

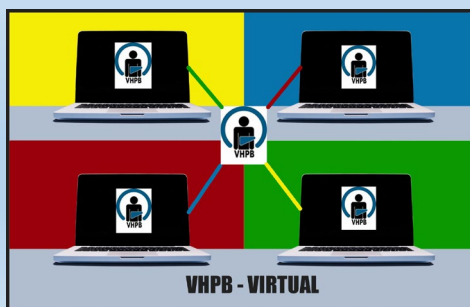


VHPB TECHNICAL MEETING

Hepatitis A vaccination: One dose

Background document

11 June 2020 – 17h tot 20h



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Table of Content

MEETING OBJECTIVES	3
PARTICIPANTS (± 35)	3
INTENDED IMPACT	3
OUTLINE OF THE MEETING	3
GENERAL BACKGROUND INFORMATION	4
MEETING AGENDA	8
Session 1: Introduction of the participants.....	8
Session 2: Key messages of presentation - Questions.....	8
Presentation 1 : Experience with one dose in Latin America	8
Presentation 2 : Experience with one dose in Asia	15
Presentation 3 : Immune memory with one dose of hepatitis A vaccine – booster dose?	23
Presentation 4 : Economic analysis of the use of single dose	28
Presentation 5 : Scientific evidence for the use of one dose	34
Session 3 : Groups discussion.....	41
PARTICIPANTS LIST	42

MEETING OBJECTIVES

Hepatitis A vaccination one dose

- review long-term efficacy of hepatitis A vaccine one dose and field effectiveness of hepatitis A vaccination programmes
- discuss current efficacy, effectiveness and scientific evidence for one dose hepatitis A vaccination

PARTICIPANTS (± 35)

Global scientists, opinion leaders, infectiologists, hepatologists, vaccinologists, paediatricians and public health representatives who are experts in the field of viral hepatitis prevention.

INTENDED IMPACT

Draft guidelines on how to address hepatitis A vaccination in the future.

OUTLINE OF THE MEETING

Presentations on latest scientific evidence of hepatitis A vaccination and the use of one dose will be pre-recorded by the speakers and made available latest one week before the meeting.

NOTE: This pre-meeting document contains general background information on the topic of the VHPB meeting. It contains a list of selected abstracts/references from a Pubmed MEDLINE search on different search terms depending on the topic discussed in a session of the meeting. The references are sorted by publication year (most recent first) and for each year in alphabetical order of the first author's name. This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully, it will give an overview of what has been published on the topics of the meeting



Hepatitis A

Vaccine

Two types of HAV vaccines are currently available internationally:

1. Formaldehyde-inactivated vaccines: Inactivated HAV vaccines are used in most countries. Monovalent inactivated HAV vaccines are available in paediatric dose (0.5 ml) for children aged 1 year to 15 years, and in adult dose (1 ml).
2. Live attenuated vaccines (based on H2 or LA-1 HAV strains): These vaccines are manufactured and used mainly in China and sporadically in the private sector in India.

1. Inactivated hepatitis A vaccines are safe and highly effective. Traditionally, a two-dose schedule is recommended, particularly in travellers at substantial risk of contracting hepatitis A and in immunocompromised individuals. However, in healthy individuals, comparable effectiveness has been achieved with a single dose. Results from mathematical models indicate that, after completion of the primary two-dose series, anti-HAV antibodies may persist for 25 years or more. Serological testing to assess antibody levels after vaccination is not indicated.

A combination hepatitis A/typhoid (ViCPS) vaccine, administered as a single dose, confers high levels of protection against both these waterborne diseases.

A combination vaccine that provides protection against both hepatitis A and hepatitis B should be considered for travellers who may be exposed to both organisms (see under Hepatitis B vaccines).

2. The Chinese live attenuated hepatitis A vaccines have been shown to be safe and highly protective (95%) against clinical infection for at least 3 years.

Type of vaccine: Inactivated or live, both given i.m.

Number of doses: Inactivated vaccine: two; live vaccine: one

Schedule: Inactivated vaccine: two doses, the second dose normally 6 months after the first. If needed, this interval may be extended to 18–36 months). In healthy individuals, a single dose seems to be similarly efficacious.

Live vaccine: one dose

Minimum age for HAV vaccination is 1 year

boosters: May not be necessary

Contraindications: Hypersensitivity to previous dose

Adverse reactions: Inactivated vaccine: mild local reaction of short duration, mild systemic reaction Live vaccine: few reported

Before departure: Inactivated and live vaccines: protection is achieved 2–4 weeks after first dose. Given the long incubation period of hepatitis A (average 2–4 weeks), the vaccine can be administered up to the day of departure and still protect travellers.

Recommended for: Hepatitis A vaccination should be considered for individuals aged ≥ 1 year who are travelling to countries or areas with moderate to high risk of infection. Those at high risk of acquiring severe disease, such as immunosuppressed patients and patients with chronic liver disease, should be strongly encouraged to be vaccinated regardless of where they travel.

Special precautions: None

Shouval D, Van Damme P, [WHO The Immunological Basis for Immunization Series; Module 18: Hepatitis A, Update 2019](#). In: World Health Organization-Geneve; **2019**

[WHO position paper on hepatitis A vaccines - June 2012](#). (2012) *Wkly Epidemiol Rec* 87(28/29): 261-276.

General information

[CDC current recommendations on Hepatitis A vaccines.](#)

Shouval D. [Immunization against Hepatitis A](#). Cold Spring Harb Perspect Med **2019**;9.

Worldwide, there are multiple formaldehyde-inactivated and at least two live attenuated hepatitis A vaccines now in clinical use. The impressive immunogenicity of inactivated vaccines is reflected in rapid seroconversion rates, enabling both preexposure and postexposure prophylaxis. Universal childhood vaccination programs targeting young children have led to significant drops in the incidence of hepatitis A both in toddlers and in susceptible nonimmune adults in regions with intermediate endemicity for hepatitis A. Although the safety of inactivated vaccines is well established, further studies are needed concerning the implications of fecal virus shedding by recipients of attenuated vaccines, as well as the long-term persistence of immune memory in children receiving novel immunization schedules consisting of single doses of inactivated vaccines.

Stuurman AL, Marano C, Bunge EM, De Moerlooze L, Shouval D. [Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines - A systematic review](#). Hum Vaccin Immunother **2017**;13:724-36.

The WHO recommends integration of universal mass vaccination (UMV) against hepatitis A virus (HAV) in national immunization schedules for children aged ≥ 1 year, if justified on the basis of acute HAV incidence, declining endemicity from high to intermediate and cost-effectiveness. This recommendation has been implemented in several countries. Our aim was to assess the impact of UMV using monovalent inactivated hepatitis A vaccines on incidence and persistence of anti-HAV (IgG) antibodies in pediatric populations. We conducted a systematic review of literature published between 2000 and 2015 in PubMed, Cochrane Library, LILACS, IBECs identifying a total of 27 studies (Argentina, Belgium, China, Greece, Israel, Panama, the United States and Uruguay). All except one study showed a marked decline in the incidence of hepatitis A post introduction of UMV. The incidence in non-vaccinated age groups decreased as well, suggesting herd immunity but also rising susceptibility. Long-term anti-HAV antibody persistence was documented up to 17 y after a 2-dose primary vaccination. In conclusion, introduction of UMV in countries with intermediate endemicity for HAV infection led to a considerable decrease in the incidence of hepatitis A in vaccinated and in non-vaccinated age groups alike.

Hendrickx G, Vorsters A, Van Damme P. (2012). "[Advances in hepatitis immunization \(A, B, E\): public health policy and novel vaccine delivery](#)." *Curr Opin Infect Dis* **25**(5): 578-583.

PURPOSE OF REVIEW: This review offers an update on hepatitis A, B and E vaccines based on relevant literature published in 2011-2012. Hepatitis A and B vaccines have been commercially available for years; however, the development of the hepatitis E vaccine is still facing some challenges. RECENT FINDINGS: Current scientific evidence shows that both hepatitis A and B vaccines confer long-term protection. These data supported the updated recommendations from the WHO on hepatitis A and B vaccines and the respective booster policy. In addition, a single-dose hepatitis A vaccination programme may be an option for some intermediate endemic countries, as far as the epidemiological situation is further monitored. Recent data illustrate the co-administration of hepatitis A with infant vaccines, as well as the interchangeability with other hepatitis A vaccines. Two genetically engineered hepatitis E vaccines are currently in development, showing more than 95% protective efficacy. SUMMARY: Follow-up of vaccinated individuals confirms the long-term protection offered by the hepatitis A as well as hepatitis B vaccines. Data confirm the safety and immunogenicity profile of both vaccines, also when used in patient groups. The first data on the hepatitis E vaccine look promising, but questions on cross-protection, long-term efficacy and safety and immunogenicity in pregnant women and children less than 2 years remain unanswered.

Ott JJ, Irving G, Wiersma ST. [Long-term protective effects of hepatitis A vaccines](#). A systematic review. *Vaccine*. **2012**;31:3-11.

Objective: Data on duration and long-term protective effects of hepatitis A vaccines (HepA) have not been reviewed using a systematic approach. Our objective is to provide a comprehensive review of evidence on the duration of protection achieved by HepA, which is needed for revising existing vaccine policies. Limitations in data availability and implications for future research in this area are discussed.

Methods: A systematic literature review was conducted including all studies published between 1997 and 2011 reporting on long-term protection of HepA. The outcomes considered were hepatitis A virus (HAV) infection and sero-protection measured by anti-HAV antibodies after follow-up times of over 5 years post-vaccination. Results: 299 studies were identified from MEDLINE and 51 studies from EMBASE. 13 manuscripts met our inclusion criteria. The maximum observation times and reported persistence levels of sero-protective anti-HAV antibodies was 15 years for live attenuated HepA and 14 years for inactivated HepA. All data were from observational studies and showed that higher number of doses of live attenuated vaccine led to higher seropositivity and GMT, but dosage and schedule did not significantly impact the long-term protection following inactivated vaccine. Few comparisons were made between the two vaccine types indicating highest levels of antibody titers achieved by multiple doses of live attenuated vaccines 7 years post-vaccination. Conclusion: Available data indicate that both inactivated and live attenuated HepA are capable of providing protection up to 15 years as defined by currently accepted, conservative correlates of protection. Further investigations are needed to continue to monitor the long-term protection afforded by these vaccines. Standardized methods are required for vaccine-follow-up studies including assessment of co-variables potentially affecting long-term protection.

Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, Roper M, Shouval D, Ward J and Van Damme P. [Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology.](#) *Journal of Viral Hepatitis*, **2008**, 15 (Suppl. 2), 1–15

SUMMARY. For the first time a global meeting on hepatitis A virus (HAV) infection as vaccine preventable disease was organized at the end of 2007. More than 200 experts from 46 countries gathered to investigate the changing global HAV epidemiology reflecting the increasing numbers of persons at risk for severe clinical disease and mortality from HAV infection. The benefits of childhood and adult hepatitis A (HepA) vaccination strategies and the data needed by individual countries and international health organizations to assess current HepA prevention strategies were discussed. New approaches in preventing HAV infection including universal HepA vaccination were considered. This introductory paper summarizes the major findings of the meeting and describes the changing epidemiology of HAV infections and the impact of HepA vaccination strategies in various countries. Implementation of HepA vaccination strategies should take into account the level of endemicity, the level of the socio-economic development and sanitation, and the risk of outbreaks. A stepwise strategy for introduction of HepA universal immunisation of children was recommended. This strategy should be based on accurate surveillance of cases and qualitative documentation of outbreaks and their control, secure political support on the basis of high-quality results, and comprehensive cost-effectiveness studies. The recognition of the need for increased global attention towards HepA prevention is an important outcome of this meeting.

