization regimen (primary and booster dose) were asked to participate in this follow-up study. Yearly anti-HAV titers up to 6 years following booster vaccination, and then once 9-11 years after booster were measured using two assays, Enzygnost and AxSYM HAVAB 2.0. Based on the Enzygnost assay, the seroprotection rate 9-11 years after booster was 100%, with a geometric mean concentration (GMC) of anti-HAV antibodies of 526 mIU/ml. Females had markedly higher GMCs than males (741 mIU/ml vs. 332 mIU/ml). Using an anti-HAV cut-off titer of >or=10 mIU/ml, a linear mixed mathematical model predicted a median duration of protection of 52.1 years. A duration of protection >or= 35.7 years was predicted for 95% of subjects. A more stringent cut-off of >or=20 mIU/ml shortened the median predicted duration of protection to 45.0 years. In conclusion, a two-dose Epaxal vaccination regimen confers in healthy adults a real-time protection of at least 9-11 years; this protection

is predicted to last at least 30 years in over 95% of individuals. Further studies are necessary to assess the real duration of seroprotection and whether an additional booster is necessary later.

**Bovier PA, Farinelli T, Loutan L. Interchangeability and tolerability of a virosomal and an aluminum-adsorbed hepatitis A vaccine. Vaccine, 2005, 23:2424-2429.**

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.

**Ciocca M. Clinical course and consequences of hepatitis A infection. Vaccine. 2000 Feb 18;18 Suppl 1:S7 1-4.**

Hepatitis A virus (HAV) is a small, non-enveloped RNA virus belonging to the Picornaviridae, for which only one serotype has been identified. Transmission is usually through the faecal-oral route by person-to-person contact. The most common risk factors are household or sexual contact with a sufferer, attendance or working at a day-care centre, international travel, and association with food or waterborne outbreaks; 55% of cases have no identifiable risk factors. HAV infection may be symptomatic or asymptomatic, and shows three phases. Virus is shed during the incubation phase, anti-HAV IgM appears during the symptomatic phase and can be used for diagnosis, and anti-HAV IgG appears at the same time but persists lifelong. Unusual clinical manifestations of hepatitis A include cholestatic, relapsing and fulminant hepatitis. Hepatitis A accounts for 93% of cases of acute hepatitis in Argentina, including 7% of atypical clinical cases. Hepatitis A is the major cause of fulminant hepatitis, and has been reported to account for 10% of liver transplants in children in France and 20% in Argentina. One-year survival after liver transplantation is 64%. Prevention must be considered as the main means of averting this severe illness.

**Cooksley WG. What did we learn from the Shanghai hepatitis A epidemic? Journal of Viral Hepatology, 2000, Suppl 1:1-3.**

A major outbreak of hepatitis A (HAV), associated with consumption of raw clams, occurred in Shanghai, China in 1988. Over 300 000 cases were reported, of which 47 (0.015%) were fatal. An elevated mortality rate was observed in hepatitis B surface antigen (HBsAg)-positive patients (0.05%). The majority of these patients were also hepatitis B e antigen (HBeAg)-positive, indicating active liver disease and high viral replication rates. The increased mortality in hepatitis B virus (HBV)/HAV coinfecting individuals is hypothesized to be the result of T-cell-mediated destruction of HBV-infected hepatocytes, enhanced by acute HAV infection. Following recovery from HAV there is an increase in HBV expression and activated cytotoxic cells and subsequent cytolysis. Patients with chronic HBV infection are clearly at considerable risk of severe disease and increased mortality in the event of HAV infection. The period of greatest risk is during the immunoejective phase of HBV infection, which generally occurs in early adulthood. With the prevalence of HBV approaching 10% in this group, there is a clear opportunity for benefit from vaccination.

**Dagan R, Amir J, Livni G, Greenberg D, Abu-Abed J, Guy L, Ashkenazi S, Foresner G, Tewald F, Schätzl HM, Hoffmann D, Ibanez R, Herzog C. Concomitant administration of a virosome-adjuncted hepatitis a vaccine with routine childhood vaccines at age twelve to fifteen months: a randomized controlled trial. Pediatric Infectious Disease Journal, 2007, 26:787-793.**

**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-adjuncted 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 ( $\geq$  or  $\approx$  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.

**Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA, 2005, 294:202-210.**

**CONTEXT:** In Israel, the mean annual incidence of hepatitis A disease was 50.4 per 100 000 during 1993-1998. A 2-dose universal hepatitis A immunization program aimed at children aged 18 and 24 months (without a catch-up campaign) was started in 1999.

**OBJECTIVE:** To observe the impact of toddlers-only universal vaccination on hepatitis A virus disease in Israel.

**DESIGN AND SETTING:** Ongoing passive national surveillance of hepatitis A cases in Israel has been conducted since 1993 by the Ministry of Health. An active surveillance program in the Jerusalem district in 1999-2003 provided validation for the passive program.

**MAIN OUTCOME MEASURE:** Incidence of reported hepatitis A disease, 1993-2004.

**RESULTS:** Overall vaccine coverage in Israel in 2001-2002 was 90% for the first dose and 85% for the second dose. A decline in disease rates was observed before 1999 among the Jewish but not the non-Jewish population. After initiation of the program, a sharp decrease in disease rates was observed in both populations. The annual incidence of 2.2 to 2.5 per 100 000 during 2002-2004 represents a 95% or greater reduction for each year with respect to the mean incidence during 1993-1998 ( $P < .001$ ). For children aged 1 through 4 years, a 98.2% reduction in disease was observed in 2002-2004, compared with the prevaccination period ( $P < .001$ ). However, a sharp decline was also observed in all other age groups (84.3% [ $< 1$  year], 96.5% [5-9 years], 95.2% [10-14 years], 91.3% [15-44 years], 90.6% [45-64 years], and 77.3% [ $\geq 65$  years]). Among the Jewish population in the Jerusalem district, in whom the active surveillance program was successfully conducted, a more than 90% reduction of disease was demonstrated. Of the 433 cases reported nationwide in 2002-2004 in whom vaccination status could be ascertained, 424 (97.9%) received no vaccine and none received 2 doses.

**CONCLUSION:** This universal toddlers-only immunization program in Israel demonstrated not only high effectiveness of hepatitis A vaccination but also marked herd protection, challenging the need for catch-up hepatitis A vaccination programs.

**D'Acromont V, Herzog C, Genton B. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal) in the elderly. Journal of Travel Medicine, 2006,13:78-83.**

**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  $\leq 50$  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  $\leq 50$  years of age. The proportional increase in GMT after the booster dose, however, was similar in younger and older subjects. Seroprotection ( $\leq 20$  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.

**Demicheli V, Tiberti D. The effectiveness and safety of hepatitis A vaccine: a systematic review. *Vaccine*, 2003,21:2242-2245.**

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.

**Domínguez A, Salleras L, Carmona G, Batalla J. Effectiveness of a mass hepatitis A vaccination program in preadolescents. *Vaccine*, 2003, 21:698-701.**

A program of mass hepatitis A+B vaccination in preadolescents in schools was begun in the Catalonia in the last quarter of 1998. This study investigated the impact of the program by comparing the incidence of hepatitis A in vaccinated and unvaccinated cohort. The greatest reduction of the incidence rate of hepatitis A was observed in the 10-14 years age group, from 10.3 per 100000 persons-year in the period 1996-1998 to 1.8 per 100000 persons-year in the period 1999-2001. The global incidence decreased from 6.2 to 2.6 per 100000 persons-year. After analysis of cases occurring in the vaccinated and non vaccinated cohort, the effectiveness of the vaccination program was estimated at 97.0% (95% CI: 78.6-99.6).

**Ekwall E, Ulgemo A, Watson M, Boissard F, Thomas S, Goulet F. 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, 24:4450-4457.**

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.

**Fangcheng Z, Xuanyi W, Mingding C, Liming J, Jie W, Qi J, Yuanping G, Wen Q, Yajuan X, Jiangsen M. Era of vaccination heralds a decline in incidence of hepatitis A in high-risk groups in China. *Hepat Mon*. 2012 Feb;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.

**Fiore AE, Wasley A, Bell BP. 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.

**Garner-Spitzer E, Kundi M, Rendi-Wagner P, Winkler B, Wiedermann G, Holzmann H, Herzog C, Kollaritsch H, Wiedermann U. Correlation between humoral and cellular immune responses and the expression of the hepatitis A receptor HAVcr-1 on T cells after hepatitis A re-vaccination in high and low-responder vaccinees. Vaccine, 2009, 27:197-204.**

**INTRODUCTION:** We recently published a study on the persistence of seroprotection 10 years after primary hepatitis A vaccination in an unselected study population of 1014 vaccinees. The majority of these vaccinees still exhibited sufficient protective antibody levels, while 2% displayed antibody concentrations below detection level. In order to investigate whether the low antibody levels were due to decline after primary vaccination or due to an intrinsic inability to sufficiently respond to hepatitis A antigen, we sought to recruit these low/no responder vaccinees to characterize their immune responses in more detail after booster vaccination in comparison to high responder vaccinees.

**MATERIALS AND METHODS:** Prior to and one week after booster vaccination with a hepatitis A vaccine, antibody levels, cytokine levels (IL-2, IFN-gamma and IL-10) and CD surface marker expression on peripheral blood mononuclear cells were determined in a study population comprised of 52 individuals. Additionally, the

hepatitis A HAV cellular receptor 1 (HAVcr-1) TIM-1, being also expressed on CD4+ T cells and associated with immunomodulatory properties, was measured by RT-PCR before and after hepatitis A booster.

**RESULTS:** Our data indicate that there is indeed a small group of hepatitis A vaccinees that can be classified as low/no responders as their antibody levels remain below the seroprotection level of 20mIU/ml after booster vaccination. We further describe a good correlation between antibody concentrations and cellular responses, showing that low antibody production is associated with low antigen specific cytokine levels (IL-2, IFN-gamma, IL-10) and vice versa. While there was no significant difference in the expression of the most common surface markers on T and B cells before and after booster vaccination in low and high responder vaccinees, the expression of HAVcr-1 on CD4 T cells correlated significantly with the antibody responses and cytokine levels, suggesting this receptor as cellular prediction marker of immune responsiveness to hepatitis A.

**CONCLUSION:** Whether hepatitis A low/non-responders deserve particular attention as a risk group or might display certain resistance to hepatitis A infection due to a lack of the hepatitis A receptor needs further investigations. At this stage we suggest that persons at high exposure risk should be carefully observed.

**Glikson M, Galun E, Oren R, Tur-Kaspa R, Shouval D. Relapsing hepatitis A. Review of 14 cases and literature survey. *Medicine (Baltimore)*, 1992,71:14-23.**

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.

**Hanna JN, Hills SL, Humphreys JL. Impact of hepatitis A vaccination of Indigenous children on notifications of hepatitis A in north Queensland. *The Medical Journal of Australia*, 2004,181:482-485.**

**OBJECTIVE:** To describe the impact of a hepatitis A vaccination program for Indigenous children in north Queensland.

**DESIGN:** Enhanced surveillance of all notified cases of hepatitis A in north Queensland from 1996 to 2003.

**SETTING:** North Queensland; population, 596 500 people, including about 6900 Indigenous children aged under five years.

**INTERVENTIONS:** Hepatitis A vaccine was provided to Indigenous children in north Queensland from February 1999; two doses were recommended (at 18 months and 2 years of age), as was catch-up vaccination up to the sixth birthday.