[Proceedings of the First Global Meeting on Hepatitis A Virus Infection, 2007, Miami, Florida, USA.](#) *J Viral Hepat.* **2008** Oct;15 Suppl 2:1-72.

[Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers.](#) Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* **2007**;56:1080–4

MEETING AGENDA

Session 1: Introduction of the participants

Chairs:

- 17:00-17:20** Welcome and opening of the meeting
- Welcome and opening
 - Introduction of the participants

Session 2: Key messages of presentation - Questions

Chairs:

17:20-17:30

Presentation 1 : Experience with one dose in Latin America

Experience after Seven year of follow up and Statistical modelling alongside observational data predicts long-term immunogenicity of one dose and two doses of paediatric hepatitis A vaccine in the Mendoza province of Argentina.

Carlos Espul

From speaker:

Espul C, Cuello H, Lo Castro I, Bravo C, Thollot Y, Voznica J, Vigne C, Coudeville L. [Statistical modelling alongside observational data predicts long-term immunogenicity of one dose and two doses of paediatric hepatitis A vaccine in the Mendoza province of Argentina.](#)

Vaccine. **2020** Feb 11;38(7):1715-1722. doi: 10.1016/j.vaccine.2019.12.049. Epub 2020 Jan 9.

BACKGROUND:

Follow-up for anti-hepatitis A (HA) antibody persistence up to 10 years was conducted after implementation of universal vaccination against HA virus (HAV) in Mendoza, Argentina. Based on these data, statistical modeling was used to predict the antibody persistence to 30 years.

METHODS:

A non-interventional study evaluated long-term immunogenicity (geometric mean concentrations [GMCs] and seroprotection rate) following routine vaccination with 1 dose (Group 1: N = 436) or 2 doses (Group 2: N = 108) of HA vaccine. Associated statistical modeling based on a Bayesian approach of mixed effects models on log transformed titers evaluated three models (linear, piecewise linear, and exponential decay, with and without a natural boosting effect).

RESULTS:

From the initial cohort, 9 participants (Group 1) and 1 participant (Group 2) showed antibody titers below the seroprotective threshold and received a booster. At Year 10, 190 (Group 1) and 51 (Group 2) participants remained in the study without a booster dose and all were seroprotected. Regarding statistical modeling, the piecewise linear model showed the best fit and demonstrated high and similar seroprotection for each schedule up to 30 years (89% [1-dose schedule], 85% [2-dose schedule]). The 2-dose schedule showed higher GMC (95% CI) than the 1-dose schedule (Year 10: 352 [271-456] versus 78 [69.8-87.6] mIU/mL) and Year 30 (predicted) (37 [13-97] versus 19 [11-34] mIU/mL). Natural boosting had little impact on predicted seroprotection rates at 30 years for the 1-dose schedule (89% [0.8-0.96] and 84% [0.73-0.94] with and without a natural booster, respectively).

CONCLUSIONS:

Long-term persistence of anti-HAV antibodies was observed up to 10 years with 1-dose and 2-dose vaccine schedules, supporting booster flexibility. Statistical modeling predicted good persistence of seroprotection for each schedule up to 30 years. Natural boosting had a limited impact on seroprotection rate predictions, enabling extrapolation of these results to non-endemic settings for traveler vaccination.

Espul, C., Benedetti, L., Linares, M., Cuello, H., Lo Castro, I., Thollot, Y. and Rasuli, A. "[Seven-year follow-up of the immune response after one or 2 doses of inactivated hepatitis A vaccine given at 1 year of age in the Mendoza Province of Argentina.](#)" *Hum Vaccin Immunother* **2017** 13(11): 2707-2712. a Ministerio de Salud/Hospital Central de Mendoza, Mendoza, Argentina b Ministerio de Salud, Mendoza, Argentina. c Seccion Virologia, Hospital Central de Mendoza, Mendoza, Argentina. d Sanofi Pasteur, Lyon, France.

This monocenter, descriptive, prospective, non-interventional study evaluated the long-term immune responses following routine vaccination with one or 2 doses of a licensed inactivated hepatitis A (HA) vaccine (Avaxim® 80U Pediatric) at age 11-23 months in a cohort of children from Mendoza, Argentina. Antibodies to hepatitis A virus (anti-HAV) were quantified annually up to Y5, and at Y7. Children whose titer decreased to below the seroprotection threshold (defined as an anti-HAV antibody concentration of ≥ 10 mIU/mL in a microparticle enzyme immunoassay up to Y5, or ≥ 3 mIU/mL in an electrochemiluminescence immunoassay at Y7) received a routine booster dose of the same HA vaccine. This report summarizes the data at 7 year after the first vaccination. Of 546 participants initially included, 264 participants remained at Y7 and provided blood samples. Of these, 204 having received one HA primary dose as a toddler were still seroprotected at Y7; titers for a further 7 also having received one HA dose as a toddler fell to below the seroprotection threshold and they therefore received a booster; all 53 having received 2 HA doses as a toddler and still present at Y7 remained seroprotected at Y7. One or 2 primary doses of this HA vaccine in toddlers result in very good persistence of anti-HAV up to 7 year post-first vaccination.

Espul, C., Benedetti, L., Linares, M., Cuello, H. and Rasuli, A. "[Five-year follow-up of immune response after one or two doses of inactivated hepatitis A vaccine given at 1 year of age in the Mendoza Province of Argentina.](#)" *J Viral Hepat* **2015** 22(4): 453-458. Programa de lucha contra las hepatitis virales (PRHEVI), Ministerio de Salud/Hospital Central de Mendoza, Mendoza, Argentina.

Our study was conducted to further investigate the single-dose approach of hepatitis A vaccination, while providing supportive data on the flexibility of booster administration. Participants received at least one dose of Avaxim 80U Pediatric at 11-23 months of age, and they will be followed for 10 years. We report here the fourth and fifth years after the first vaccination. Group assignment was based on whether the children received 1 dose and no booster during the study (Group 1) or 2 doses and no further booster (Group 2). Anti-HAV antibody concentrations were assessed at each annual visit. Of the 546 initial participants, 441 (80.8%) and 412 (75.5%) were followed up 4 and 5 years after vaccination, respectively. Of the 411 subjects evaluable at Year 5, 318 had received one vaccine dose and 85 had received two. Seroprotection rates were still high in Group 1 (99.7%) and in Group 2 (100%) 5 years after one or two doses of Avaxim 80U Pediatric, correspondingly. Anti-HAV geometric mean concentrations decreased in both groups compared to what they were 3 years after vaccination, while remaining well above the 10 mIU/mL threshold 5 years after vaccination. The highest concentrations were found in the children who received 2 vaccine doses. Hepatitis A humoral immunity induced by a single dose of inactivated hepatitis A vaccine can persist for at least 5 years in a paediatric population. The study results also support recommendations in favour of a flexible time window for booster vaccination.

Espul C, Benedetti L, Cuello H, Houillon G, Rasuli A. (2012). "[Persistence of immunity from 1 year of age after one or two doses of hepatitis A vaccine given to children in Argentina.](#)" *Hepat Med* **4**: 53-60.

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

From Pubmed search:

Argentina

Uruena, A., Gonzalez, J. E., Rearte, A., Perez Carrega, M. E., Calli, R., Pagani, M. F., Uboldi, A., Vicentin, R., Caglio, P., Canero-Velasco, M. C., Gentile A., Ramonet M., Vizzotti C. "[Single-dose Universal Hepatitis A Immunization in One-year-old Children in Argentina: High Prevalence of Protective Antibodies up to 9 Years After Vaccination.](#)" *Pediatr Infect Dis J* **2016** 35(12): 1339-1342

BACKGROUND:

Single-dose hepatitis A virus (HAV) vaccination was implemented in all Argentinean children 12 months of age in 2005. Previous studies demonstrated high prevalence of protective antibody response 4 years after single-dose vaccination. This study assessed long-term seroprotection against HAV after vaccination.

METHODS:

Children who received 1 dose of HAV vaccine at 1 year of age at least 6 years before enrollment were included at 5 centers in Argentina between 2013 and 2014. Demographic and socioeconomic characteristics were collected through a questionnaire. Blood samples were tested for anti-HAV antibodies. Antibody values ≥ 10 mIU/mL were considered seroprotective. Logistic regression analysis was performed to evaluate the association between demographic and socioeconomic variables and seroprotection.

RESULTS:

A total of 1088 children were included, with a median postvaccination interval of 7.7 years (range 6.3-9.2 years). Of these children, 97.4% (95% confidence interval: 96.3%-98.3%) had protective antibodies against HAV. No association between demographic or socioeconomic variables and seroprotection was found. Geometric

mean concentration of antibody levels against HAV was 170.5 mIU/mL (95% confidence interval: 163.2-178.2 mIU/mL).

CONCLUSIONS:

Single-dose universal hepatitis A immunization in 1-year-old children resulted in sustained immunologic protection for up to 9 years in Argentina. These findings, along with the low current disease burden, confirm the success of the intervention.

Vizzotti, C., Gonzalez, J., Rearte, A., Uruena, A., Perez Carrega, M., Calli, R., Gentile, A., Uboldi, A., Ramonet, M., Canero-Velasco, M., Diosque, M. "[Single-Dose Universal Hepatitis A Immunization in Argentina: Low Viral Circulation and High Persistence of Protective Antibodies Up to 4 Years.](#)" *J Pediatric Infect Dis Soc* **2015** 4(4): e62-67.

BACKGROUND:

Single-dose hepatitis A virus (HAV) vaccination was implemented in all Argentinean children aged 12 months in 2005. Between 2005 and 2011, a dramatic decline was observed in HAV infection rates, fulminant hepatitis, and liver transplantation. This study assessed current viral circulation and estimated protective antibody persistence 4 years after vaccination.

METHODS:

Prevalence of prevaccination anti-HAV antibodies in 12-month-old children was evaluated as an indirect estimation of viral circulation (Group A). Seroprevalence was also measured in 5-year-old children who received 1 dose of HAV vaccine at 1 year of age (Group B). Blood samples were tested for immunoglobulin (Ig)G anti-HAV antibodies (seroprotection = ≥ 10 mIU/mL). All Group A-positive samples were tested for IgM anti-HAV antibodies to identify recent infections. Logistic regression analysis was done to evaluate associations between demographic and socioeconomic variables and seroprotection.

RESULTS:

Of 433 children from Group A, 29.5% (95% confidence interval [CI], 25.2-33.8) were positive for IgG anti-HAV antibodies with a geometric mean concentration (GMC) of 6.17 mIU/mL (95% CI, 5.33-7.15 mIU/mL); all IgM anti-HAV were negative. From 1139 in Group B, 93% (95% CI, 91.7-94.6) maintained seroprotection with a GMC of 97.96 mIU/mL (95% CI, 89.21-107.57 mIU/mL). Kindergarten attendance was associated with seroprotection in Group B (odds ratio [OR], 2.0; 95% CI, 1.26-3.3). In contrast, high maternal educational level was associated with a lack of seroprotection in this group (OR, .26; 95% CI, .09-.8).

CONCLUSIONS:

Single-dose, universal hepatitis A immunization in infants resulted in low HAV circulation and persistent immunologic protection up to 4 years in Argentina. Variables associated with presence or absence of seroprotection in vaccinated children could be related to differences in hygiene habits in settings with residual viral circulation.

Vizzotti C, González J, Gentile A, Rearte A, Ramonet M, Cañero-Velasco MC, Pérez Carrega ME, Uruena A, Diosque M. (2014). "[Impact of the single-dose immunization strategy against hepatitis A in Argentina.](#)" *Pediatr Infect Dis J* **33**(1): 84-88.

BACKGROUND: After a country wide outbreak occurred during 2003-2004, 1 dose of hepatitis A vaccine was introduced into Argentinian regular immunization schedule for all children aged 12 months in June 2005. The aim of this study was to assess the impact of this novel intervention. **METHODS:** A longitudinal analysis was done of hepatitis A virus (HAV) infection rates reported to the National Epidemiological Surveillance System from 2000 to 2011. Occurrence of fulminant hepatic failure (FHF) and liver transplantation cases up to 2011 were also assessed. Incidence rates and clinical impact were compared between pre- and postvaccination periods (2000-2002 vs. 2006-2011). Notification rates were also compared by age groups and geographical regions. **RESULTS:** Since 2006, an abrupt decline was observed in HAV infection rates, as well as in FHF and liver transplantation cases. The mean incidence rate of

7.9/100,000 in the postvaccination period represents a reduction of 88.1% ($P < 0.001$) when compared with the prevaccination period. Neither FHF nor liver transplantation due to HAV infection were observed since March 2007. Decline in incidence rates was evident in all geographical regions and all age groups but was higher in the prevaccination most affected areas and in young children. Although an absolute decrease was observed for cases and rates in all age groups, since 2006, a higher proportion of cases was observed in people >14 years of age. CONCLUSIONS: The single-dose vaccination strategy has been highly effective for controlling HAV infection in all age groups till now in Argentina. Long-term surveillance will be critical to document the sustained success of this unique intervention.

Gentile A, Ramonet MD, Ciocca M. (2013). "[[Hepatitis A immunisation in the Argentinean mandatory schedule](#)]." *Arch Argent Pediatr* **111**(2): 155-161.

Hepatitis A (HA) presents a benign evolution, but occasionally some patients develop a more severe disease. Previously to 2005 hepatitis A was an important cause of acute liver failure (ALF) and hepatic transplant. In 2003, a consensus in the Argentinian Pediatrics Society was done; it had just recommended the inclusion of the vaccine in the mandatory immunisation schedule. This was issued by the Health Ministry, and was applied on June 1st, 2005. The schedule was one dose at the age of one year of age. Since then, an important reduction of HA was registered, without any case of ALF since 2006. Follow-up studies so far showed low viral circulation and persistence of antibodies to 5 years later.

Blanco Fernández MD, Torres C, Riviello-López G, Poma HR, Rajal VB, Nates S, Cisterna DM, Campos RH, Mbayed VA. (2012). "[Analysis of the circulation of hepatitis A virus in Argentina since vaccine introduction](#)." *Clin Microbiol Infect* **18**(12): E548-551.

Hepatitis A virus (HAV) has shown intermediate endemicity in Argentina, but its incidence has decreased since vaccine introduction in 2005. Environmental surveillance was conducted in five rivers from Argentina from 2005 to 2012, complementing clinical information. HAV detection decreased since 2005, although its circulation continues, maintaining viral diversity but not undergoing antigenic drift. Most sequences belonged to subgenotype IA, closely related to Argentinean clinical sequences, but one belonged to proposed subgenotype IC, previously undetected in the country. Environmental surveillance might contribute to monitoring the single-dose vaccination schedule, representing not only strains causing disease but also the circulating population and the viral introductions.

Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Armoni J, Debbag R. (2011). "[Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program](#)." *Hepat Med* **3**: 99-106.

INTRODUCTION: Hepatitis A virus (HAV) infection is a vaccine-preventable disease. The most severe complication in children is fulminant hepatic failure (FHF), estimated to occur in 0.4% of cases; patients with FHF often require a liver transplant (LT). Following another outbreak of HAV infection in Argentina during 2003-2004, a one-dose HAV universal immunization (UI) program was started in 2005, resulting in a reduction in the incidence of HAV infection. We have investigated the impact of HAV UI on the trends in the occurrence of FHF and LT in children. METHODS: All pediatric cases of FHF admitted to four pediatric centers in Buenos Aires during March 1993-July 2005 were retrospectively reviewed, and data of cases during August 2005-December 2008 were collected. Information about demography, HAV infections and vaccination status, diagnostic data for FHF using the Pediatric Acute Liver Failure criteria, clinical laboratory results, encephalopathy, the severity of liver disease using the Pediatric End Stage Liver Disease score, assessment of patients on the LT waiting list using King's College Criteria for LT, treatment given for FHF (pre- and post-transplant), and clinical outcome were collected using a case report form. The frequency and outcomes of HAV-associated FHF and LT cases before and after UI were analyzed. RESULTS: During the pre-immunization period, March 1993-July 2005, 54.6% ($N = 165$) of FHF cases

were caused by HAV; HAV-associated FHF cases peaked during 2003-2004. During the post-immunization period, August 2005-December 2008, only 27.7% (N = 18) of FHF cases were caused by HAV infection; only one of these patients had received the HAV vaccine (one dose only). The number of HAV-associated FHF cases decreased from 2005, and no cases were reported from November 2006-December 2008. Multivariate analyses showed that the association of FHF with HAV infection rather than other etiologies decreased with increasing age (P = 0.03), UI against HAV (P = 0.002), and anti-actin antibodies (P = 0.002), and increased with increasing weight (P = 0.0004). CONCLUSIONS: The number of children with HAV-associated FHF in Argentina has strongly decreased since the initiation of the UI program. Further monitoring is required to confirm the long-term health and economic benefits of UI against HAV infection.

Vacchino, M. N. (2008). "[Incidence of Hepatitis A in Argentina after vaccination.](#)" *J Viral Hepat* **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.

Brazil

Souto, F. J. D., de Brito, W. I. and Fontes, C. J. F. [Impact of the single-dose universal mass vaccination strategy against hepatitis A in Brazil.](#) *Vaccine* **2019** 37(6): 771-775.

Universal vaccination of children against hepatitis A was introduced in 2014 in Brazil as a single-dose schedule. We analyzed the numbers of reported cases of hepatitis A virus infection (HAV) from 2010 to 2017 to evaluate the initial impact of that intervention. Data were assessed and has been freely available on the Brazilian Ministry of Health website. The HAV incidence was steady around 6000 cases per year until 2014. Between 2014 and 2016, there was a 85.5% cumulative drop, independent of gender and geographical macroregions. The fall was especially significant among toddlers (96.8%). In 2017, cases increased due to an outbreak among male adults in São Paulo. Decrease in incidence continued to occur for females and for those under 15 years of age. Data show that there was a significant decrease in HAV cases number in Brazil from 2015 after the introduction of single-dose HAV vaccine program.

Brito, W. I., Alves-Junior, E. R., Oliveira, R. M. and Souto, F. J. D. "[Initial evaluation of universal immunization with a single dose against hepatitis A virus in Central Brazil.](#)" *Braz J Infect Dis* **2018** 22(3): 166-170. Universidade Federal de Mato Grosso, Hospital Universitario Julio Muller, Cuiaba, MT, Brazil.

Vaccination against the hepatitis A virus (HAV) administered in two doses has been used effectively in universal child immunization programs in several countries. A single-dose vaccination was adopted in some low-income countries in an attempt to reduce costs without losing effectiveness. In 2014, single-dose universal vaccination was introduced in Brazil for children aged two years. Since such strategy is still not universally accepted, its efficacy should be compared to the two-dose strategy. To assess the humoral response after the single-dose HAV vaccination schedule, a cross-sectional study was conducted in Primavera do Leste, in Mato Grosso state, Central Brazil, including 265 children vaccinated through the National Immunization Program. Blood was collected by using a digital puncture and further applied to filter paper cards. Anti-HAV was detected in 218 out of 265 dried blood spots (DBS). Blood venous samples were collected from 34 out of 47 children who were not anti-HAV positive in DBS samples. Eighteen of them tested positive for anti-HAV, giving a final score of 93.6% (236/252) of seropositivity. In conclusion, this study demonstrated a high rate of anti-HAV positivity in the short term after single-dose hepatitis A vaccination in the population investigated. Moreover, the DBS was shown to be a reliable tool for detecting anti-HAV antibodies.

Nicaragua

Mayorga O, Bühler S, Jaeger VK, Bally S, Hatz C, Frösner G, Protzer U, Van Damme P, Egger M, Herzog C. (2016). ["Single-Dose Hepatitis A Immunization: 7.5-Year Observational Pilot Study in Nicaraguan Children to Assess Protective Effectiveness and Humoral Immune Memory Response."](#) J Infect Dis 214(10): 1498-1506.

BACKGROUND: Universal 2-dose hepatitis A virus (HAV) vaccination of toddlers effectively controls hepatitis A. High vaccine costs, however, impede implementation in endemic countries. To test single-dose vaccination as a possible alternative, we initiated an observational, longitudinal study in Nicaragua, to assess protective effectiveness and-through challenge vaccination-humoral immune memory response. METHODS: After a 2003 serosurvey, 130 originally seronegative children received one dose of virosomal HAV vaccine in 2005, followed by yearly serological and clinical assessments until 2012. After 7.5 years, a vaccine booster was administered. Concurrent antibody screening of patients presenting with hepatitis symptoms documented persistent HAV circulation in the communities studied. RESULTS: Between serosurvey and vaccination, 25 children contracted hepatitis A subclinically (>8000 mIU/mL anti-HAV). In the remaining 105 children, immunization resulted in anti-HAV levels of 17-572 mIU/mL. Based on the $\geq 15\%$ annual infection risk, an estimated 60% of children were exposed to HAV encounters during follow-up. No child presented with hepatitis symptoms. Serological breakthrough infection (7106 mIU/mL) was documented in 1 child, representing an estimated protective effectiveness of 98.3% (95% confidence interval, 87.9-99.8). Boosting elicited an average 29.7-fold increase of anti-HAV levels. CONCLUSIONS: In children living in hyperendemic settings, a single dose of virosomal HAV vaccine is sufficient to activate immune memory and may provide long-term protection.

Mayorga O, Herzog C, Zellmeyer M, Loáisiga A, Frösner G, Egger M. (2003). ["Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial."](#) J Infect Dis 188(5): 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.

17:30-17:40

Presentation 2 : Experience with one dose in Asia

An update on the use of single dose hepatitis A vaccines in China.