**RESULTS:** In the 4 years 1996-1999, 787 cases of hepatitis A were notified in north Queensland, 237 (30%) of which were in Indigenous people. The average annual notification rates in Indigenous and non-Indigenous people during this period were 110 and 25 cases per 100 000 persons, respectively. In the first 4 years after introduction of the vaccination program (2000-2003), 66 cases of hepatitis A were notified. Only nine of the 66 (14%) were in Indigenous people. The average annual notification rates in Indigenous and non-Indigenous people in 2000-2003 were 4 and 2.5 cases per 100 000 persons, respectively.

**CONCLUSION:** Hepatitis A seems to have been eradicated from Indigenous communities in north Queensland very soon after the vaccination program began. The rapid decline in notifications in non-Indigenous as well as Indigenous people suggests the program quickly interrupted chains of transmission from Indigenous children to the broader community. To our knowledge this is the first evidence that a hepatitis A vaccination program targeting a high-risk population within a community can reduce disease in the broader community. Hepatitis A vaccine should be provided to other high-risk Indigenous children elsewhere in Australia.

**Hatz C, van der Ploeg R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis A vaccine delayed up to 11 years. Clin Vaccine Immunol. 2011 May;18(5):885-7.**

Boosting adult travelers with the virosome-formulated, aluminum-free hepatitis A vaccine Epaxal up to 128 months after a single primary dose confers full protection against hepatitis A, even in travelers aged 50 years and above. Delaying the booster dose did not influence the immune memory response to Epaxal.

**Hollinger FB, Ticehurst JR. Hepatitis A virus. In: Fields Virology, 3rd ed. Philadelphia: Lippincott-Raven; 1996. P. 735-782. (No abstract)**

**Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, Suntayakorn S, Suknuntapong T, Safary A, Tang DB, et al. Protection against hepatitis A by an inactivated vaccine. JAMA, 1994, 271:1328-1334.**

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.

**Iwarson S, Lindh M, Widerström L. Excellent booster response 4-6 y after a single primary dose of an inactivated hepatitis A vaccine. Scandinavian Journal of Infectious Diseases, 2002, 34:110-111.**

We studied the immune response of an inactivated hepatitis A vaccine (Havrix 1440) given to middle-aged travellers 4-6 y after a single, primary dose. Anti-HAV antibodies in serum were checked before and 28-35 d after the booster. All 25 vaccinees showed an impressive anamnestic booster response (geometric mean titres 32 and 2993 mIU/ml before and after the booster, respectively). The study confirms experimental data indicating that 1 dose of inactivated hepatitis A vaccine induces a long-term proliferative T-cell response in addition to producing anti-HAV antibody. As recall memory for this vaccine is elicited several years after a single dose there is probably no need for a second vaccine dose.

**Jacobs RJ, Meyerhoff AS. Comparative cost effectiveness of varicella, hepatitis A, and pneumococcal conjugate vaccines. Prev Med. 2001 Dec;33(6):639-45.**

BACKGROUND: Several state and local U.S. governments are considering making varicella, hepatitis A, and/or pneumococcal conjugate vaccination conditions of day care or school entry. These requirements will likely be

issued sequentially, because simultaneous mandates exacerbate budget constraints and complicate communication with parents and providers. Cost-effectiveness assessments should aid the establishment of vaccination priorities, but comparing results of published studies is confounded by their dissimilar methods.

**METHODS:** We reviewed U.S. cost-effectiveness studies of childhood varicella, hepatitis A, and pneumococcal conjugate vaccines and identified four providing data required to standardize methods. Vaccination, disease treatment, and work-loss costs were estimated from original study results and current prices. Estimated life-years saved were derived from original study results, epidemiological evidence, and alternative procedures for discounting to present values.

**RESULTS:** Hepatitis A vaccine would have the lowest health system costs per life-year saved. Varicella vaccine would provide the greatest reduction in societal costs, mainly through reduced parent work loss. Pneumococcal conjugate vaccine would cost twice the amount of varicella and hepatitis A vaccines combined and be less cost effective than the other vaccines.

**CONCLUSIONS:** Hepatitis A and varicella vaccines, but not pneumococcal conjugate vaccine, meet or exceed conventional standards of cost effectiveness.

**Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine, 2010;28:6653-6657.**

**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.

**Jiang WP, Chen JT, Wang X, et al. Immunogenicity and safety of three consecutive lots of a new preservative-free inactivated hepatitis A vaccine (Healive): a double-blind, randomized and controlled trial. Vaccine 2008;26(18):2297-301.**

Immunization is considered as the most effective way for the prophylaxis of hepatitis A virus (HAV) infection. This study aimed to evaluate the immunogenicity and safety of three consecutive lots of a new preservative-free inactivated hepatitis A vaccine (Healive) in healthy children. A double-blind, randomized and controlled clinical trial was conducted in healthy volunteers aged from 1 to 8 years. Total 400 subjects were enrolled and assigned into four groups, receiving one of the three lots of Healive or an established control vaccine. The vaccination was two-dose regimen with 6 months apart. Anti-HAV titers were determined at the 1st, 6th and 7th month. The results showed that Healive was highly immunogenic in children with 100% seroconversion rate (SR) and 3237-3814 mIU/ml geometry mean titer (GMT) 1 month after the second dose. The immunogenicity of Healive was statistically higher than that of the control vaccine with respect to GMT and SR ( $P=0.037$  to  $P<0.001$ ). Both Healive and control vaccine were well tolerated with 1-5% incidence of overall adverse reactions ( $P>0.298$ ). Severe adverse reaction was not reported. Both SRs (1, 6 and 7 months) and GMTs (1 and 7 months) in subjects receiving one of the three consecutive lots of Healive had not statistical difference ( $P=0.114-0.710$ ), suggesting that Healive was well consistent. The immune responses in younger children (1-3 years) and older children (4-8 years) were similar to each other ( $P=0.187-0.963$ ). The present study indicated that Healive was greatly

consistent between production lots, well tolerated and highly immunogenic in children, which made the preservative-free inactivated hepatitis A vaccine well suitable for inclusion in the routine programme of children vaccination.

**Kim YJ, Lee HS. Increasing incidence of hepatitis A in Korean adults. *Intervirology*, 2010,53:10-14.**

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.

**Lemon SM. Immunologic approaches to assessing the response to inactivated hepatitis A vaccine. *Journal of Hepatology*, 1993, Suppl 2:S15-19.**

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.

**Lopalco PL, Salleras L, Barbuti S, Germinario C, Bruguera M, Buti M, Domínguez A. Hepatitis A and B in children and adolescents--what can we learn from Puglia (Italy) and Catalonia (Spain)? *Vaccine*, 2000,19:470-474.**

Viral hepatitis remains a major contributor to the global disease burden. Mass immunisation strategies against hepatitis B have been adopted by more than 90 developing and industrialised countries. Countries with low hepatitis A endemicity are experiencing cyclical outbreaks and an epidemiological shift, with larger numbers of individuals at risk of infection at an older age, resulting in increased morbidity. The high cost of outbreaks in these countries has made immunisation strategies cost-effective. The development of a vaccine against hepatitis A and a combined vaccine against hepatitis A and hepatitis B offers potentially exciting opportunities for a preventative approach in areas of both low and high endemicity. Existing mass immunisation programmes against hepatitis B will facilitate the adoption of joint strategies illustrated by the examples of Puglia (Italy) and Catalonia (Spain).

**Martin A, Lemon SM. Hepatitis A virus: from discovery to vaccines. *Hepatology*, 2006, 43:S164-172.**

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.

**Mao JS, Chai SA, Xie RY, Chen NL, Jiang Q, Zhu XZ, Zhang SY, Huang HY, Mao HW, Bao XN, Liu CJ. Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H2-strain) in humans. *Vaccine*, 1997,15:944-947.**

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.

**Mayorga Pérez O, Herzog C, Zellmeyer M, Loáisiga A, Frösner G, Egger M. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. *Journal of Infectious Diseases*, 2003,188:671-677.**

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.

**Meltzer MI, Shapiro CN, Mast EE, Arcari C. The economics of vaccinating restaurant workers against hepatitis A. *Vaccine*, 2001, 19:2138-2145.**

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.

**Mohd Hanafiah K, Jacobsen KH, Wiersma ST. Challenges to mapping the health risk of hepatitis A virus infection. *Int J Health Geogr*. 2011 Oct 18;10:57.**

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.

**Munné MS, Vladimirov S, Moreira R, Ciocca M, Cuarterolo M, Otegui L, Soto S, Brajterman L, Castro R, Sasbón J, Gianivelli S, Buamscha D, Quarleri J, González JE. Molecular characterization of hepatitis A virus in children with fulminant hepatic failure in Argentina. *Liver International*, 2008, 28:47-53.**

**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.

**Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of hepatitis a virus infection: a molecular approach. *Clinical Microbiology Reviews*, 2006, 19:63-79.**

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.

**Overton ET, Nurutdinova D, Sungkanuparph S, Seyfried W, Groger RK, Powderly WG. Predictors of immunity after hepatitis A vaccination in HIV-infected persons. *Journal of Viral Hepatitis*, 2007, 14:189-193.**

Hepatitis A virus (HAV) infection remains a health risk for human immunodeficiency virus (HIV)-infected persons. While the inactivated HAV vaccine affords protection to immunocompetent persons >95% of the time, rates of developing protective antibody (anti-HAV) in HIV+ persons are considerably lower. Although low

CD4+ T-cell counts have previously been reported to be correlated with this poor response, the effect of HIV viraemia on HAV vaccine response has not previously been reported. The medical records of HIV-infected patients who had received at least one dose of HAV vaccine (Havrix, 1440 EIU) were reviewed for factors associated with the development of a protective anti-HAV response. Serological data with regard to anti-HAV status after vaccination were available in 238 patients with 133 individuals (49.6%) developing immunity after vaccination. In a logistic regression model, the only factors associated with a protective antibody response were an HIV plasma RNA I SAGE Hepatitis A Working Group. Evidence based recommendations for use of hepatitis A vaccines in immunization services: Background paper for SAGE discussions. 17 October 2011. <http://www.who.int/immunization/sage/previous/en/index.html>. (No abstract) level <1000 copies/mL at the time of vaccination (P = 0.011) and male gender (P = 0.016). Neither nadir CD4+ T cell count nor CD4+ T-cell count at time of vaccination were predictive of the development of anti-HAV. Suppression of HIV replication at time of vaccination is associated with a protective antibody response to HAV vaccination in HIV-infected adults. The low rate of response warrants further research in alternative strategies for HAV vaccination among HIV-infected persons.

**SAGE Hepatitis A Working Group. Evidence based recommendations for use of hepatitis A vaccines in immunization services: Background paper for SAGE discussions. 17 October 2011.**  
<http://www.who.int/immunization/sage/previous/en/index.html>. (No abstract)

**Santos DC, Martinho JM, Pacheco-Moreira LF, Araújo CC, Oliveira BC, Lago BV, Pinto MA, Paula VS. Fulminant hepatitis failure in adults and children from a Public Hospital in Rio de Janeiro, Brazil. The Brazilian journal of infectious diseases, 2009,13:323-329.**

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.

**Schmidtke P, Habermehl P, Knuf M, Meyer CU, Sanger R, Zepp F. Cell mediated and antibody immune response to inactivated hepatitis A vaccine. Vaccine, 2005, 23:5127-5132.**

The humoral and cellular immune response to inactivated hepatitis A vaccine was investigated dynamically in a time elapse study over 1 year. Fourty-five healthy volunteers, seronegative for anti-HAV, were vaccinated with 1440 enzyme-linked immunosorbent assay units (EU) of formalin-inactivated hepatitis A virus following a 0--6-month schedule. Serum anti-HAV levels and HAV-specific proliferation of peripheral blood mononuclear cells were measured at several time points over a 26- and 28-week period after the first and second injection, respectively. Distinct B and T cell responses were determined within 14 days after primary vaccination. The booster vaccination-induced immediate peak levels for the humoral (anti-HAV GMC=5376mIU/ml) as well as the cellular (median Deltacpm=14173cpm) response.