Xuan-Yi Wang

From speaker:

Chen, Y., Zhou, C. L., Zhang, X. J., Hao, Z. Y., Zhang, Y. H., Wang, S. M., Ma, J. C., Zhao, G., Qiu, C., Zhao, Y. L., Wang B., Wang X.Y. [Immune memory at 17-years of follow-up of a single dose of live attenuated hepatitis A vaccine.](#) *Vaccine* **2018** 36(1): 114-121.

BACKGROUND:

In recent years, hepatitis A virus (HAV) infection has declined considerably in **China**, associated with wide deployment of HAV vaccines and improvement in socio-economic indicators. Towards the elimination of HA in the country, we assessed the duration and characteristics of immunity conferred by the widely used, locally manufactured HAV vaccine.

METHODS:

This is a longitudinal cohort study that followed recipients of a live attenuated HAV vaccine 17 years after the initial administration. Blood samples were collected from participants pre- and two-week post-booster HAV vaccine dose. Serum anti-HAV antibody was measured by ELISA method. Memory B and T cells were determined by ELISPOT and Flow Cytometry assays, respectively.

RESULTS:

A robust anamnestic response was observed two-week post-challenge. Both HAV-specific memory B cell and T cells remained, and responded quickly when re-encountering HAV. The magnitude of recall responses was present, regardless of the status of the serum anti-HAV antibody pre-booster.

CONCLUSIONS:

We demonstrated long-term immunity from the live attenuated HAV vaccine, including antibody persistence and immunological memory. Considering the conditions that make elimination of infectious diseases feasible, following polio, hepatitis A could be targeted for elimination in China.

Xu, Z. Y. and X. Y. Wang (2014). "[Live attenuated hepatitis A vaccines developed in China.](#)" *Hum Vaccin Immunother* **10**(3): 659-666.

Two live, attenuated hepatitis A vaccines, H 2 and LA-1 virus strains, were developed through serial passages of the viruses in cell cultures at 32 degrees C and 35 degrees C respectively. Both vaccines were safe and immunogenic, providing protection against clinical hepatitis A in 95% of the vaccinees, with a single dose by subcutaneous injection. The vaccine recipients were not protected from asymptomatic, subclinical hepatitis A virus (HAV) infection, which induced a similar antibody response as for unvaccinated subjects. A second dose caused anamnestic response and can be used for boosting. Oral immunization of human with H 2 vaccine or of marmoset with LA-1 vaccine failed, and no evidence was found for person-to-person transmission of the H 2 strain or for marmoset-to-marmoset transmission of LA-1 strain, by close contact. H 2 strain was genetically stable when passaged in marmosets, humans or cell cultures at 37 degrees C; 3 consecutive passages of the virus in marmosets did not cause virulence mutation. The live vaccines offer the benefits of low cost, single dose injection, long-term protection, and increased duration of immunity through subclinical infection. Improved sanitation and administration of 150 million doses of the live vaccines to

children had led to a 90% reduction in the annual national incidence rate of hepatitis A in China during the 16-year period, from 1991 to 2006. Hepatitis A immunization with both live and inactivated HA vaccines was implemented in the national routine childhood immunization program in 2008 and around 92% of the 16 million annual births received the affordable live, attenuated vaccines at 18 months of age. Near elimination of the disease was achieved in China for 14 years following introduction of the H 2 live vaccine into the Expanded Immunization Program (EPI) in 1992.

From Pubmed search:

China

Liu X, Yang C, Qu X, Li N, Huang X, Yang Y, Zhao Y, Wang Y, Zhou H. (2019). "[Vaccination coverage and its determinants of live attenuated hepatitis A vaccine among children aged 24-59 months in 20 rural counties of 10 provinces of China in 2016.](#)" *Hum Vaccin Immunother*: 1-5.

Objective: To understand one single dose coverage of live attenuated hepatitis A vaccine and its determinants among children aged 24-59 months in 20 rural counties of 10 provinces of China in 2016. **Methods:** In 20 counties, using three-stage probability proportion to size sampling, 1979 children aged 24-59 months with a vaccination card were selected from 20 rural counties in 2016. Socio-demographic and socio-economic characteristics of children and their caregivers were acquired from face-to-face questionnaire survey and copies of the vaccination cards. We used multivariate logistic regression models to identify the determinants of one single dose coverage of live attenuated hepatitis A vaccine. **Results:** In 2016, the overall one single dose coverage of live attenuated hepatitis A vaccine among children aged 24-59 months in rural areas of China was 77.1%. The adjusted analysis showed that being in second birth order (adjusted OR: 1.40; 95%CI: 1.03-1.90), being in third birth order or more (adjusted OR: 2.10; 95%CI: 1.26-3.51), being born at home (adjusted OR: 2.01; 95%CI: 1.04-3.88) and having the lowest per capita income of household (adjusted OR: 2.36; 95%CI: 1.11-4.99) were significantly related to being unvaccinated one single dose coverage of live attenuated hepatitis A vaccine against hepatitis A virus. **Conclusion:** one single dose coverage of live attenuated hepatitis A vaccine was still at a low level in 20 rural counties of 10 provinces in China. To improve the coverage of live attenuated hepatitis A vaccine, the government should pay more attention to the disadvantaged groups, especially the children who were in second birth order or higher, or delivered at home, or who have the lowest per capita income of household.

Sun, X., Wang, F., Zheng, H., Miao, N., Yuan, Q., Cui, F., Yin, Z., Zhang, G. and Levine, H. "[The impact of expanded program on immunization with live attenuated and inactivated Hepatitis A vaccines in China, 2004-2016.](#)" *Vaccine* **2018** 36(10): 1279-1284.

INTRODUCTION:

Since 2008, two types of hepatitis A (HepA) vaccines were integrated into the expanded program on immunization (EPI) in China. Children were given either one dose of live attenuated HepA (L-HepA) or two doses of inactivated HepA (I-HepA), depending on geographic regions. We sought to evaluate the impact of the EPI on HepA incidence in China.

METHODS:

We reviewed the epidemiology of HepA during 2004-2016 from National Notifiable Disease Reporting System (NNDRS). We collected data of L-HepA and I-HepA coverage from Children Immunization Information Management System (CIIMS). Based on the regions where two types of HepA vaccines were used, the coverage and incidence of HepA were compared over time.

RESULTS:

In 2008-2016, the HepA vaccine coverage was 98.8% among target children, with 99.6% in I-HepA region and 98.7% in L-HepA region. HepA incidence declined by 78.0% and 82.3% in L-HepA region and I-HepA region, respectively, without significant difference. Dramatic decline were seen in all age groups of both regions.

CONCLUSION:

The study suggests that the EPI, with high coverage for both I-HepA and L-HepA, had positive impact on HepA incidence in China.

Zhang, Z., Zhu, X., Hu, Y., Liang, M., Sun, J., Song, Y., Yang, Q., Ji, H., Zeng, G., Song, L., Chen J. "[Five-year antibody persistence in children after one dose of inactivated or live attenuated hepatitis A vaccine.](#)" *Hum Vaccin Immunother* **2017** 13(6): 1-6.

In **China**, both inactivated hepatitis A (HA) vaccine and live attenuated HA vaccine are available. We conducted a trial to evaluate 5-year immune persistence induced by one dose of inactivated or live attenuated HA vaccines in children. Subjects with no HA vaccination history had randomly received one dose of inactivated or live attenuated HA vaccine at 18–60 months of age. Anti-HAV antibody concentrations were measured before vaccination and at the first, second, and fifth year after vaccination. Suspected cases of hepatitis A were monitored during the study period. A total of 332 subjects were enrolled and 182 provided evaluable serum samples at all planned time points. seropositive rate at 5 y was 85.9% in the inactivated HA vaccine group and 90.7% in the live attenuated HA vaccine group. GMCs were 76.3% mIU/ml (95% CI: 61.7 – 94.4) and 66.8mIU/ml (95% CI: 57.8 – 77.3), respectively. No significant difference in antibody persistence between 2 groups was found. No clinical hepatitis A case was reported. A single dose of an inactivated or live attenuated HA vaccine at 18–60 months of age resulted in high HAV seropositive rate and anti-HAV antibody concentrations that lasted for at least 5 y.

Cui F, Liang X, Wang F, Zheng H, Hutin YJ, Yang W. [Development, production, and postmarketing surveillance of hepatitis A vaccines in China.](#) *J Epidemiol.* **2014**;24:169–77.

China has long experience using live attenuated and inactivated vaccines against hepatitis A virus (HAV) infection. We summarize this experience and provide recent data on adverse events after immunization (AEFIs) with hepatitis A vaccines in China. We reviewed the published literature (in Chinese and English) and the published Chinese regulatory documents on hepatitis A vaccine development, production, and postmarketing surveillance of AEFI. We described the safety, immunogenicity, and efficacy of hepatitis A vaccines and horizontal transmission of live HAV vaccine in China. In clinical trials, live HAV vaccine was associated with fever (0.4%–5% of vaccinees), rash (0%–1.1%), and elevated alanine aminotransferase (0.015%). Inactivated HAV vaccine was associated with fever (1%–8%), but no serious AEFIs were reported. Live HAV vaccine had seroconversion rates of 83% to 91%, while inactivated HAV vaccine had seroconversion rates of 95% to 100%. Community trials showed efficacy rates of 90% to 95% for live HAV and 95% to 100% for inactivated HAV vaccine. Postmarketing surveillance showed that HAV vaccination resulted in an AEFI incidence rate of 34 per million vaccinees, which accounted for 0.7% of adverse events reported to the China AEFI monitoring system. There was no difference in AEFI rates between live and inactivated HAV vaccines. Live and inactivated HAV vaccines manufactured in China were immunogenic, effective, and safe. Live HAV vaccine had substantial horizontal transmission due to vaccine virus shedding; thus, further monitoring of the safety of virus shedding is warranted.

Liu, X. E., Wushouer, F., Gou, A., Kuerban, M., Li, X., Sun, Y., Zhang, J., Liu, Y., Li, J. and Zhuang, H. "[Comparison of immunogenicity between inactivated and live attenuated hepatitis A vaccines: a single-blind, randomized, parallel-group clinical trial among children in Xinjiang Uighur Autonomous Region, China.](#)" *Hum Vaccin Immunother* **2013** 9(7): 1460-1465.

OBJECTIVES:

To compare immunogenicity among an inactivated hepatitis A vaccine (Healive®) with one-dose and two-dose regimens, and three kinds of live attenuated vaccines in children.

METHODS:

A single-blind, randomized, parallel-group clinical trial was conducted among healthy children aged 1.5-6 y in Xinjiang Uighur Autonomous Region, China. Subjects were

randomly assigned to 5 groups. Two groups were administered one-dose or two-dose inactivated vaccine and the remaining groups were immunized with one of three kinds of attenuated vaccines, respectively. Serum samples were collected at 6- and 12-mo follow-ups. Anti-HAV IgG was measured with a microparticle enzyme immunoassay.