**Shouval D, Ashur Y, Adler R, Lewis JA, Miller W, Kuter B, Brown L, Nalin DR. Safety, tolerability, and immunogenicity of an inactivated hepatitis A vaccine: effects of single and booster injections, and comparison to administration of immune globulin. Journal of Hepatology,1993, Suppl 2:S32-37.**

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)

**Usonis V, Meriste S, Bakasenas V, Lutsar I, Collard F, Stoffel M, Tornieporth N. 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, 2005,23:2602-2606.**

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.

**Vacchino MN. Incidence of Hepatitis A in Argentina after vaccination. J Viral Hepat. 2008 Oct;15 Suppl 2:47-50.**

In Argentina, the annual incidence rate of reported hepatitis A disease ranged from 70.5 to 173.8 per 100,000 during 1995-2004. A single dose universal hepatitis A immunization program aimed at children aged 12 months was started in June 2005. The aim was to observe the impact of universal vaccination against hepatitis A in Argentina. A longitudinal analysis of hepatitis A rates reported in Argentina since 1995 to the National Notifiable Diseases Surveillance System (SINAVE). Incidence rates in 2007 were compared with those for the prevaccination baseline period (1998-2002), overall and by age group and geographical regions. Overall vaccine coverage in Argentina was 95% in 2006 for the single dose. After initiating the program, a sharp decrease in disease rates was observed. The annual incidence of 10.2 per 100,000 during 2007 represents 88.0% reduction with respect to the average incidence rate for the period 1998-2002 ( $P < 0.001$ ). For children aged 1 year, an 83.1% reduction in disease was observed in 2007, compared with the baseline period ( $P < 0.001$ ). Furthermore, a sharp decline was also observed in all other age groups 87.1% [2-4 years], 88.7% [5-9 years], 83.6% [10-14 years], 78.8% [15-49 years], 20.7% [ $>50$  years]. Also important reductions were observed in all Argentinian regions. Following the implementation of universal hepatitis vaccination with a single dose to children at 12 months of age, hepatitis A rates have declined substantially in Argentina. Monitoring is needed to verify that vaccination continues to proceed and that low rates are sustained.

**Van Damme P, Van Herck K. A review of the long-term protection after hepatitis A and B vaccination. Travel Medicine and Infectious Disease, 2007, 5:79-84.**

Vaccine-preventable viral hepatitis continues to be a cause of considerable morbidity and mortality: on worldwide basis, approximately 1.4 million cases of hepatitis A are reported every year. The true incidence, however, has been estimated to be 3-10 times higher. Regarding hepatitis B, more than a third of the world's population has been infected. The World Health Organization has estimated (2000) that there are 367 million chronic carriers of hepatitis B worldwide, and approximately 1 million deaths per year as a consequence of chronic complications and acute fulminant disease. Hepatitis B vaccines have been licensed since 1982, and hepatitis A vaccines since 1992. In 1996, a combined hepatitis A and B vaccine became available. An update on the long-term protection conferred by hepatitis A and hepatitis B vaccines as well as the combined hepatitis A and B vaccine is offered in this paper. Long-term efficacy and booster policy for hepatitis B vaccines have often been a topic of discussion. Based on current data and field experience there is, in general, no necessity for booster doses for fully vaccinated immunocompetent individuals. Long-term protection has been demonstrated

by the rapid (5-7 days) development of anamnestic antibody responses among vaccinees who no longer have detectable anti-HBs. Anamnestic responses correlate with lymphoproliferative T-cell responses following challenge with hepatitis B vaccine. Furthermore, employing Spot-ELISA techniques, circulating B-cells were shown to be able to produce anti-HBs in vaccinees who lost their detectable antibodies. The accumulated data from a large number of studies indicate that despite antibody decline or loss, immune memory exhibits long-term persistence. There is somewhat less information available for hepatitis A vaccines, yet an increasing number of studies indicate that the findings for hepatitis B vaccines are also applicable to hepatitis A vaccines. The necessity to provide a booster dose was based on early projections of observed antibody levels. However, recent follow-up studies with up to 12 year observation, as well as studies employing mathematical models predict that following primary vaccination, antibodies will persist for at least 25 years. In addition, experimental studies confirm that vaccination against hepatitis A induces immunological memory. Therefore hepatitis A booster vaccination is presently considered as unnecessary in fully vaccinated individuals. The above findings are of importance in the context of administering combined hepatitis A and B vaccine for which similar long-term data have been observed. All available data on monovalent and combined hepatitis A and hepatitis B vaccines indicates that there is no support for a hepatitis A or hepatitis B booster when a complete primary vaccination course is offered to immunocompetent individuals.

**Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. Expert Review of Vaccines, 2004, 3:249-267.**

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.

**Van Herck K, Jacquet JM, Van Damme P. 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 Nov;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 El.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.

**Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, Margolis HS, Bell BP. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. New England Journal of Medicine, 2007, 357:1685-1694.**

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]).

**Wang XY, Xu ZY, Ma JC, von Seidlein L, Zhang Y, Hao ZY, Han OP, Zhang YL, Tian MY, Ouyang PY, Zhang ZY, Han CQ, Xing ZC, Chen JC. Long-term immunogenicity after single and booster dose of a live attenuated hepatitis A vaccine: results from 8-year follow-up. Vaccine, 2007, 25:446-449.**

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.

**Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA, 2005,294:194-201.**

**CONTEXT:** In the United States, hepatitis A is a frequently reported vaccine-preventable disease. Vaccination has been recommended for persons at increased risk since 1996. In 1999, it was recommended that children living in 11 states with the highest incidence of hepatitis A be routinely vaccinated, and that children living in 6 additional states, with incidence above the national average, be considered for routine vaccination.

**OBJECTIVE:** To assess impact of the current vaccination strategy by evaluating trends in reported cases of hepatitis A since implementation. **DESIGN, SETTING, AND CASES:** A longitudinal analysis of characteristics of cases of hepatitis A reported in the United States since 1990 to the National Notifiable Diseases Surveillance System.

**MAIN OUTCOME MEASURE:** Incidence rates of reported cases of hepatitis A. Incidence rates in 2003 were compared with those for the prevaccination baseline period (1990-1997) overall and in the 17 states in which children should be routinely vaccinated or considered for routine vaccination (vaccinating states). Incidence rates in vaccinating states were also compared with those in the remaining states where there is no recommendation for statewide vaccination of children (nonvaccinating states).

**RESULTS:** Between the baseline period (1990-1997) and 2003, overall hepatitis A rates declined 76% to 2.6 per 100,000, significantly lower than previous nadirs in 1983 (9.2/100,000) and 1992 (9.1/100,000). The rate in

vaccinating states declined 88% to 2.5 per 100,000 compared with 53% elsewhere (to 2.7/100 000). In 2003, cases from vaccinating states accounted for 33% of the national total vs 65% during the baseline period. Declines were greater among children aged 2 to 18 years (87%) than among persons older than age 18 years (69%); the proportion of cases in children dropped from 35% to 19%. Since 2001, rates in adults have been higher than among children, with the highest rates now among men aged 25 through 39 years.

**CONCLUSIONS:** Following implementation of routine hepatitis A vaccination of children, hepatitis A rates have declined to historic lows, accompanied by substantial changes in the epidemiologic profile. Greater decreases in the age groups and regions where routine vaccination of children is recommended likely reflect the results of implementation of this novel vaccination strategy. Continued monitoring is needed to verify that implementation continues to proceed and that low rates are sustained.

**Werzberger A, Mensch B, Nalin DR, Kuter BJ. Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after the Monroe field trial of VAQTA. Vaccine 2002;20(13-14):1699-701.**

The Kiryas Joel community in Monroe, N.Y. was the site of the first clinical trial which proved the protective efficacy of hepatitis A vaccine. The vaccine used was VAQTA J. Med. Virol (hepatitis A vaccine, inactivated). In the 9 years since the trial ended vaccination of infants reaching 2 years of age has continued along with monitoring for hepatitis A cases. The prevaccine pattern of frequent outbreaks has converted to a sustained pattern of no outbreaks, despite sporadic introduction of hepatitis A into the community in nonvaccinees. Community use of VAQTA in children 2 years of age and older has proven capable of providing long-term prevention of hepatitis A outbreaks in a formerly frequently affected community despite prolonged sporadic introduction of the virus.

**Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, Miller W, Shouval D, Wiens B, Calandra G, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. New England Journal of Medicine, 1992, 327:453-457.**

**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.

**WHA Resolution 63.18 available at [http://apps.who.int/gb/ebwha/pdf\\_files/WHA63-REC1/WHA63\\_REC1-P2-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-P2-en.pdf) (see pp. 34-37).**

**WHO: The immunological basis for immunization series: module 18- hepatitis A. Geneva, World Health Organization, 2010. (Available from [http://whqlibdoc.who.int/publications/2011/9789241501422\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501422_eng.pdf)**

**WHO, TRS 858, Annex 2, Requirements for hepatitis A vaccine (inactivated) 1995. [www.who.int/entity/biologicals/publications/trs/areas/biological\\_products/en/](http://www.who.int/entity/biologicals/publications/trs/areas/biological_products/en/)**

**Zamir C, Rishpon S, Zamir D, Leventhal A, Rimon N, Ben-Porath E. Control of a community-wide outbreak of hepatitis A by mass vaccination with inactivated hepatitis A vaccine. *European Journal of Clinical Microbiology and Infectious Disease*, 2001, 20:185-187.**

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.

**Zhao YL, Meng ZD, Xu ZY, Guo JJ, Chai SA, Duo CG, Wang XY, Yao JF, Liu HB, Qi SX, Zhu HB. H2 strain attenuated live hepatitis A vaccines: protective efficacy in a hepatitis A outbreak. *World Journal of Gastroenterology*, 2000, 6:829-832.**

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<sup>6.5</sup> TCID<sub>50</sub>) 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.

## II References used in the Grading Tables

### Table Ia

**Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, Suntayakorn S, Suknuntapong T, Safary A, Tang DB, et al. Protection against hepatitis A by an inactivated vaccine. *JAMA*, 1994, 271:1328-1334.**

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.

**Mayorga Pérez O, Herzog C, Zellmeyer M, Loáisiga A, Frösner G, Egger M. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. *Journal of Infectious Diseases*, 2003,188:671-677.**

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.

**Riedemann S, Reinhardt G. Placebo-controlled efficacy study of hepatitis A vaccine in Valdivia, Chile. *Vaccine* 1992;10:S152-155.**

A placebo-controlled, double-blind study on the efficacy of a hepatitis A vaccine (SmithKline Beecham Biologicals) was started in a region of Chile in September 1990, using hepatitis B vaccine as control. A total of 260 healthy children, 6-15 years of age, negative for antibody to hepatitis A virus (anti-HAV), antibody to HAV immunoglobulin M (IgM), hepatitis B surface antigen, and antibody to hepatitis B surface and core antigens by ELISA tests within 7 days before vaccination, were randomly assigned to two study groups: 128 children received the vaccine with a yellow label (group 1), and 132 children the vaccine with an orange label (group 2) at months 0, 1 and 6. Blood for serology and transaminase determination was drawn at months 1, 2, 6, 7 and 12. Both vaccines were tolerated equally well and no serious side effects were seen. In group 1 (presumed hepatitis A vaccine group), anti-HAV was detected (20% inhibition was used as the cut-off level) in 122 of 128 children (95.5%) tested at month 1, in 126 of 127 (99.2%) at month 2, in 126 of 127 (99.2%) at month 6 and in 126 of 126 (100%) at month 7. One anti-HAV seroconversion seen at month 1 was associated with presence of anti-HAV IgM and therefore probably represents HAV infection. Geometric mean anti-HAV concentration of the other children was 128, 342, 214 and 2301 mIU/ml at months 1, 2, 6 and 7, respectively. (ABSTRACT TRUNCATED AT 250 WORDS)

**Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, Miller W, Shouval D, Wiens B, Calandra G, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *New England Journal of Medicine*, 1992,327:453-457.**

**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.

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**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.

## Table Ib

**Gong J, Li R, Yang J. Protective efficacy of large scale immunization with a live attenuated hepatitis A vaccine (LA-1 strain. Guangxi Journal of Preventative Medicine 2000;6(5):257-259. (No abstract available)**

**Jiang S, Huang J, Chen J. The epidemiological Efficacy Assessment of Attenuated Live Hepatitis A Vaccine in Masses in Liuzhou. Chinese Journal of Epidemiology 1995;16(3):140-142.**

An 24-month prospective epidemiological investigation on the results of China-mode Hepatitis A attenuated live vaccine against hepatitis A by random group sampling was carried out. The incidence of case group was 15.91/10(5) (5/31421), the incidence of control group was 95.92/10(5) (30/ 31277) which showed a significant difference. In case group 2081 persons who missed vaccination, there was one person developed hepatitis A, making the incidence 48.05/10(5). In control group 760 persons were vaccinated by mistake and there was no case developed in this sub-population. There were 644 cases of hepatitis A in the external control group, the incidence was 90.14/10(5). Data showed that there was no significant difference among external control group, control group and persons from case group who missed vaccination. Comparing the data from case group and from the above 3 groups, the protective rates were 82.35%, 83.41% and 66.89%. respectively. When comparing the data from persons who had been mistakenly vaccinated in control group, there was no significant difference being noticed.

**Jiang W, Niu X. Observation on the efficacy of attenuated live Hepatitis A Vaccine's Vaccination Contingency. Modern Preventative Medicine 2001;28(1):59-61. (No abstract available)**

**Li Y, Wu H, Xu T. Observation of Immunogenicity and Epidemiological Efficacy Assessment of Attenuated Live Hepatitis A Vaccine. Chinese Journal of Public Health 2000;16(8):737-738. (No abstract available)**

**Lin F, Gu X, Wang F. Assessment on the spot of Attenuated Live Hepatitis A Vaccine's Efficacy. Acta Academiae Medicinae Suzhou 1997;17(5):868-869. (No abstract available)**

**Luo D, Li R, Gong J. Epidemiological efficacy of Standardized Live Attenuated Hepatitis A Vaccine(LA-1 strain). Chinese Journal of Vaccination and Immunization 2004;10(2):210-212. (No abstract available)**

**Meng Z, Yao J, Zhao Y. Observation on the Immunization effects of Attenuated Live Hepatitis A Vaccine. National Medical Journal of China 2000;80(1):9-11.**

**OBJECTIVE:** To further survey the protective efficacy of the standard attenuated live hepatitis A vaccines (H(2) strain).

**METHODS:** Randomized and controlled trials were performed in Fucheng county, Hebei province. A total of 12 036 children were assigned into vaccine group (5 551) and control group (6 485) by cluster sampling. The morbidity of hepatitis A was observed and the blood was collected once hepatitis A showed epidemic to detect anti-HAV IgG and IgM.

**RESULTS:** During the period of the first 7 months after vaccination, hepatitis A was sporadic, the morbidity of hepatitis A was 0.55/100 000, and only 1 case occurred in the control group and no case in the vaccine group. From January to August 1998, hepatitis A showed epidemic in a township of this county. The morbidities were 0.37% and 6.69% for vaccine group and control group, respectively. The protective efficacy of the vaccine was 94.47%. The ratios of clinical cases to subclinical infections were 1 to 11 and 1 to 1 for vaccine and control groups, respectively ( $P < 0.05$ ).

**CONCLUSION:** The H(2) strain vaccine has a very good protective efficacy, and obviously decreases the attack rate, new infection rate and clinical cases by HAV infection.

**Wu W, Xu Zhiyi, Xia J. Assessment of Attenuated Live Hepatitis A Vaccines protective efficacy on spot. Chinese journal of public health 1996;12(12):535-536. (No abstract available)**

**Xu Z, Li R, Meng Z. Immunogenicity and efficacy trials of live attenuated hepatitis A vaccines. National Medical Journal of China 1998;78(4):254-256.**

**OBJECTIVE:** To study two live vaccines, H2 and LA-1 strains, both attenuated in growth on human diploid cell culture at lower temperature (32 degrees C).

**METHODS:** Randomized, controlled trials were performed among half million children. 135,340 children were divided into vaccine or control groups by individual and 360,012 by cluster. Those susceptibles with negative anti-HAV were bled at 2-6 months after the vaccination and blood test for anti-HAV.

**RESULTS:** 37 hepatitis A cases were found in the control group. The protective efficacy of the two vaccines was 100%, and the 95% lower confidence limit (one sided) of combined efficacy of the two vaccines was 92.1%, that was comparable with the two inactivated vaccines produced by SmithKline beecham or Merck Sharp Dhome.

**CONCLUSION:** The vaccines are safe, and the seroconversion to H2 strain (10(7.0) TCID<sub>50</sub>) and LA-1 strain (10(6.75) TCID<sub>50</sub>) is 94.87% and 83.16% respectively.

**Xu Z, Wang X, Li R, Meng Z, Zhang Y, Gong J, Ma J, Li Y, Zhao S, Li Y, Zhao Y, Huang Q, Luo D, Xia J, Liu H, Liu X, Ouyang P. [Immunogenicity and efficacy of two live attenuated hepatitis A vaccines (H(2) strains and LA-1 strains)]. Zhonghua Yi Xue Za Zhi. 2002 May 25;82(10):678-81. [Article in Chinese]**

**OBJECTIVE:** To assess the efficacy and immunogenicity of two live attenuated hepatitis A vaccines.

**METHODS:** Randomized and controlled clinical trials were conducted in Guanxi, Hebei and Shanghai, 457 251 children were enrolled. The efficacy for preventing clinical hepatitis A was calculated by the comparison of incidence rate of disease between vaccine group and control group. Susceptible subjects tested anti-HAV negative before the study were followed up after vaccination for determination of the immunogenicity and vaccine efficacy to prevent subclinical infection.

**RESULTS:** The protective efficacy to prevent clinical infection by both H(2) and LA-1 vaccines were 95%. The peak of seroconversion was observed in 94.9% and 86.0% respectively for the two vaccines. The seroconversion rate decreased to 75% approximately 80% in the third year, but the vaccine protection against clinical hepatitis A has remained unchanged throughout the 3 years.

**CONCLUSION:** Both strains of the live attenuated hepatitis A vaccines have good immunogenicity and high protection against clinical disease, the efficacy to prevent subclinical infection is not significant. The subclinical HAV infection serves as a natural booster for the vaccinees.

## Table Ic

**Mayorga Pérez O, Herzog C, Zellmeyer M, Loáisiga A, Frösner G, Egger M. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. *Journal of Infectious Diseases*, 2003;188:671-677.**

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.

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**Meng Z, Yao J, Zhao Y. Observation on the Immunization effects of Attenuated Live Hepatitis A Vaccine. National Medical Journal of China 2000;80(1):9-11.**

**OBJECTIVE:** To further survey the protective efficacy of the standard attenuated live hepatitis A vaccines (H(2) strain).

**METHODS:** Randomized and controlled trials were performed in Fucheng county, Hebei province. A total of 12 036 children were assigned into vaccine group (5 551) and control group (6 485) by cluster sampling. The morbidity of hepatitis A was observed and the blood was collected once hepatitis A showed epidemic to detect anti-HAV IgG and IgM.

**RESULTS:** During the period of the first 7 months after vaccination, hepatitis A was sporadic, the morbidity of hepatitis A was 0.55/100 000, and only 1 case occurred in the control group and no case in the vaccine group. From January to August 1998, hepatitis A showed epidemic in a township of this county. The morbidities were 0.37% and 6.69% for vaccine group and control group, respectively. The protective efficacy of the vaccine was 94.47%. The ratios of clinical cases to subclinical infections were 1 to 11 and 1 to 1 for vaccine and control groups, respectively ( $P < 0.05$ ).

**CONCLUSION:** The H(2) strain vaccine has a very good protective efficacy, and obviously decreases the attack rate, new infection rate and clinical cases by HAV infection.

**Wu W, Xu Zhiyi, Xia J. Assessment of Attenuated Live Hepatitis A Vaccines protective efficacy on spot. Chinese journal of public health 1996;12(12):535-536. (No abstract available)**

**Xu Z, Li R, Meng Z. Immunogenicity and efficacy trials of live attenuated hepatitis A vaccines. National Medical Journal of China 1998;78(4):254-256.**

**OBJECTIVE:** To study two live vaccines, H2 and LA-1 strains, both attenuated in growth on human diploid cell culture at lower temperature (32 degrees C).

**METHODS:** Randomized, controlled trials were performed among half million children. 135,340 children were divided into vaccine or control groups by individual and 360,012 by cluster. Those susceptibles with negative anti-HAV were bled at 2-6 months after the vaccination and blood test for anti-HAV.

**RESULTS:** 37 hepatitis A cases were found in the control group. The protective efficacy of the two vaccines was 100%, and the 95% lower confidence limit (one sided) of combined efficacy of the two vaccines was 92.1%, that was comparable with the two inactivated vaccines produced by SmithKline beecham or Merck Sharp Dhome.

**CONCLUSION:** The vaccines are safe, and the seroconversion to H2 strain (10(7.0) TCID<sub>50</sub>) and LA-1 strain (10(6.75) TCID<sub>50</sub>) is 94.87% and 83.16% respectively.

**Xu Z, Wang X, Li R, Meng Z, Zhang Y, Gong J, Ma J, Li Y, Zhao S, Li Y, Zhao Y, Huang Q, Luo D, Xia J, Liu H, Liu X, Ouyang P. [Immunogenicity and efficacy of two live attenuated hepatitis A vaccines (H(2) strains and LA-1 strains)]. Zhonghua Yi Xue Za Zhi. 2002 May 25;82(10):678-81. [Article in Chinese] **OBJECTIVE:** To assess the efficacy and immunogenicity of two live attenuated hepatitis A vaccines.**

**METHODS:** Randomized and controlled clinical trials were conducted in Guanxi, Hebei and Shanghai, 457 251 children were enrolled. The efficacy for preventing clinical hepatitis A was calculated by the comparison of incidence rate of disease between vaccine group and control group. Susceptible subjects tested anti-HAV negative before the study were followed up after vaccination for determination of the immunogenicity and vaccine efficacy to prevent subclinical infection.

**RESULTS:** The protective efficacy to prevent clinical infection by both H(2) and LA-1 vaccines were 95%. The peak of seroconversion was observed in 94.9% and 86.0% respectively for the two vaccines. The seroconversion rate decreased to 75% approximately 80% in the third year, but the vaccine protection against clinical hepatitis A has remained unchanged throughout the 3 years.

**CONCLUSION:** Both strains of the live attenuated hepatitis A vaccines have good immunogenicity and high protection against clinical disease, the efficacy to prevent subclinical infection is not significant. The subclinical HAV infection serves as a natural booster for the vaccinees.