RESULTS:

No significant differences were observed in seroconversion rates (seroprotection rates) among the five groups at 6 or 12 mo ($p>0.05$). The geometric mean concentration (GMC) of anti-HAV IgG was significantly higher in the two-dose Healive(®) group than in the one-dose Healive(®) group and the attenuated vaccine groups at 12 mo (932.4 vs. 112.7, 135.8, 203.3, 212.8 mIU/ml, respectively, $p<0.05$). In the one-dose Healive(®) group, the GMC was significantly lower than that in the attenuated vaccine B and C groups at 6 mo (152.6 vs. 212, 204 mIU/ml, $p<0.05$) and at 12 mo (112.7 vs. 203.3, 212.8, $p<0.05$), but was similar to the attenuated vaccine A group at 12 mo (112.7 vs. 135.8 mIU/ml, $p>0.05$). The GMCs were significantly higher in the 1-2 y of age group than in the 3-6 y of age group for all types of vaccines except the attenuated vaccine C ($p<0.05$) at 12 mo.

CONCLUSIONS:

A higher GMC of anti-HAV IgG was induced in the two-dose Healive(®) than in the one-dose and the attenuated vaccines at 12 mo. The attenuated vaccine B or C produced higher GMCs than the one-dose Healive(®) at 6-12 mo after vaccination.

Zheng H, Chen Y, Wang F, Gong X, Wu Z, Miao N, Zhang X, Li H, Chen C, Hou X, Cui F, Wang H. (2011). "[Comparing live attenuated and inactivated hepatitis A vaccines: an immunogenicity study after one single dose.](#)" *Vaccine* **29**(48): 9098-9103.

INTRODUCTION: While three types of hepatitis A vaccines are available in **China**, little data are available to compare them in terms of early antibody response. We conducted a trial to compare antibody response at 7, 14 and 28 days. **METHODS:** We randomized primary school children in Gansu and Jilin provinces into four groups to receive either (1) Chinese live attenuated hepatitis A vaccine (H2 strain), (2) domestic inactivated hepatitis A vaccine (Healive((R))), (3) imported inactivated hepatitis A vaccine (Havrix((R))) or (4) hepatitis B vaccine (Control group). We compared groups at 7, 14 and 28 days in terms of proportion of sero-conversions (≥ 10 mIU/ml), and Geometric Mean Concentration (GMC) of antibodies measured with a Microparticle Enzyme Immunoassay (MEIA). We compared rates of self-reported adverse events following immunization (AEFI) in the first three days. **RESULTS:** 204 children received the H2 vaccine, 208 received Healive((R)), 214 received Havrix((R)), and 215 received hepatitis B vaccine (no differences across groups in terms of age, sex, weight and height). At seven days, sero-conversion proportions were 25%, 35%, 27% and 2% ($p<0.0001$) with GMC of 6 mIU/ml, 8 mIU/ml, 6 mIU/ml and 3 mIU/ml, respectively for the four groups. At 28 days, sero-conversion proportions were 98%, 100%, 93% and 3% ($p<0.0001$) with GMC of 47 mIU/ml, 71 mIU/ml, 67 mIU/ml and 3 mIU/ml, respectively. AEFI were benign and did not differ across groups ($p=0.94$). **CONCLUSIONS:** While our study was not able to identify differences between Havrix((R)), Healive((R)) and H2 vaccine in terms of sero-conversion proportion and GMC between seven and 28 days, further studies should evaluate non-inferiority or equivalence of the Chinese vaccines, particularly with respect to the GMC concentration for the H2 vaccine since it could affect long-term protection.

Zhuang FC, Mao ZA, Jiang LM, Wu J, Chen YG, Jiang Q, Chen NL, Chai SA, Mao JS. (2010). "[\[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* **31**(12): 1332-1335. **China**

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.

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**;19:189-95.

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 105/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.

India

Rao, S., Mao, J. S., Motlekar, S., Fangcheng, Z. and Kadhe, G. "[A review of immunogenicity and tolerability of live attenuated Hepatitis A vaccine in children](#)." *Hum Vaccin Immunother* **2016** 12(12): 3160-3165.

Changing epidemiology of Hepatitis A virus (HAV) has led to an increased susceptibility of adolescents and adults to the infection. Vaccination can remarkably reduce the incidence and associated morbidity of HAV infection. This review is focused on the safety and efficacy of H2 strain derived live attenuated Hepatitis A vaccine. We

found the vaccine to be highly immunogenic with minimal or negligible safety issues. Moreover, a single dose of live attenuated vaccine persists a long term immune response and can be a preferred option for developing countries. In 2014, **Indian Academy of Paediatrics (IAP)** also updated their recommendations for H2 vaccine as a single dose as against the previous 2 dose schedule. A focused approach to include the vaccine in national immunization program should be explored.

Mitra, M., Shah, N., Faridi, M., Ghosh, A., Sankaranarayanan, V. S., Aggarwal, A., Chatterjee, S., Bhattacharyya, N., Kadhe, G., Vishnoi, G., Mane, A. "[Long term follow-up study to evaluate immunogenicity and safety of a single dose of live attenuated hepatitis a vaccine in children.](#)" *Hum Vaccin Immunother* **2015** 11(5): 1147-1152.

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

Bhave S, Sapru A, Bavdekar A, Kapatkar V, Mane A. [Long-term immunogenicity of single dose of live attenuated hepatitis A vaccine in Indian children.](#) *Indian Pediatr*. **2015** Aug;52(8):687-90.

OBJECTIVES:

To assess immunogenicity of a single dose of live attenuated hepatitis A vaccine in Indian children, ten years after immunization.

METHODS:

Of 143 children vaccinated in 2004, 121 children were evaluated in 2014, clinically and for anti-HAV antibodies.

RESULTS:

13 children were early vaccine failures who received two doses of HAV vaccine subsequently. 106 (98%) of 108 remaining children had seroprotective levels with a geometric mean titer of 100.5 mIU/mL. On analysis of all 121 children, the immunogenicity was 87.6%.

CONCLUSION:

Single dose of live attenuated hepatitis A vaccine provides long-term immunity in Indian children.

Patwari, A. K. "[Programmatic perspective of single dose hepatitis A vaccine administered in childhood.](#)" *Indian Pediatr* **2015** 52(8): 661-662.

Comment on:

Long-term immunogenicity of single dose of live attenuated hepatitis A vaccine in Indian children. [*Indian Pediatr*. 2015]

Vashishtha, V. M., Choudhury, P., Kalra, A., Bose, A., Thacker, N., Yewale, V. N., Bansal, C. P. and Mehta, P. J. "[Indian Academy of Pediatrics \(IAP\) recommended immunization schedule](#)

[for children aged 0 through 18 years--India, 2014 and updates on immunization.](#) *Indian Pediatr* **2014** 51(10): 785-800.

Justification: There is a need to review/revise recommendations about existing vaccines in light of recent developments in the field of vaccinology.

Process: Following an IAP ACVIP meeting on April 19 and 20, 2014, a draft of revised recommendations for the year 2014 and updates on certain vaccine formulations was prepared and circulated among the meeting participants to arrive at a consensus.

Objectives: To review and revise recommendations for 2014 Immunization timetable for pediatricians in office practice and issue statements on certain new and existing vaccine formulations.

Recommendations: The major changes in the 2014 Immunization Timetable include two doses of MMR vaccine at 9 and 15 months of age, single dose recommendation for administration of live attenuated H2 strain hepatitis A vaccine, inclusion of two new situations in high-risk category of children in context with pre-exposure prophylaxis of rabies, creation of a new slot at 9-12 months of age for typhoid conjugate vaccine for primary immunization, and recommendation of two doses of human papilloma virus vaccines with a minimum interval of 6 months between doses for primary schedule of adolescent/preadolescent girls aged 9-14 years. There would not be any change to the committee's last year's (2013) recommendations on pertussis vaccination and administration schedule of monovalent human rotavirus vaccine. There is no need of providing additional doses of whole-cell pertussis vaccine to children who have earlier completed their primary schedule with acellular pertussis vaccine-containing products. A brief update on the new Indian Rotavirus vaccine, 116E is also provided. The committee has reviewed and offered its recommendations on the currently available pentavalent vaccine (DTwP+Hib+Hepatitis-B) combinations in Indian market. The comments and footnotes for several vaccines are also updated and revised.

Bhave S, Bavdekar A, Sapru A, Bawangade S, Pandi A. (2011). "[Immunogenicity of single dose live attenuated hepatitis a vaccine.](#)" *Indian Pediatr* 48(2): 135-137. **India**

A long-term immunogenicity study of a single dose live attenuated H2 strain hepatitis A vaccine is being conducted in healthy Indian children at KEM Hospital, Pune. 131 of the original 143 children vaccinated in 2004, were evaluated for anti-HAV antibodies 30 months post vaccination (2007). Seroprotective antibody levels >20 mIU/mL were demonstrated in 87.8 % subjects with an overall GMT of 92.02 mIU/mL. No hepatitis like illness was recorded in any of the subjects since vaccination.

Faridi MM, Shah N, Ghosh TK, Arankalle V, Aggarwal A, Sathiyasekaran M, Bhattacharya N, Vasanthi T, Chatterjee S, Choudhury J, Mitra M. [Immunogenicity and safety of live attenuated hepatitis A vaccine: a multicentric study.](#) *Indian Pediatr.* **2009**;46:29–34.

Objective: To evaluate immunogenicity and tolerability of single dose live attenuated injectable hepatitis A vaccine in four metropolitan cities of **India**.

Methods: Live attenuated hepatitis A vaccine was administered to 505 children aged 18 to 60 months in four centers across India. Immunogenicity of the vaccine was assessed by estimation of anti-HAV antibody titer at 6 weeks and 6 months following administration of the vaccine. Safety evaluation of the vaccine was also done during the visits.

Results: At 6 weeks, 480 subjects (95%) came for the follow-up and 411 (81.4%) subjects reported at the end of 6 months. The geometric mean titer (GMT) of anti-HAV antibody of the subjects who did not have the seroprotective titer at the baseline were assessed at 6 weeks and 6 months which was 81.04 mIU/ml and 150.66 mIU/ml respectively. At 6 weeks, 95.1 % seroconverted and at the end of 6 months, 97.9 % had seroconverted. Both solicited and unsolicited vaccine-induced local and systemic adverse events were insignificant at all the centers, except swelling and induration in a few.

Conclusion: Live attenuated injectable hepatitis A vaccine was immunogenic and tolerable with minimal reactogenicity, in this study of single dose schedule. Safety profile was also satisfactory in the study population.

Korea

Im, J. H., Woo, H. T., Ha, B. and Jung, J. "[Effectiveness of single-dose administration of inactivated hepatitis A virus vaccination in the Republic of Korea armed forces, 2013-2016.](#)" *J Viral Hepat* **2019**. Department of Infectious diseases, Inha University Hospital, Incheon, Republic of Korea.

The Republic of Korea Armed Forces has implemented the hepatitis A virus (HAV) vaccination programme with a single-dose administration schedule in new recruits since 2013. A single-dose administration was selected for economic feasibility. We analysed the effectiveness of the single-dose HAV vaccination in a young and healthy population. To measure the effectiveness of the programme, we observed the incidence of HAV between the vaccinated and unvaccinated groups. A comparison between the two groups during the vaccine introduction period (2013-2016) revealed a lower incidence rate of infection in the vaccinated group (3 cases/603 550 person-years) than in the unvaccinated group (21 cases/1 020 450 person-years). The effectiveness of single-dose HAV vaccination was found to be 75.85%.