**Yuan Q, Luo S, Wu X. Observations on the Immunization effects of Attenuated Live Hepatitis A Vaccine. National Medical Journal of China 1995;80(1):9-11. (No abstract available)**

**Zhang S, Ma J, Han C. Primary research on Efficacy of Attenuated Live Hepatitis A Vaccine. Chinese Journal of Epidemiology 1994;13(6):341-343. (No abstract available)**

**Zhang Y, Liu X, Ma J. A field evaluation of the epidemiological efficacy of an attenuated live hepatitis A vaccine (H2 strain). Chinese Journal of Preventative Medicine 2001;35(6):363-365.**

**OBJECTIVE:** To evaluate the epidemiological efficacy of an attenuated live hepatitis A vaccine (H2 strain).

**METHODS:** A randomized and controlled field trial was carried out in part of Zhengding County and the Jiaoqu District of Shijiazhuang city. There were about 37,000 children in these areas involved in the study and they were randomly divided into a vaccine group and a control group according to the months they were born. Children in the vaccine group were given a dose of 10(6.5) TCID<sub>50</sub>/ml attenuated live hepatitis A vaccine while those in the control group were given nothing. As soon as the children in the vaccine group had been vaccinated, all the subjects were carefully followed up for hepatitis A cases.

**RESULTS:** In the 3.5 years of follow-up, there were 20 hepatitis A cases in the control group and the incidence rate was 136.4 per 100,000 population. There was only one hepatitis A case in the vaccine group and the incidence rate was 8.1 per 100,000 population. The difference of the incidence rates between the two groups was highly significant ( $P < 0.001$ ) and the protective efficacy of the vaccine was 94.4% (95% CI: 67.1%-100%).

**CONCLUSION:** The protective efficacy of the vaccine was excellent and the vaccine is suitable to be widely used.

## Table IIa

**Sagliocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G, Esposito C, Buonocore S, Pierri P, Mele A. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. Lancet 1999; 353:1136-9.**

**BACKGROUND:** Hepatitis A vaccination stops outbreaks of hepatitis A infection, but its efficacy against infection after exposure has not been proven. We investigated the use of hepatitis A vaccine to prevent secondary infections with hepatitis A virus (HAV).

**METHODS:** We did a randomised controlled trial of hepatitis A vaccine in household contacts of people with sporadic HAV infection (index cases). Households (index cases and contacts) were randomly assigned to the vaccine group or unvaccinated group, according to the study week in which they were enrolled. All household contacts in the vaccine group received vaccination at the time of entry to the study.

**FINDINGS:** During 45 days of follow-up, secondary infection had occurred in ten (13.3%) of 75 households (two families had two cases each) in the untreated group and in two (2.8%) of 71 households in the vaccine group. The protective efficacy of the vaccine was 79% (95% CI 7-95). The number of secondary infections among household contacts was 12 (5.8%) of 207 in the unvaccinated group and two (1.0%) of 197 in the vaccinated group. Therefore, 18 individuals needed to be vaccinated to prevent one secondary infection.

**INTERPRETATION:** Hepatitis A vaccine is effective in the prevention of secondary infection of HAV and should be recommended for household contacts of primary cases of HAV infection.

## Table IIb

**Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, Margolis HS, Bell BP. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *New England Journal of Medicine*, 2007, 357:1685-1694.**

**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]).

## Table III

**Barkai G, Belmaker I, Givon-Lavi N, Dagan R. The effect of universal toddlers-only hepatitis A virus vaccination program on seropositivity rate in unvaccinated toddlers: evidence for reduced virus circulation in the community. *Pediatr Infect Dis J* 2009; 28: 391-3.**

**BACKGROUND:** In July 1999, a national toddler-only hepatitis A virus (HAV) vaccination program was introduced in Israel. Passive and active surveillance showed a large reduction in disease rate, but an objective measurement was needed. We hypothesized that toddler's vaccination in a population living in an endemic area would reduce virus circulation, resulting in reduced HAV seropositivity rates in unvaccinated toddlers.

**METHODS:** The study was conducted among Bedouin children in southern Israel, for whom HAV vaccine coverage reached 85.5% and 74.9% for first and second HAV vaccine doses, respectively, in 2000. Toddlers received 2 doses of HAV vaccine at 18 and 24 months. Data on vaccine coverage was received from well-baby clinics. Sera were obtained from healthy unvaccinated 16- to 20-month-old toddlers. Anti-HAV immunoglobulin (Ig)G concentrations were tested by enzyme-linked immunosorbent assay.

**RESULTS:** A total of 629 sera were tested (209 obtained in 1991-2000 and 420 obtained in 2001-2002). Seropositivity rates of  $\geq 100$  mIU/mL ranged from 16.2% to 19.6% in 1991 through 2000 (children born before immunization program). These rates dropped to 2% in 2001-2002 and to 0% in 2003 through 2007. Furthermore, IgG concentrations were significantly lower ( $P < 0.001$ ) in samples taken in 2000, only a few months after beginning of vaccination, than in those taken before initiation of the HAV immunization program (1991-1998), suggesting a marked reduction in circulating HAV resulting in natural boosting.

**CONCLUSIONS:** Because HAV vaccines are licensed in children  $\geq 12$  months old, rates of anti-HAV seropositivity in unvaccinated toddlers can be an objective and sensitive tool to evaluate the effect of immunization program on virus circulation. This method is of special value in communities where no appropriate surveillance is in place.

**Belmaker I, Dukhan L, Yosef Y, Leventhal A, Dagan R. Elimination of hepatitis A infection outbreaks in day care and school settings in southern Israel after introduction of the national universal toddler hepatitis A immunization program. *Pediatr Infect Dis J* 2007; 26:36-40.**

**BACKGROUND:** In 1999, Israel became the first country to begin universal toddler immunization against hepatitis A infection with a 2-dose schedule at 18 and 24 months. The effect of the Israeli program on outbreaks of Hepatitis A in day care and school settings was studied.

**METHODS:** The records of all hepatitis A illness outbreaks in day care and school settings reported to the Ministry of Health in Southern Israel during 1993 through 2005 were reviewed. The number of exposed contacts for whom postexposure prophylaxis was administered was retrieved from records of epidemiologic investigations. Rates of immunization coverage were extracted from records of Maternal and Child Health Clinics.

**RESULTS:** Three hundred nineteen cases of hepatitis A illness during the years 1993 through 2005 were associated with 113 outbreaks in day care and school settings of which 92% occurred before the institution of universal toddler immunization. Since 2000, no hepatitis A infection outbreaks have been reported in any day care and school settings in the region. An average of 732 children received immunoglobulin prophylaxis yearly because of exposure to an outbreak in an educational setting during the preimmunization period, 106 in 2000 and zero in the 5 years since 2001. The data showed marked herd immunity since school-aged children born before 1999 were not immunized, but elimination of outbreaks occurred equally in that age group. Immunization coverage was 86.4% for one dose of hepatitis A vaccine by age 3 years and 77.3% for 2 doses among the birth cohort of 2000.

**CONCLUSIONS:** Universal hepatitis A immunization of toddlers was associated with disappearance of outbreaks in educational settings. This included cohorts of nonimmunized children representing marked herd immunity.

**Chen YZ, Jiang RJ, Yu WX, Li CH. Study on the effects of controlling hepatitis A epidemics by building the colony immune defence. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2003 24; 366-9.**

**OBJECTIVE:** To build the colony immune defence and to control the periodic epidemics of hepatitis A after a mass vaccination of live attenuated hepatitis A vaccine.

**METHODS:** Through yearly observing the correlation of the accumulative inoculation rates of live attenuated hepatitis A vaccine, the crowd immune standard and the morbidity of hepatitis A after administered live attenuated hepatitis A vaccine among susceptible population and surveilling anti-HAV IgG in the different epidemic areas.

**RESULTS:** (1) The accumulative inoculation rates of live attenuated hepatitis A vaccine was 34.15% in 8 years from 1993 to 2000, among which they were 84.46%, 82.23% and 15.14% in the preschool children, primary and middle school student and 15 - 45 age groups respectively. The morbidity of hepatitis A decreased to 8.26/100,000 in 2000. (2) The crowd positive rates of anti-HAV IgG were 74.24% in 1998 and 83.68% by 2000. Among which they were 74.02%, 68.49%, 79.41%, 85.71% and 90.80% in 2 - 4, 6 - 8, 13 - 15, 20- and 30 - 39 age groups respectively. (3) The accumulative inoculation rates were 37.36%, 51.08% and 28.68% in the inspection areas of Tongtai, Binhai and Yandu respectively. The crowd positive rates of anti-HAV IgG in three inspect area were 85.71%, 85.94% and 78.63% respectively. It was noticed the correlation between the accumulative inoculation rates and the crowd positive rates of anti-HAV IgG was ( $r(\text{city}) = 0.91$ ,  $F = 15.10$ ,  $P < 0.03$ ).

**CONCLUSION:** The results showed that the crowd positive rates of anti-HAV IgG had increased to 85% while, the colony immune defence of hepatitis A was effectively built to break the periodic epidemics of hepatitis A. The morbidity of hepatitis A decreased to the lowest level in the history.

**Cui F, Hadler SC, Zheng H, Wang F, Zhenhua W, Yuansheng H, Gong X, Chen Y, Liang X. Hepatitis A surveillance and vaccine use in China from 1990 through 2007. J Epidemiol. 2009;19(4):189-95. Epub 2009 Jun 27. BACKGROUND:**

Hepatitis A vaccines have been highly effective in preventing hepatitis A. To investigate the epidemiology of hepatitis A in China after hepatitis A vaccine became available, we reviewed reported cases of hepatitis A and the use of hepatitis A vaccine in China during the period from 1990 through 2007.

**METHODS:** Data from the National Notifiable Disease Reporting System from 1990 to 2007 and the Emergency Events Reporting System from 2004 to 2007 were reviewed and epidemiologic characteristics analyzed. Hepatitis A vaccine distribution between 1992 and 2007 was also reviewed.

**RESULTS:** The incidence of hepatitis A has declined by 90% since 1990, from 56 to 5.9 per 10(5)/year. Declines in age-specific incidence were seen in all age groups, most dramatically among children younger than 10 years. Disease incidence still varies substantially: poorer western provinces have had the highest incidences since 2000. In high-incidence provinces, children younger than 10 years continue to have a high disease incidence. Only 50% of cases were laboratory-confirmed, and only 3% occurred in reported local outbreaks. Over 156 million doses of hepatitis A vaccine have been distributed since 1992, and use has continued to increase since 2003.

**CONCLUSIONS:** Incidence of hepatitis A has decreased in all age groups, likely due to changing socioeconomic conditions and increasing hepatitis A vaccine use. Nevertheless, western populations remain at high risk, with transmission predominantly occurring among children. The epidemiology of hepatitis A transmission is not well understood. Improved surveillance with better laboratory confirmation is needed to monitor the impact of universal hepatitis A vaccination of young children; this strategy began to be implemented in 2008.

**Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA 2005;294:202-10.**

**CONTEXT:** In Israel, the mean annual incidence of hepatitis A disease was 50.4 per 100 000 during 1993-1998. A 2-dose universal hepatitis A immunization program aimed at children aged 18 and 24 months (without a catch-up campaign) was started in 1999.

**OBJECTIVE:** To observe the impact of toddlers-only universal vaccination on hepatitis A virus disease in Israel.

**DESIGN AND SETTING:** Ongoing passive national surveillance of hepatitis A cases in Israel has been conducted since 1993 by the Ministry of Health. An active surveillance program in the Jerusalem district in 1999-2003 provided validation for the passive program.

**MAIN OUTCOME MEASURE:** Incidence of reported hepatitis A disease, 1993-2004.

**RESULTS:** Overall vaccine coverage in Israel in 2001-2002 was 90% for the first dose and 85% for the second dose. A decline in disease rates was observed before 1999 among the Jewish but not the non-Jewish population. After initiation of the program, a sharp decrease in disease rates was observed in both populations. The annual incidence of 2.2 to 2.5 per 100 000 during 2002-2004 represents a 95% or greater reduction for each year with respect to the mean incidence during 1993-1998 ( $P < .001$ ). For children aged 1 through 4 years, a 98.2% reduction in disease was observed in 2002-2004, compared with the prevaccination period ( $P < .001$ ). However, a sharp decline was also observed in all other age groups (84.3% [ $<1$  year], 96.5% [5-9 years], 95.2% [10-14 years], 91.3% [15-44 years], 90.6% [45-64 years], and 77.3% [ $\geq 65$  years]). Among the Jewish population in the Jerusalem district, in whom the active surveillance program was successfully conducted, a more than 90% reduction of disease was demonstrated. Of the 433 cases reported nationwide in 2002-2004 in whom vaccination status could be ascertained, 424 (97.9%) received no vaccine and none received 2 doses.

**CONCLUSION:** This universal toddlers-only immunization program in Israel demonstrated not only high effectiveness of hepatitis A vaccination but also marked herd protection, challenging the need for catch-up hepatitis A vaccination programs.

**Domínguez A, Oviedo M, Carmona G, Jansá JM, Borrás E, Salleras L, Plasència A. Epidemiology of hepatitis A before and after the introduction of a universal vaccination programme in Catalonia, Spain. J Viral Hepat. 2008;15 Suppl 2:51-6.**

A universal vaccination program for preadolescents, aged 12 years, with the hepatitis A + B vaccine was introduced in 1998 in Catalonia (Spain) with the aim of protecting the whole population against hepatitis A. The hepatitis A + B vaccine program replaced the hepatitis B vaccination program for preadolescent started in 1991. The impact of the hepatitis A + B vaccination program was studied by assessment of the trend of reported cases of hepatitis A. All cases of viral hepatitis reported from 1992 to 2006 were included in the study. To evaluate changes in the epidemiology of hepatitis A, two periods were considered: a prevaccination period (1992-1998) and a post-vaccination period (2001-2006). The ratios of the rates were calculated according to age and sex. The comparison of rates and proportions was made by calculation of the normal z statistic. A total of 7536 cases of viral hepatitis were reported, of which 4109 (54.52%) were hepatitis A. The incidence rate of hepatitis A fell from 5.44 per 100 000 person-years in the prevaccination period to 3.02 in the post-vaccination period. In males, the rate fell from 6.85 to 3.89 and in females from 4.10 to 2.18. The male-female ratio of incidence rates was lower in the post-vaccination period. In males the global decline of incidence rate was 43.26% and in females 46.96%. The greatest decline occurred in the 15 to 19 years age group in both sexes (79.1% in men and 78.34% in women) but declines in the 10-14 years age group were also very important (69.21% and 67.88%, respectively). In conclusion, hepatitis A incidence fell in Catalonia in the post-vaccination period in vaccinated adolescents and also in other unvaccinated groups who have benefited from the indirect effects of the vaccination program.

**Domínguez A, Oviedo M, Carmona G, Batalla J, Bruguera M, Salleras L, Plasència A. Impact and effectiveness of a mass hepatitis A vaccination programme of preadolescents seven years after introduction. Vaccine. 2008a; 26:1737-41.**

**AIM:** To investigate the impact of a mass hepatitis A vaccination programme in preadolescents seven years after introduction in terms of its effectiveness and the prevented fraction.

**SETTING:** The age distribution of notified cases and incidence rates in Catalonia (Spain) in the periods before (1992-1998) and after (1999-2005) introduction of the vaccination programme were compared.

**MAIN RESULTS:** The incidence rates in the whole population were 5.51 per 100,000 person-years in the 1992-1998 period and 2.98 in the 1999-2005 period. The rate reduction in the 10-19 years age group was 72.43% and was more than 45% in the 5-9 years and 20-29 years age groups. The effectiveness of the vaccination programme was 99.04 (95% CI: 93.11-99.88) and the prevented fraction in the 12-19 years age group was 90.13% (95% CI: 84.47-90.89).

**CONCLUSIONS:** The universal vaccination programme of preadolescents has had an important impact on hepatitis A in Catalonia, not only in vaccinated cohorts but also in non-vaccinated age groups due to a herd immunity effect.

**Fisenka EG, Germanovich FA, Glinskaya IN, Lyabis OI, Rasuli AM. Effectiveness of universal hepatitis A immunization of children in Minsk City, Belarus: four-year follow-up. J Viral Hepat. 2008;15 Suppl 2:57-61.**

Hepatitis A is a reportable disease in Belarus. Universal hepatitis A vaccination of children aged 6 years in Minsk City began in 2003. This analysis was conducted to evaluate the short-term impact of the program. Hepatitis A incidence data from 1954 to 2006 was compiled. Vaccination effectiveness was estimated by comparing the incidence of reported hepatitis A cases after 4 years of immunization (2006) with the incidence when the vaccination program started (2003). The vaccines used were Avaxim 160 or Avaxim 80 (95%) and Havrix 720 (5%). From 2003 through 2006, hepatitis A incidence in vaccinated children under 14 years was 20-fold lower than the incidence in unvaccinated children (0.3 cases/10000 vs 5.98/10000; odds ratio = 0.05, 95% CI: 0.012-0.202), for a vaccination effectiveness of 95%. The decreased incidence of hepatitis A in all age groups in 2006 (by 12 times in preschool children aged 1-5 years, 13 times in children aged 10-14 years and 4-6 times among adults), including those without high coverage by vaccination, suggest a herd effect. Routine

vaccination also resulted in a shift of the age pattern of hepatitis A morbidity. The proportion of cases in children under 14 years decreased from 33% to 41% in 2000-2002 to 7% in 2005-2006. We conclude that introduction of universal hepatitis A vaccination in Minsk resulted in sharply reduced incidence in both vaccinated and unvaccinated children. Hepatitis A virus circulation might decrease further by beginning vaccination at a younger age.

**Hanna JN, Hills SL, Humphreys JL. Impact of hepatitis A vaccination of indigenous children on notifications of hepatitis A in north Queensland. Med J Aust 2004; 181: 482-485**

OBJECTIVE: To describe the impact of a hepatitis A vaccination program for Indigenous children in north Queensland.

DESIGN: Enhanced surveillance of all notified cases of hepatitis A in north Queensland from 1996 to 2003.

SETTING: North Queensland; population, 596 500 people, including about 6900 Indigenous children aged under five years.

INTERVENTIONS: Hepatitis A vaccine was provided to Indigenous children in north Queensland from February 1999; two doses were recommended (at 18 months and 2 years of age), as was catch-up vaccination up to the sixth birthday.

RESULTS: In the 4 years 1996-1999, 787 cases of hepatitis A were notified in north Queensland, 237 (30%) of which were in Indigenous people. The average annual notification rates in Indigenous and non-Indigenous people during this period were 110 and 25 cases per 100 000 persons, respectively. In the first 4 years after introduction of the vaccination program (2000-2003), 66 cases of hepatitis A were notified. Only nine of the 66 (14%) were in Indigenous people. The average annual notification rates in Indigenous and non-Indigenous people in 2000-2003 were 4 and 2.5 cases per 100 000 persons, respectively.

CONCLUSION: Hepatitis A seems to have been eradicated from Indigenous communities in north Queensland very soon after the vaccination program began. The rapid decline in notifications in non-Indigenous as well as Indigenous people suggests the program quickly interrupted chains of transmission from Indigenous children to the broader community. To our knowledge this is the first evidence that a hepatitis A vaccination program targeting a high-risk population within a community can reduce disease in the broader community. Hepatitis A vaccine should be provided to other high-risk Indigenous children elsewhere in Australia.

**Lopalco PL, Prato R, Chironna M, Germinario C, Quarto M. Control of hepatitis by universal vaccination of adolescents, Puglia, Italy. Emerg Infect Dis 2008; 14: 526-8. (No abstract available)**

**Tsou TP, Liu CC, Huang JJ, Tsai KJ, Chang HF. Change in hepatitis A epidemiology after vaccinating high risk children in Taiwan, 1995-2008. Vaccine 2011; 29:2956-61.**

Taiwan started to immunize children in 30 indigenous townships against hepatitis A since June 1995. The program was further expanded to 19 non-indigenous townships with higher incidence or increased risk of epidemic in 1997-2002, covering 2% of total population. Annual incidence of hepatitis A decreased from 2.96 in 1995 (baseline period) to 0.90/100,000 in 2003-2008 (vaccination period). The incidence in vaccinated townships and unvaccinated townships declined 98.3% (49.66-0.86/100,000) and 52.6% (1.90-0.90/100,000). In 2003-2008, incidence doubled in people aged  $\geq 30$  years, mostly in unvaccinated townships (0.42-0.92). During 2003-2008, travel to endemic countries was the most commonly reported risk factor (13.5%). First dose vaccine coverage was 78.8% in 1994-2005 birth cohort. Taiwan's experience demonstrates the great, long-term efficacy of hepatitis A vaccine in disease control in vaccinated townships, and out-of-cohort effect in unvaccinated townships. Further reduction can be achieved by improving vaccination coverage of adults at risk.

**Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis 2008; 197:1282-8.**

BACKGROUND: Since the mid-1990s, hepatitis A vaccine has been recommended for US children living in historically high-incidence states and for persons with other risk factors or chronic liver disease (CLD). The incidence of hepatitis A has declined dramatically during the era of vaccination, but trends in mortality are largely unknown.

**METHODS:** US death certificates from 1990 to 2004 for which hepatitis A was listed as the underlying cause of death were analyzed. Average annual age-adjusted mortality rates during the prevaccine (1990-1995) and post-vaccination recommendation (2000-2004) periods were compared using a Mantel-Haenszel test of association. The number of deaths for which CLD was listed as a contributing cause was determined.

**RESULTS:** Overall, 1436 deaths due to hepatitis A occurred, averaging 96 annually (range, 142 in 1995 to 54 in 2003). CLD contributed to nearly half of these deaths. Mortality rates paralleled incidence rates, beginning to decline in the mid-1990s and achieving low points in 2003 and 2004. Average rates were 32% lower in the post-vaccination recommendation period than in the prevaccine period ( $P < .01$ ). The decline was more dramatic for states with (45%;  $P < .001$ ) than without (23%;  $P = .002$ ) recommendations.

**CONCLUSIONS:** Hepatitis A mortality rates have declined over the past decade. CLD remains an important and preventable contributing cause of death due to hepatitis A.

**Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA, 2005,294:194-201.**

**CONTEXT:** In the United States, hepatitis A is a frequently reported vaccine-preventable disease. Vaccination has been recommended for persons at increased risk since 1996. In 1999, it was recommended that children living in 11 states with the highest incidence of hepatitis A be routinely vaccinated, and that children living in 6 additional states, with incidence above the national average, be considered for routine vaccination.

**OBJECTIVE:** To assess impact of the current vaccination strategy by evaluating trends in reported cases of hepatitis A since implementation. **DESIGN, SETTING, AND CASES:** A longitudinal analysis of characteristics of cases of hepatitis A reported in the United States since 1990 to the National Notifiable Diseases Surveillance System.

**MAIN OUTCOME MEASURE:** Incidence rates of reported cases of hepatitis A. Incidence rates in 2003 were compared with those for the prevaccination baseline period (1990-1997) overall and in the 17 states in which children should be routinely vaccinated or considered for routine vaccination (vaccinating states). Incidence rates in vaccinating states were also compared with those in the remaining states where there is no recommendation for statewide vaccination of children (nonvaccinating states).