Song, Y. J., Lim, J., Park, W. S., Sohn, H., Lee, M. S., Shin, D. H., Kim, C. B., Kim, H., Oh, G. J. and Ki, M. "[Seropositivity among Korean Young Adults Approximately 2 Years after a Single-Dose Vaccination against Hepatitis A Virus.](#)" *PLoS One* **2015** 10(11): e0142297.

We previously observed 80.7% seropositivity and a significant interaction between gender and hepatitis A virus (HAV) vaccine type (Havrix vs. Epaxal) on the seropositivity approximately 11 months after single-dose HAV vaccinations in Korean young adults. Our objective was to evaluate seropositivity approximately 2 years after a single-dose HAV vaccination and the influence of demographic characteristics on seropositivity, including the interaction between gender and vaccine type. Seronegative medical school students were randomly vaccinated with Havrix or Epaxal. Based on a total serum anti-HAV antibody titer cutoff of 20 IU/mL, 338 participants (76.0%) of the 445 vaccinees were seropositive 20-25 months after a single-dose HAV vaccination. The seropositive rates were similar after vaccination with Havrix (77.0%) and Epaxal (74.9%). Univariate analysis indicated that female ($p = 0.052$) and less obese ($p < 0.001$) participants had a higher seropositive rate, whereas other characteristics such as age, alcohol use, smoking history, vaccine type, and follow-up duration were not associated with seropositivity. Multivariate analysis indicated that women ($p = 0.026$) and participants with moderate alcohol use ($p < 0.001$) showed significantly higher seropositive rates than men and participants with no or low alcohol use, respectively. The seropositive rates after vaccination with Havrix and Epaxal were 70.9% and 67.5% in men and 87.7% and 91.3% in women, respectively (p for interaction = 0.304). Compared with the seropositive rate approximately 11 months after vaccination, the seropositive rate decreased substantially only in men in the Havrix group (11.0% points), and consequently, the interaction between gender and vaccine type disappeared while seropositivity remained high (87.7% and 91.3% in Havrix and Epaxal groups, respectively) among women approximately 2 years after vaccination. Further studies are needed to assess whether the seropositive rate would be maintained in all groups more than 2 years after a single-dose HAV vaccination.

Lim, J., Song, Y. J., Park, W. S., Sohn, H., Lee, M. S., Shin, D. H., Kim, C. B., Kim, H., Oh, G. J. and Ki, M. "[The immunogenicity of a single dose of hepatitis A virus vaccines \(Havrix\(R\) and Epaxal\(R\)\) in Korean young adults.](#)" *Yonsei Med J* **2014** 55(1): 126-131.

PURPOSE:

Assessing the immunogenicity of a single dose of hepatitis A virus (HAV) vaccines is important because some people receive only a single dose. However, previous studies have shown variable results and have not examined the effects of demographic characteristics other than gender. This study was performed to examine the immunogenicity of a single dose of HAV vaccine according to the vaccine type and demographic characteristics in young adults.

MATERIALS AND METHODS:

Seronegative medical school students were randomly allocated to receive either Havrix or Epaxal.

RESULTS:

After approximately 11 months, the seroconversion rate in 451 participants was 80.7%. In men, the Havrix group showed a significantly higher seroconversion rate (81.9%) than the Epaxal group (69.2%), whereas both vaccine groups showed similarly high immunogenicity in women (Havrix: 90.1%, Epaxal: 92.9%; P for interaction=0.062). According to the results of a multivariate analysis, Epaxal showed significantly lower immunogenicity than Havrix only in men. Age, obesity, drinking, smoking, and follow-up time did not significantly affect seroconversion in either gender.

CONCLUSION:

The seroconversion rate of single-dose HAV vaccines was low in men, particularly in those who received Epaxal. Our results suggest that gender effects should be considered when comparing the immunogenicity of different HAV vaccines.

17:40-17:50

Presentation 3 : Immune memory with one dose of hepatitis A vaccine – booster dose?

A single dose of inactivated hepatitis A vaccine promotes HAV-specific memory cellular response similar to that induced by a natural infection.

Juliana Gil Melgaço

From speaker:

Melgaco JG, Morgado LN, Santiago MA, Mendes de Oliveira J, Lewis-Ximenez LL, Hasselmann B, Cruz OG, Pinto MA, Vitral CL. [A single dose of inactivated hepatitis A vaccine promotes HAV-specific memory cellular response similar to that induced by a natural infection.](#) Vaccine. **2015**;33:3813–20.

Based on current studies on the effects of single dose vaccines on antibody production, Latin American countries have adopted a single dose vaccine program. However, no data are available on the activation of cellular response to a single dose of hepatitis A. Our study investigated the functional reactivity of the memory cell phenotype after hepatitis A virus (HAV) stimulation through administration of the first or second dose of HAV vaccine and compared the response to that of a baseline group to an initial natural infection. Proliferation assays showed that the first vaccine dose induced HAV-specific cellular response; this response was similar to that induced by a second dose or an initial natural infection. Thus, from the first dose to the second dose, increase in the frequencies of classical memory B cells, TCD8 cells, and central memory TCD4 and TCD8 cells were observed. Regarding cytokine production, increased IL-6, IL-10, TNF, and IFN γ levels were observed after vaccination. Our findings suggest that a single dose of HAV vaccine promotes HAV-specific memory cell response similar to that induced by a natural infection. The HAV-specific T cell immunity induced by primary vaccination persisted independently of the protective plasma antibody level. In addition, our results suggest that a single dose immunization system could serve as an alternative strategy for the prevention of hepatitis A in developing countries.

From Pubmed search:

Chen, G. J., Sun, H. Y., Lin, K. Y., Cheng, A., Huang, Y. C., Hsieh, S. M., Sheng, W. H., Liu, W. C., Hung, C. C. and Chang, S. C. "[Serological responses to revaccination with hepatitis A virus \(HAV\) vaccines among HIV-positive individuals whose anti-HAV antibody waned after primary vaccination.](#)" *Liver Int* **2018** 38(7): 1198-1205.

BACKGROUND:

Among HIV-positive individuals, seroprotection for hepatitis A virus (HAV) following primary vaccination may wane with time. However, seroresponses to HAV revaccination are rarely investigated among HIV-positive patients who have lost protective antibodies after primary vaccination.

METHODS:

During the outbreak of acute hepatitis A in Taiwan after June 2015, HAV-seronegative, HIV-positive individuals were advised to receive two doses of HAV vaccines at 24 weeks apart. A retrospective 1:2 matched case-control study was conducted to compare the seroresponses at weeks 4, 24, 28 and 48 of HAV vaccination between those who underwent revaccination after having lost protective antibodies (case patients) and those who underwent primary vaccination (controls).

RESULTS:

Seventy-five case patients and 150 matched controls were included. The serological response rates were consistently higher among the case patients than controls: 88.1% vs 10.5% at week 4 following the first dose of HAV vaccination ($P < .001$); 93.3% vs 46.0% at week 24 (immediately before the second dose; $P < .001$); 98.7% vs 62.7% at week 28 (4 weeks after the second dose; $P < .001$) and 98.7% vs 92.7% at week 48 ($P = .06$). The anti-HAV antibody titres as reflected by the semi-quantitative assay for the case patients were also significantly higher than the controls at weeks 24, 28 and 48 following HAV vaccination.

CONCLUSIONS:

We demonstrated faster and better serological responses to HAV revaccination among the HIV-positive individuals who had lost their anti-HAV antibodies after primary vaccination. Single dose of HAV revaccination may provide rapid and sufficient seroresponses for HAV during the outbreak of acute hepatitis A.

Rosdahl, A., Herzog, C., Frosner, G., Noren, T., Rombo, L. and Askling, H. H. "[An extra priming dose of hepatitis A vaccine to adult patients with rheumatoid arthritis and drug induced immunosuppression - A prospective, open-label, multi-center study.](#)" *Travel Med Infect Dis* **2018** 21: 43-50.

Erratum In

[Corrigendum to " An extra priming dose of hepatitis A vaccine to adult patients with rheumatoid arthritis and drug induced immunosuppression - A prospective, open-label, multi-center study"](#) [*Trav. Med. Infect. Dis.* 21, January-February 2018, 43-50].

[*Travel Med Infect Dis.* 2019]

BACKGROUND:

Previous studies have indicated that a pre-travel single dose of hepatitis A vaccine is not sufficient as protection against hepatitis A in immunocompromised travelers. We evaluated if an extra dose of hepatitis A vaccine given shortly prior to traveling ensures seroconversion.

METHOD:

Patients with rheumatoid arthritis ($n = 69$, median age = 55 years) treated with Tumor Necrosis Factor inhibitor (TNFi) and/or Methotrexate (MTX) were immunized with two doses of hepatitis A vaccine, either as double dose or four weeks apart, followed by a booster dose at six months. Furthermore, 48 healthy individuals, median age = 60 years were immunized with two doses, six months apart. Anti-hepatitis A antibodies were measured at 0, 1, 2, 6, 7 and 12 months.

RESULTS:

Two months after the initial vaccination, 88% of the RA patients had protective antibodies, compared to 85% of the healthy individuals. There was no significant difference between the two vaccine schedules. At twelve months, 99% of RA patients and 100% of healthy individuals had seroprotective antibodies.

CONCLUSION:

An extra priming dose of hepatitis A vaccine prior to traveling offered an acceptable protection in individuals treated with TNFi and/or MTX. This constitutes an attractive pre-travel solution to this vulnerable group of patients.

Liao, Z., Feng, X. W., Liu, X. E., Zhou, Y. S., Wen, H. R., Peng, S. H., Zhang, Y. X., Xu, B., Zhuang, H. and Chen, H. Y. "[Immune response to one booster dose of inactivated hepatitis A vaccine in college students](#)." *Zhonghua Liu Xing Bing Xue Za Zhi* **2017** 38(5): 625-628.

Objective: To evaluate the safety and immunogenicity of one booster dose of inactivated hepatitis A vaccine in young adults. Methods: The subjects were selected from participants in the clinical trial of immunogenicity of inactivated and attenuated live hepatitis A vaccine in young adults. Eligible subjects were those who had received one dose of inactivated or attenuated hepatitis A vaccine, could be contacted and were sero-negative before primary vaccination. All qualified subjects were immunized with one booster dose of inactivated hepatitis A vaccine. The blood samples were collected before booster dose vaccination and 28 days after the immunization. Anti-HAV antibody titer ≥ 20 mIU/ml was considered to be sero-protected against hepatitis A virus. Results: The GMCs in the inactivated HAV vaccine group and attenuated live vaccine group before booster dose vaccination were 70.80 mIU/ml and 50.12 mIU/ml, respectively, and the sero-protection rates were 94.7% and 65.0%, respectively. After the vaccination of the booster dose, the sero-protection rates in both groups were 100.0%, and the GMCs were 2 816.09 mIU/ml and 2 654.55 mIU/ml, respectively. Conclusion: The GMCs and sero-protection rates of anti-HAV antibody in young adults declined after three years of the primary vaccination. However, the higher GMC and sero-protection rate were observed in the inactivated vaccine group than in the attenuated live vaccine group. Significant increases of GMC levels were observed in both groups after one booster dose vaccination.