**RESULTS:** Between the baseline period (1990-1997) and 2003, overall hepatitis A rates declined 76% to 2.6 per 100,000, significantly lower than previous nadirs in 1983 (9.2/100,000) and 1992 (9.1/100,000). The rate in vaccinating states declined 88% to 2.5 per 100,000 compared with 53% elsewhere (to 2.7/100,000). In 2003, cases from vaccinating states accounted for 33% of the national total vs 65% during the baseline period. Declines were greater among children aged 2 to 18 years (87%) than among persons older than age 18 years (69%); the proportion of cases in children dropped from 35% to 19%. Since 2001, rates in adults have been higher than among children, with the highest rates now among men aged 25 through 39 years.

**CONCLUSIONS:** Following implementation of routine hepatitis A vaccination of children, hepatitis A rates have declined to historic lows, accompanied by substantial changes in the epidemiologic profile. Greater decreases in the age groups and regions where routine vaccination of children is recommended likely reflect the results of implementation of this novel vaccination strategy. Continued monitoring is needed to verify that implementation continues to proceed and that low rates are sustained.

**Zhang ZL, Zhu XJ, Ding YX, Xie XH, Gao ZG, Li YC, Zhang Y, Xia WD, Liu Y. Evaluation on the role of hepatitis A vaccine in the prevention and control of hepatitis A in Tianjin city. Zhonghua Liu Xing Bing Xue Za Zhi. 2007; 28:1000-3.**

**OBJECTIVE:** To evaluate the effects of prevention and control strategies on hepatitis A.

**METHODS:** Surveillance data on hepatitis A from 1990 to 2006 in Tianjin was analyzed, and the coverage rate of hepatitis A vaccine among targeted population was estimated, to compare the anti-HAV IgG level of children younger than 15 years old in 1999 and in 2005.

**RESULTS:** Results showed that a) the morbidity of hepatitis A decreased from 25.26/10(5) in 1990 to 0.82/10(5) in 2006; b) the ratio of hepatitis A in viral hepatitis decreased from 30.43% in 1990 to 1.05% in 2006; c) the estimated coverage rate was 72.7%; d) the positive rate of anti-HAV among children younger than 15 years old in 2005 was distinctly higher than that in 1999.

**CONCLUSION:** Positive results showed that it was successful to use hepatitis A vaccine as the strategy to prevent and control hepatitis A in the past five years in Tianjin.

**Zhuang FC, Qian W, Mao ZA, Gong YP, Jiang Q, Jiang LM, Chen NL, Chai SA, Mao JS. Persistent efficacy of live attenuated hepatitis A vaccine (H2-strain) after a mass vaccination program. Chin Med J (Engl). 2005; 118:1851-6.**

**BACKGROUND:** Live attenuated hepatitis A vaccine (H2 strain) is widely applied in prevention of hepatitis A epidemic in China and other countries now. It is essential to observe and confirm the vaccine immune efficacy, population antibody level and its persistent efficacy after mass immunization.

**METHODS:** A total of 220 children with negative anti-HAV antibody (aged 1 - 3 years) were taken for follow-up assay to observe seroconversion and geometric mean titre (GMT) level 2 months, 12 months, 6 years, and 10 years after inoculation. Another survey sampled from subjects of different age groups (3, 6, 9, 15, 18, 25 and 35 years) to compare anti-HA antibody positive rate before and after inoculation performed 10 years previously. Epidemiological observations were taken for 10 years to evaluate the relationship between vaccine coverage and hepatitis A morbidity. Serum antibody to HAV was detected by enzyme linked immunoassay (ELISA, calibrated by WHO international reference) and ABBOTT Axsym HAVAB microparticle enzyme immunoassay.

**RESULTS:** Seroconversion in follow-up assay 2 months and 10 years after inoculation was 98.6% and 80.2% respectively. For children, the vaccination anti-HA antibody positive rates were significantly different before and after 10 years, 7.69% cf 70.45% (aged 3 years) and 52.58% cf 71.78% (aged 18 years). When vaccine coverage rose from 57% to 74%, there were no any HA epidemics. When vaccine coverage reached 85%, there were no any HA cases. With vaccine coverage between 85% and 91%, there were no any HA cases in cohorts from the age of 1 year to 15 years during the 10 years.

**CONCLUSIONS:** Live attenuated hepatitis A vaccine has an obvious long-term effectiveness in prevention and control of HA epidemics through mass vaccination.

## Table IVa

**Bian GL, Ma R, Dong HJ, Ni HX, Hu FJ, Chen YR, Chen JQ, Zhou SY, Lin YX, Xu GZ. Long-term clinical observation of the immunogenicity of inactivated hepatitis A vaccine in children. Vaccine. 2010 Jul 5;28(30):4798-801.**

110 children who were given the complete course of the inactivated hepatitis A vaccine (Havrix) were followed up 10 years later. Age-matched healthy children who were not inoculated served as controls. One month after two primary injections, all children were positive for serum antibody. After 10 years, 99.09% of inoculated children remained positive for serum anti-HAV antibody, with a geometric mean concentration (GMC) of 61.59mIU/mL. GMC values following a secondary immunization in children with antibody levels <20mIU/mL were significantly elevated (567.9mIU/mL), compared with the primary injection alone. Havrix appears to induce persistent immunity and potent immune memory.

**Bovier PA, Farinelli T, Loutan L. Interchangeability and tolerability of a virosomal and an aluminum-adsorbed hepatitis A vaccine. Vaccine, 2005, 23:2424-2429.**

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.

**Bovier PA, Bock J, Ebengo TF, Frösner G, Glaus J, Herzog C, Loutan L. Predicted 30-year protection after vaccination with an aluminum-free virosomal hepatitis A vaccine. J Med Virol. 2010 Oct;82(10):1629-34.**

Few studies have examined the duration of protection following vaccination against hepatitis A virus (HAV) with currently licensed HAV vaccines. This study explored the long-term immunogenicity in individuals vaccinated with the virosomal hepatitis A virus, Epaxal. Adult volunteers (N = 130) previously enrolled into four different studies between 1992 and 1994 and who had completed a 0/12-month immunization regimen (primary and booster dose) were asked to participate in this follow-up study. Yearly anti-HAV titers up to 6 years following booster vaccination, and then once 9-11 years after booster were measured using two assays, Enzygnost and AxSYM HAVAB 2.0. Based on the Enzygnost assay, the seroprotection rate 9-11 years after booster was 100%, with a geometric mean concentration (GMC) of anti-HAV antibodies of 526 mIU/ml. Females had markedly higher GMCs than males (741 mIU/ml vs. 332 mIU/ml). Using an anti-HAV cut-off titer of  $\geq 10$  mIU/ml, a linear mixed mathematical model predicted a median duration of protection of 52.1 years. A duration of protection  $\geq 35.7$  years was predicted for 95% of subjects. A more stringent cut-off of  $\geq 20$  mIU/ml shortened the median predicted duration of protection to 45.0 years. In conclusion, a two-dose Epaxal vaccination regimen confers in healthy adults a real-time protection of at least 9-11 years; this protection is predicted to last at least 30 years in over 95% of individuals. Further studies are necessary to assess the real duration of seroprotection and whether an additional booster is necessary later.

**Byrd KK, Bruden DL, Bruce MG, Bulkow LR, Zanis CL, Snowball MM, Homan CE, Hennessy TW, Williams JL, Dunaway E, Chaves SS, McMahon BJ. Long-term immunogenicity of inactivated hepatitis A vaccine: Follow-up at 15 years. Journal of Pediatric Infectious Diseases 2010; 5: 321-26. (No abstract available)**

**Crum-Cianflone NF, Wilkins K, Lee AW et al. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. J Inf Dis 2011; 203: 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  $\geq 10$  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/mm<sup>3</sup> 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 log<sub>10</sub> 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.

**Lopez EL, Contrini MM, Mistchenko A, Debbag R. Long-term immunity after two doses of inactivated hepatitis A vaccine, in Argentinean children. Pediatr Infect Dis J 2010; 29: 568-70**

We examined long-term anti-hepatitis A virus antibody persistence in Argentinean children 10 years after the initial study in which they received 2 doses of inactivated hepatitis A vaccine (Avaxim 80U). Of the 111

children, 48 from the initial trial were enrolled. Of 48, 47 (97.9%) participants had serum anti-hepatitis A virus antibody titers  $\geq 20$  mIU/mL, with the geometric mean concentration of 390.91 (+/-370.14) mIU/mL; (95% confidence interval, 282.2-499.5 mIU/mL), range, 36 to 1860.

**Van Herck K, Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. J Med Virol 2001;63:1-7.**

To estimate the long-term persistence of anti-HAV antibodies, 120 (schedule 0-6) and 194 (schedule 0-12) adults were vaccinated and followed-up annually for 6 years. Shortly after the last dose, anti-HAV levels fell sharply (annual decline rate  $\Delta > 65\%$ ). Thereafter,  $\Delta$  diminished to 10-15%. GMTs 5.5 years after the last dose were 522 mIU/ml (0-6 group) and 749 mIU/ml (0-12 group); all subjects except one maintained detectable antibodies. The average  $\Delta$  over the whole follow-up period was 15-20%, resulting in an estimated persistence of anti-HAV levels  $\geq 20$  mIU/ml for 20-25 years. These estimates were similar for both applied calculation methods (GMT or individual based) and both vaccination schedules. Because the individual antibody levels tended to stabilise between the last two measurements, the hypothesis of a slow, log-linear decrease and its matching calculation methods might be subject to reconsideration. With the current methodology, however, detectable antibodies are estimated to persist for 20-25 years.

**Wiedermann G, Kundi M, Ambrosch F, Safary A, D'Hondt E, Delem A. Inactivated hepatitis A vaccine: long-term antibody persistence. Vaccine 1997; 15: 612-5.**

During the clinical development of safe, well tolerated and immunogenic vaccines against hepatitis A the persistence of protective antibodies was estimated, based on relatively short observation periods of 18 months to 3 years. We report here on longterm persistence of antibodies in volunteers who participated in one of the early clinical trials on inactivated hepatitis A candidate vaccines. In a randomized trial three groups of altogether 110 healthy adults, initially hepatitis A virus (HAV) seronegative persons were vaccinated with an inactivated hepatitis A vaccine according to the schedule 0-1-2-12 months. One group received 180 ELISA units, one group 360, and one 720 ELISA units per dose. Blood samples were taken prior to the first vaccination and at months 1, 2, 3, 4, 6, 12, 13, 18, 24, 36 and 84. The decrease of antibodies was characterized by two disappearance rates: a rapidly decreasing component and a slower decreasing one becoming predominant ca 12 months after booster vaccination. The disappearance of antibodies could be described by a two-component model which holds for  $t > \text{or} = 13$  months. The estimated disappearance rates for the slow component (annual decrease) was found to be 11 and 13% for the 180 and 360 ELISA units groups, respectively (the 720 ELISA units group showed no decline, which was probably due to the small sample size). The estimated persistence of antibodies within protective range varied between 24 and 47 years depending on individual titres reached at month 13 and vaccination dose.

## Table IVb

**Liu HF, Zhang XJ, Zhang JL, Hao ZY, Zhang ZY, Ma JC, Chen JC, Chu J, Wang XY, Xu ZY. [The immunological effects of three doses of a live attenuated hepatitis A vaccine (H2 strain) in 8 years]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. 2009;23:180-1.**

**OBJECTIVE:** To observe the immunological effects of three doses of H2 strain live attenuated hepatitis A vaccine 8 years after the administration and to compare with that of one dose of the vaccine.

**METHODS:** In a country area, 110 children of 1 to 7 years old susceptible to HAV were screened and administered with one dose of the vaccine, as group B; Group A were 42 children from one of the villages and administered with 3 doses of the vaccine according to 0, 2, 6 month schedule. Blood samples were taken for the children 1, 2, 6, 7, 8, 12, 24, 36 and 96 months after the administrations respectively and detected for anti-HAV antibody.