Ott, J. J. and Wiersma, S. T. "[Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations](#)." *Int J Infect Dis* **2013** 17(11): e939-944.

OBJECTIVES:

Our objective was to identify evidence on the protection achieved by single-dose use of inactivated hepatitis A vaccines in order to evaluate the potential of a flexible booster administration in the form of a second dose.

METHODS:

A search was conducted for evidence on single-dose administration of inactivated hepatitis A vaccine and its potential impacts on long-term seropositivity rates. The main pharmaceutical vaccine manufacturer federations and the corresponding authors of manuscripts were approached for additional epidemiologic data. Correspondence was also sent to the Argentinean Ministry of Health.

RESULTS:

We identified 15 data sources reporting on protection achieved by a single dose of inactivated hepatitis A vaccine. The consistent finding was that the immune and memory response to the booster dose, or post-booster geometric mean titer, was independent of the time since initial vaccination. The impact of the booster on seroprotection was the same across sexes and age-groups. The longest time interval between initial and booster dose was 10.67 years, indicating that booster doses can be highly immunogenic for up to 10.67 years after primary vaccination.

CONCLUSIONS:

Protective anti-hepatitis A virus antibody levels after a single dose of inactivated hepatitis A vaccine can persist for almost 11 years and increase or reappear after booster vaccination. Further research on the vaccine doses needed to achieve long-term protection against hepatitis A infection is required.

Hatz C, van der Ploeg R, Beck BR, Frösner G, Hunt M, Herzog C. (2011). "[Successful memory response following a booster dose with a virosome-formulated hepatitis a vaccine delayed up to 11 years](#)." *Clin Vaccine Immunol* 18(5): 885-887.

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.

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 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.

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**;24:4450–7.

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

Beck BR, Hatz C, Bronnimann R, Herzog C. [Successful booster antibody response up to 54 months after single primary vaccination with virosome-formulated, aluminum-free hepatitis A vaccine.](#) *Clin Infect Dis*. **2003**;37:e126–8.

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.

Usonis V, Bakasenas V, Valentelis R, Katiliene G, Vidzeniene D, Herzog C. [Antibody titres after primary and booster vaccination of infants and young children with a virosomal hepatitis A vaccine \(Epaxal\).](#) *Vaccine*. **2003**;21:4588–92.

To evaluate the immunogenicity and tolerability of Epaxal in infants and children, 30 infants (aged 6-7 months) and 30 children (aged 5-7 years) received a single intramuscular dose of the aluminium-free virosomal hepatitis A virus (HAV) vaccine Epaxal and a booster dose after 12 months. Anti-HAV antibody titres were measured at baseline (before injection), at 1 and 12 months after primary vaccination, and 1 month after the booster vaccination. Sixteen evaluable infants had maternal anti-HAV antibodies at baseline. Complete seroprotection (titre \geq 20 mIU/ml) was achieved by

all infants and children at Month 1 and at Month 12. Additionally, all subjects showed a strong antibody response to booster vaccination. In infants without maternal anti-HAV antibodies, the response was four-fold higher than in those with maternal anti-HAV antibodies. Both doses of Epaxal were well tolerated. These preliminary data suggest that Epaxal is an effective hepatitis A vaccine for children and infants from 6 months of age.

Iwarson S, Lindh M, Widerstrom L. [Excellent booster response 4–6 y after a single primary dose of an inactivated hepatitis A vaccine](#). *Scand J Infect Dis*. **2002**;34:110–1.

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.

Yu Liang Zhao, Zong Da Meng, Zhi Yi Xu, Jun Jie Guo, Shao Ai Chai, Cheng Gang Duo, Xuan Yi Wang, Jin Feng Yao, Hong Bin Liu, Shun Xiang Qi, and Hui Bin Zhu. [H2 strain attenuated live hepatitis A vaccines: Protective efficacy in a hepatitis A outbreak](#). *World J Gastroenterol*. **2000** Dec 15; 6(6): 829–832.

AIM: To investigate the protective efficacy of H2 strain attenuated live hepatitis A vaccines (H2-strain vaccines) in hepatitis A (HA) out breaks.

METHODS: With the permission of their parents, 5551 pre-school and grade 1-3 primary school children were inoculated with 1 dose (106.5TCID50) 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 d. 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.

Landry P, Tremblay S, Darioli R, Genton B (2000). ["Inactivated hepatitis A vaccine booster given >/=24 months after the primary dose."](#) *Vaccine* 19(4-5): 399-402.

We investigated what happens with the immune response when people come back for their booster dose of inactivated hepatitis A vaccine later than the recommended time of 6-12 months after the primary dose. We recruited a group of 124 travellers who received either the primary doses of Havrix 720 (two doses) or of Havrix 1440 (one dose) >/=24 months before study entry. They received a booster dose of Havrix 1440 and blood was drawn 1 month later. As a control group, we recruited a group of 125 travellers who followed a recommended schedule with a primary dose at month 0 and a booster dose at months 6-12. For both study groups, the GMTs increased dramatically and similarly upon the booster immunisation. Although significantly more late travellers (32%) had lost detectable antibodies than controls (11%) before administration of the booster dose, all these subjects showed an anamnestic response to the booster dose. Delaying the booster dose up to 66 months after primary

vaccination did not seem to influence the immunogenicity of the booster dose. However, the recommended 6-12-month interval remains if detectable antibody titers are to be warranted constantly.

17:50-18:00

Presentation 4 : Economic analysis of the use of single dose

Economic analysis of the single-dose immunization strategy against hepatitis A in Argentina

Analia Uruena

From Speaker:

Vizzotti, C., Pippo, T., Uruena, A., Altuna, J., Palopoli, G., Hernandez, M. L., Artola, M. F., Fernandez, H., Orellano, P., Canero-Velasco, M. C., Ciocca, M., Ramonet M., Diosque M. "[Economic analysis of the single-dose immunization strategy against hepatitis A in Argentina.](#)" *Vaccine* **2015** 33 Suppl 1: A227-232.

BACKGROUND:

Vaccination against hepatitis A (HA) was carried out only as part of a limited outbreak control strategy in **Argentina** until June 2005, when universal immunization in infants was introduced into the national immunization calendar. A single-dose strategy was chosen instead of the standard two-dose schedule used elsewhere. This study aimed to estimate preventive, medical, and non-medical costs related to HA and to compare these costs in the periods before and after mass vaccination.

METHODS:

A retrospective analysis estimated treatment costs of HA and unspecified hepatitis cases reported to the National Health Surveillance System from 2000 to 2010. Costs related to immunization, fulminant hepatitis (FH), liver transplantation, and death were projected as well. Using a social perspective and a healthcare system perspective, costs in two 5-year periods were compared: 2000-2004 versus 2006-2010. Finally, we evaluated the impact of different discount rates, FH risk, and exclusion of unspecified hepatitis cases in the sensitivity analysis.

RESULTS:

Total HA and unspecified hepatitis cases decreased from 157,871 in 2000-2004 to 17,784 in 2006-2010. Medical and non-medical costs decreased from US\$11,811,600 and US\$30,118,222 to US\$1,252,694 and US\$4,995,895 in those periods, respectively. Immunization costs increased from US\$6,506,711 to US\$40,912,132. Total preventive, medical, and non-medical costs decreased from US\$48,436,534 to US\$47,160,721, representing a 2.6% reduction in total costs between the two periods. When a healthcare system perspective was considered or unspecified hepatitis cases were excluded, total costs were 130.2% and 30.8% higher in 2006-2010 than in the previous period, respectively.

CONCLUSION:

After implementation of the universal single-dose vaccination against HA in infants in Argentina, an impressive decline was observed in HA cases, with a decrease in medical and non-medical costs in the first 5 years. The single-dose strategy, which is simpler and less expensive than the standard two-dose scheme, can be a good alternative for future vaccination policies in other countries where HA is endemic.

From Pubmed search:

Carlos, F., Gomez, J. A., Anaya, P. and Romano-Mazzotti, L. "[Health economic assessment of universal immunization of toddlers against Hepatitis A Virus \(HAV\) in Mexico.](#)" *Hum Vaccin Immunother* **2016** 12(1): 52-63. a R A C Salud Consultores, S.A. de C.V. ; Ciudad de Mexico , Mexico.

Hepatitis A virus (HAV) has shifted from high to intermediate endemicity in **Mexico**, which may increase the risk of clinically significant HAV infections in older children,

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

Curran, D., de Ridder, M. and Van Effelterre, T. "[The impact of assumptions regarding vaccine-induced immunity on the public health and cost-effectiveness of hepatitis A vaccination: Is one dose sufficient?](#)" *Hum Vaccin Immunother* **2016** 12(11): 2765-2771.

Hepatitis A vaccination stimulates memory cells to produce an anamnestic response. In this study, we used a mathematical model to examine how long-term immune memory might convey additional protection against clinical/icteric infections. Dynamic and decision models were used to estimate the expected number of cases, and the costs and quality-adjusted life-years (QALYs), respectively. Several scenarios were explored by assuming: (1) varying duration of vaccine-induced immune memory, (2) and/or varying levels of vaccine-induced immune memory protection (IMP), (3) and/or varying levels of infectiousness in vaccinated individuals with IMP. The base case analysis assumed a time horizon of 25 y (2012 - 2036), with additional analyses over 50 and 75 y. The analyses were conducted in the Mexican public health system perspective. In the base case that assumed no vaccine-induced IMP, the 2-dose hepatitis A vaccination strategy was cost-effective compared with the 1-dose strategy over the 3 time horizons. However, it was not cost-effective if we assumed additional IMP durations of at least 10 y in the 25-y horizon. In the 50- and 75-y horizons, the 2-dose strategy was always cost-effective, except when 100% reduction in the probability of icteric infections, 75% reduction in infectiousness, and mean durations of IMP of at least 50 y were assumed. This analysis indicates that routine vaccination of toddlers against hepatitis A virus would be cost-effective in Mexico using a single-dose vaccination strategy. However, the cost-effectiveness of a second dose depends on the assumptions of additional protection by IMP and the time horizon over which the analysis is performed.

Suwantika, A. A., Beutels, P. and Postma, M. J. "[Cost-effectiveness of hepatitis A vaccination in Indonesia.](#)" *Hum Vaccin Immunother* **2014** 10(8): 2342-2349.

Objective

This study aims to assess the cost-effectiveness of hepatitis A immunization in **Indonesia**, including an explicit comparison between one-dose and two-dose vaccines.

Methods

An age-structured cohort model based on a decision tree was developed for the 2012 Indonesia birth cohort. Using the model, we made a comparison on the use of two-dose and one-dose vaccines. The model involved a 70-year time horizon with 1-month cycles for children less than 2 years old and annually thereafter. Monte Carlo simulations were used to examine the economic acceptability and affordability of the hepatitis A vaccination.