**RESULTS:** For group B, the sero conversion rate of anti-HAV and GMC reached peak at 92.2% and 126.2 mIU/ml respectively, and then, began to drop with time; For group A, after 2 dose of the vaccine, the sero-conversion rate reached 100%, and the GMC reached peak of 2 739 mIU/ml one month after the third dose at 7 months. So that, group A has a better short-term immunological effects than that of group B. During 36 through

96 months, the anti-HAV positive rate in group B was 75%-71% and 80-89 mIU/ml respectively, and comparatively in group A were 100% and 918.2-480.6 mIU/ml respectively. The differences between group A and B were significantly important.

**CONCLUSION:** A 3-dose schedule administration of H2 strain live attenuated hepatitis A vaccine has better immunological effects than 1-dose schedule in 8years and further observations are needed.

**Liu HF, Zhang XJ, Zhang JL. [Comparison of antibody persistence between live attenuated and inactivated hepatitis A vaccines]. Zhongguo Yi Miao He Mian Yi. 2009a; 15:300-3.**

**OBJECTIVE:** To study the antibody persistence of live attenuated hepatitis A vaccine, and to compare the antibody between with inactivated vaccine.

**METHODS:** 211 HAV susceptible children were divided randomly into three groups, Group A was injected three doses HepA-L at 0, 6 and 12 monthes; Group B was administrated two dose HepA-L at 0 and 6 months, and group C was immunized with inactivated vaccine at month 0 and 6. Serum samples were detected for Anti-HAV at 1, 6, 7, 12, 13, 24, 84 months after vaccination in each group.

**RESULTS:** The seroconversion rates reached 100% after 2nd dose in all groups. The highest GMC was 2938.1 mIU/ml, founded in group C, and it was 1315.6 mIU/ml and 1586 mIU/ml in group A and B respectively. After the 3rd dose at month 12 in group A, the antibody increased dramatic, which reached 1945.3 mIU/ml. 84 months after first dose in each group, the antibody can be detected from all subjects. Though the GMC in group A declined to 336.8 mIU/ml, it was significant higher than that in group B and C.

**CONCLUSION:** The good booster effect with HepA-L was well observed in a short-term. The immune response induced by 2 to 3 doses HepA-L could compete with inactivated hepatitis A vaccine. However, long-term effects of both vaccines need further study.

**Wang XY, Xu ZY, Ma JC, von Seidlein L, Zhang Y, Hao ZY, Han OP, Zhang YL, Tian MY, Ouyang PY, Zhang ZY, Han CQ, Xing ZC, Chen JC. Long-term immunogenicity after single and booster dose of a live attenuated hepatitis A vaccine: results from 8-year follow-up. Vaccine 2007;25:446-9.**

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 administrated 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.

**Zhuang FC, Qian W, Mao ZA, Gong YP, Jiang Q, Jiang LM, Chen NL, Chai SA, Mao JS. Persistent efficacy of live attenuated hepatitis A vaccine (H2-strain) after a mass vaccination program.Chin Med J 2005;118:1851-6.**

**BACKGROUND:** Live attenuated hepatitis A vaccine (H2 strain) is widely applied in prevention of hepatitis A epidemic in China and other countries now. It is essential to observe and confirm the vaccine immune efficacy, population antibody level and its persistent efficacy after mass immunization.

**METHODS:** A total of 220 children with negative anti-HAV antibody (aged 1 - 3 years) were taken for follow-up assay to observe seroconversion and geometric mean titre (GMT) level 2 months, 12 months, 6 years, and 10 years after inoculation. Another survey sampled from subjects of different age groups (3, 6, 9, 15, 18, 25 and 35 years) to compare anti-HA antibody positive rate before and after inoculation performed 10 years previously.

Epidemiological observations were taken for 10 years to evaluate the relationship between vaccine coverage and hepatitis A morbidity. Serum antibody to HAV was detected by enzyme linked immunoassay (ELISA, calibrated by WHO international reference) and ABBOTT Axsym HAVAB microparticle enzyme immunoassay.

**RESULTS:** Seroconversion in follow-up assay 2 months and 10 years after inoculation was 98.6% and 80.2% respectively. For children, the vaccination anti-HA antibody positive rates were significantly different before and after 10 years, 7.69% cf 70.45% (aged 3 years) and 52.58% cf 71.78% (aged 18 years). When vaccine coverage rose from 57% to 74%, there were no any HA epidemics. When vaccine coverage reached 85%, there were no any HA cases. With vaccine coverage between 85% and 91%, there were no any HA cases in cohorts from the age of 1 year to 15 years during the 10 years.

**CONCLUSIONS:** Live attenuated hepatitis A vaccine has an obvious long-term effectiveness in prevention and control of HA epidemics through mass vaccination.

**Zhuang FC, Mao ZA, Jiang LM, Wu J, Chen YQ, Jiang Q, Chen NL, Chai SA, Mao JS. [Long-term immunogenicity and effectiveness of live attenuated hepatitis A vaccine (H2-strain)-a study on the result of 15 years' follow up.] Zhonghua Liu Xing Bing Xue Za Zhi. 2010 Dec;31(12):1332-1335. [Article in Chinese]**

**OBJECTIVE:** To evaluate the long-term immunogenicity and effectiveness of live attenuated hepatitis A (HA) vaccine (H2 strain) after one dose injection, through a 15 years' follow up observation.

**METHODS:** A total of 220 children with negative anti-HAV antibody (aged 1 - 3 y) were involved and followed up in Jiaojiang district, Taizhou city, Zhejiang province. Indicators would include seroconversion and geometric mean titer (GMT) levels after inoculation the vaccine with single dose at 2 m, 12 m, 6 years, 10 years and 15 years. Epidemiological observation was carried out within the 15 years to evaluate the relationship between vaccine coverage, the incidence of HA and the overall effectiveness. In the studied population, serum was tested by ELISA (calibrated by WHO international reference) and ABBOTT Axsym HAVAB mEIA.

**RESULTS:** Seroconversion rates were found to be 98.6% and 81.3% after 2 months and 15 years of inoculation and slowly decreased. GMT level was 128 mIU/ml after 15 years, significantly higher than the required protective level of 20 mIU/ml, recommended by WHO experts. Effectiveness through the 15-year follow up program showed a significant correlation between vaccine coverage and incidence of HA in 1 - 15 years aged group (Kendall-Rank test,  $\tau = -0.931$ ,  $P < 0.01$ ). There was no HA case seen among the observed accumulated 236 413 person-year vaccines, compared to 4 HA cases discovered in the 27 206 person-year of the non-vaccinees. The overall protective rate reached 100%. Through a mass vaccination program on children, the whole population established an immune-defence to enable the incidence of HA decreased by 96.7%.

**CONCLUSION:** The long-term immunogenicity and effectiveness of live attenuated hepatitis A vaccine (H2 strain) after one dose injection could last as long as 15 years.

## Table Va

**Cervio G, Trentadue J, D'Agostino D et al. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepatic Medicine: Evidence and Research 2011; 3:99-106. (No abstract available)**

**Vacchino MN. Incidence of hepatitis A in Argentina after vaccination. J Viral Hep 2008; 15 (suppl 2); 47-50.**

In Argentina, the annual incidence rate of reported hepatitis A disease ranged from 70.5 to 173.8 per 100,000 during 1995-2004. A single dose universal hepatitis A immunization program aimed at children aged 12 months was started in June 2005. The aim was to observe the impact of universal vaccination against hepatitis A in Argentina. A longitudinal analysis of hepatitis A rates reported in Argentina since 1995 to the National Notifiable Diseases Surveillance System (SINAVE). Incidence rates in 2007 were compared with those for the prevaccination baseline period (1998-2002), overall and by age group and geographical regions. Overall vaccine coverage in Argentina was 95% in 2006 for the single dose. After initiating the program, a sharp decrease in disease rates was observed. The annual incidence of 10.2 per 100,000 during 2007 represents 88.0% reduction with respect to the average incidence rate for the period 1998-2002 ( $P < 0.001$ ). For children aged 1 year, an

83.1% reduction in disease was observed in 2007, compared with the baseline period ( $P < 0.001$ ). Furthermore, a sharp decline was also observed in all other age groups 87.1% [2-4 years], 88.7% [5-9 years], 83.6% [10-14 years], 78.8% [15-49 years], 20.7% [ $>50$  years]. Also important reductions were observed in all Argentinian regions. Following the implementation of universal hepatitis vaccination with a single dose to children at 12 months of age, hepatitis A rates have declined substantially in Argentina. Monitoring is needed to verify that vaccination continues to proceed and that low rates are sustained.

## Table Vb

**Beck BR, Hatz C, Brönnimann R, Herzog C. Successful booster antibody response up to 54 months after single primary vaccination with virosome-formulated, aluminum-free hepatitis A vaccine. *Clinical Infectious Diseases* 2003; 37: 126-8.**

This study demonstrates that a booster dose of the virosome-formulated, aluminum-free hepatitis A vaccine Epaxal (Berna Biotech) is highly immunogenic in subjects who received a single primary dose of this vaccine 18-54 months earlier. There were no significant differences in geometric mean antibody titers (GMTs) among subjects who received the booster dose 18-29 months (GMT, 2330 mIU/mL), 30-41 months (GMT, 2395 mIU/mL), or 42-54 months (GMT, 2432 mIU/mL) after primary vaccination, indicating that delays in the administration of booster vaccination do not lead to a loss of immunogenicity.

**Hatz C, Ploeg van der R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis A vaccine delayed up to 11 years. *Clinical and vaccine immunology* 2011, 18: 885-7.**

Boosting adult travelers with the virosome-formulated, aluminum-free hepatitis A vaccine Epaxal up to 128 months after a single primary dose confers full protection against hepatitis A, even in travelers aged 50 years and above. Delaying the booster dose did not influence the immune memory response to Epaxal.

**Herzog C. Epaxal®- Alluminium free. Presentation and personal communication at the "SAGE hepatitis A working group meeting". 2010, Buenos Aires, Argentina. (No abstract available)**

**Iwarson S, Lindh M, Widerström L. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. *J travel Med* 2004; 11: 120-1. (No abstract available)**

**Sabanin IuV, Rikhter VV, Kuzin SN. [Assessment of effectiveness and immunogenicity of hepatitis A vaccination in servicemen of Internal Forces of Ministry of Internal Affairs of Russia]. [Article in Russian]. *Zh Mikrobiol Epidemiol Immunobiol.* 2010;1:35-9.**

AIM: Comparative assessment of immunological and epidemiological effectiveness of hepatitis A vaccination and duration of immunity after immunization in servicemen.

MATERIALS AND METHODS: During 1996-2003, immunogenicity and epidemiologic effectiveness of 3 vaccines against hepatitis A--Havrix 1440 (GlaxoSmithKline, Belgium), Hep-A-in-Vac (Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russia), and Avaxim (Sanofi Pasteur, France)--were evaluated. More than 15,000 servicemen were immunized during that time. In all cases one-dose vaccination without booster was performed.

RESULTS: Several cases of acute hepatitis A were registered 12 months and 6-8 months after vaccination in military communities immunized with Havrix 1440 and Hep-A-in-Vac vaccines respectively. Usage of Avaxim vaccine as a single dose in field trials allowed to exclude new cases of acute hepatitis A during time of military service. It was shown that 5 years after single vaccination with Avaxim protective anti-HAV antibody level (20 IU/l) persisted in 90% of Internal Forces servicemen.

CONCLUSION: On the basis of performed complex of studies, system of antiepidemic measures was developed, which leads to decrease of hepatitis A incidence. Selective immunization is proposed.

**Vizzotti C. Seroprevalence of hepatitis A antibodies four years after a single dose vaccination strategy in Argentinean children. Ministry of Health Argentina. Personal communication, January 2012. (No abstract available)**