Results

Vaccination would save US\$ 3 795 148 and US\$ 2 892 920 from the societal perspective, for the two-dose and one-dose vaccine schedules, respectively, in the context of hepatitis A treatment. It also would save 8917 and 6614 discounted quality-adjusted-life-years (QALYs), respectively. With the vaccine price of US\$ 3.21 per dose, the implementation of single dose vaccine would yield an incremental cost-effectiveness ratio (ICER) of US\$ 4933 per QALY gained versus no vaccination, whereas the two-dose versus one-dose schedule would cost US\$ 14 568 per QALY gained. Considering the 2012 gross-domestic-product (GDP) per capita in Indonesia of US\$ 3557, the results indicate that hepatitis A vaccination would be a cost-effective intervention, both for the two-dose and one-dose vaccine schedules in isolation, but two-dose vaccination would no longer be cost-effective if one-dose vaccination is a feasible option. Vaccination would be 100% affordable at budgets of US\$ 71 408 000 and US\$ 37 690 000 for the implementation of the two-dose and one-dose vaccine schedules, respectively.

Conclusions

The implementation of hepatitis A vaccination in Indonesia would be a cost-effective health intervention under the market vaccine price. Given the budget limitations, the use of a one-dose-vaccine schedule would be more realistic to be applied than a two-dose schedule. The vaccine price, mortality rate and discount rate were the most influential parameters impacting the ICERs.

Suwantika, A. A., Yegenoglu, S., Riewpaiboon, A., Tu, H. A. and Postma, M. J. "[Economic evaluations of hepatitis A vaccination in middle-income countries.](#)" *Expert Rev Vaccines* **2013** 12(12): 1479-1494.

Economic evaluations of hepatitis A vaccination are important to assist national and international policy makers in different jurisdictions on making effective decisions. Up to now, a comprehensive review of the potential health and economic benefits on hepatitis A vaccination in **middle-income countries** (MICs) has not been performed yet. In this study, we reviewed the literature on the cost-effectiveness of hepatitis A vaccination in MICs. Most of the studies confirmed that hepatitis A vaccination was cost effective or even cost saving under certain conditions. We found that vaccine price, medical costs, incidence and discount rate were the most influential parameters on the sensitivity analyses. Vaccine price has been shown as a barrier for MICs in implementing universal vaccination of hepatitis A. Given their relatively limited financial resources, implementation of single-dose vaccination could be considered. Despite our findings, we argue that further economic evaluations in MICs are still required in the near future.

Ellis A, Ruttimann RW, Jacobs RJ, Meyerhoff AS, Innis BL. [Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted.](#) *Revista panamericana de salud publica/Pan American Journal of Public Health* **2007**;21:345–56.

Objectives: To investigate the cost-effectiveness of childhood vaccination against hepatitis A in the five geographic regions of Argentina, and to determine whether adding a second dose to the current one-dose schedule would provide health gains justifying its added cost.

Methods: A Markov model was used to consider four immunization options for the 2005 birth cohort: (1) no vaccination; (2) vaccination at 12 months of age, (3) vaccinations at 12 and 72 months of age; or (4) vaccinations at 12 and 18 months of age. Hepatitis A costs and consequences were predicted over 50 years. The cost-effectiveness of first and second vaccine doses was assessed through a range of vaccine prices and assumptions regarding the duration of vaccine protection. Costs and health gains (measured in quality-adjusted life years) were adjusted to present values using a 3% annual discount rate.

Results: The one-dose vaccination policy is predicted to reduce each birth cohort member's 50-year probability of overt hepatitis A from 7.2% to 4.1%. A second dose would reduce the probability to between 2.0% and 2.2%. Vaccination at 12 months of age, at 12 and 72 months, or at 12 and 18 months would reduce cases among personal contacts by 82%, 87%, and 92%, respectively. The first vaccine dose would meet

accepted standards of cost-effectiveness in each region, and reduce costs in the Northeast, Central, and South regions. Adding a second dose at age 18 months would be cost-effective in each region, and further reduce costs in the Cuyo region. If the duration of protection with one dose is less than anticipated, the second dose would be more cost-effective.

Conclusions: Greater health gains are derived from the first than second hepatitis A vaccine dose. However, this analysis supports the cost-effectiveness of providing both first and second doses to Argentina's children.

Hepatitis A outbreak management in a vaccine shortage era

England - Plunkett, J., Mandal, S., Balogun, K., Beebeejaun, K., Ngui, S. L., Ramsay, M. and Edelstein, M. "[Hepatitis A outbreak among men who have sex with men \(MSM\) in England, 2016-2018: The contribution of past and current vaccination policy and practice.](#)" *Vaccine X* **2019** 1: 100014.

Background

We report on an outbreak of hepatitis A among men who have sex with men (MSM) in England and its associated healthcare resource burden, the strategies used to control the outbreak and the role of past and current hepatitis A vaccination policy and practice in England.

Methods

National surveillance of hepatitis A, including reference laboratory confirmation and molecular sequencing, and a case questionnaire, was enhanced in 2017 to collect demographic and risk information, disease severity and healthcare utilisation. National Health Service (NHS) data was used to calculate associated healthcare costs.

Results

During the outbreak period (July 2016 to January 2018), 670 confirmed cases were identified in England, caused by three distinct viral strains. The public health response included raising public and professional awareness, reinforcing vaccine recommendations for MSM, contact tracing for post-exposure vaccination, and mass community vaccination where spill-over of infection into the general population occurred. Hepatitis A vaccine was centrally procured to ensure sexual health clinics in England could offer vaccination to MSM. Outbreak associated healthcare costs were estimated to be approximately £1,500,000.

Conclusions

While MSM are at increased risk of hepatitis A infection, inconsistent implementation of MSM vaccination policy in previous years led to an increasingly susceptible MSM population. The large number of cases, hospital admission rate and public health actions contributed to a significant healthcare burden. Recommending hepatitis A vaccination for MSM and clarifying commissioning responsibilities is essential to prevent future outbreaks.

Reference to: [Hepatitis A vaccination in adults – temporary recommendations. \(dose sparing advice, including single dose\)](#)

France - Farfour, E., Lesprit, P., Chan Hew Wai, A., Mazaux, L., Fourn, E., Majerholc, C., Bonan, B., Vasse, M. and Zucman, D. "[Acute hepatitis A breakthrough in MSM in Paris area: implementation of targeted hepatitis A virus vaccine in a context of vaccine shortage.](#)" *Aids* **2018** 32(4): 531-532.

The incidence of the hepatitis A virus (HAV) is increasing in Europe [1]. Sixteen European countries have reported 1500 cases of confirmed HAV and 2660 cases of probable or suspected HAV since June 2016: the cases mostly involved adult MSM. Confirmed cases were related to three distinct clusters of genotype IA. In France, increased cases of HAV have been reported within the Paris area since January 2017 and this outbreak is now spreading to other regions of France [2].

In our hospital, 257 HIV-positive MSMs and 31 HIV-negative MSMs taking preexposure prophylaxis (PrEP) were followed through specialized consultations. The median age of HIV-positive MSMs was 48.9 years (range: 41–56) and was 33.7 years (range: 31.1–36.4)

for MSMs taking PrEP. Between January and May 2017, we recorded four cases of acute HAV infections among HIV-positive MSMs but no incidences amongst MSMs taking PrEP [3].

In order to control this outbreak of HAV, the European Center for Disease Control (ECDC) recommends European countries offer and promote vaccination of MSMs against HAV [1]. In France, this vaccination has been recommended for MSMs since 2002 [4]. However, this outbreak is occurring within the context of a shortage of HAV vaccine [5]. Thus, the French national-health authorities have given priority to vaccinate MSMs with HAV vaccines, and have directed HAV vaccines into hospitals and clinics specialized in sexually transmitted diseases since March 2017. Before this date, the HAV vaccine was only available in pretravel consultations.

We reviewed HAV immunization of HIV-infected MSMs and MSMs taking PrEP in March 2017 in order to vaccinate nonimmunized individuals. HAV seronegative and individuals with an unknown serological status were contacted by phone to check their serological status. Seronegative individuals were offered HAV immunization to be delivered at the hospital's pharmacy. If the HAV-immunization status was unknown, HAV serology was assessed before vaccination. HAV immunization of individuals, including those that had received a first dose of vaccine, was then assessed later on 1 October 2017.

In March 2017, HAV antibodies were found in 76% of HIV-positive MSMs, with about 25% of these cases secondary to HAV vaccination. HAV-immunization was far lower in HIV-negative MSMs taking PrEP: 61% were seronegative. Between 25 March and 31 July 2017, all but one HAV seronegative patient who could be contacted received HAV vaccination. We vaccinated 32 HIV-positive MSMs and 18 MSMs taking PrEP. After the first dose of vaccine, anti-HAV antibodies were found in 85% of vaccinated individuals.

HAV immunization of individuals, including those that had received a first dose of vaccine, increased from 76% to 84% in HIV-positive MSMs and from 20 to 89% in MSMs taking PrEP. No case of HAV was reported in our cohort between 25 March and 1 October 2017, although the HAV outbreak still remains high at a regional level. As MSMs taking PrEP are younger than HIV-positive MSMs, and because immunization against HAV increases with age [6], this younger population is at higher risk of contracting HAV infection.

Despite the recommendations of the French health authorities to give priority to vaccinate MSMs for HAV, this outbreak continues in France, probably because of the slow implementation of vaccination [2]. We show here that a targeted active vaccination program can significantly increase HAV immunization in MSMs, with a rapid and positive decrease in acute HAV infections. In the context of this outbreak spreading in France, improved access to the HAV vaccine and monitoring of the implementation of HAV vaccination are urgently needed.

France - Zucman, D., Farfour, E., Mazaux, L., Hillaire, S., Dimi, S., Lesprit, P., Kahn, J. E. and Vasse, M. "[How to Face the Outbreak of Viral Hepatitis A in Men Who Have Sex With Men in France Without Vaccines?](#)" *Clin Infect Dis* **2017** 65(6): 1053-1054.

To the Editor—Sexual transmission of hepatitis A virus (HAV) among men who have sex with men (MSM) has been well described since 1981 [1], and multiple outbreaks have already occurred worldwide. Recently, 30 cases have been reported in Berlin [2], 17 in the Netherlands [3], 28 in the United Kingdom [4], and >1000 cases in Taiwan [5]. The European Centre for Disease Prevention and Control (ECDC) launched a rapid risk assessment in December 2016 (updated 23 February 2017) reporting 287 cases in 13 European Union countries since February 2016 originating from 3 clusters of virus [6]. Vaccination against HAV is very efficacious and, according to the ECDC, vaccination is the main preventive measure in the context of current outbreaks of HAV. For the MSM population, HAV vaccination is recommended in many countries within the European Union. Herein, we draw attention to the increasing risk of HAV in the MSM population, especially in France.

From January to March 2017, 5 cases of acute hepatitis A in unvaccinated MSM were diagnosed in our hospital: the median age of patients was 30 years (range 23 to 41 years). All patients presented with jaundice, liver enzyme elevation >1000 IU/L, and positive immunoglobulin M against HAV. Two were infected with human immunodeficiency virus (HIV) and were being followed in our clinic. The 3 other patients had been admitted to the emergency department. One was HIV-negative taking preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). The 5 patients did not know each other. Genotypic analysis showed the presence of 2 epidemic strains: RVM16-090 in 4 patients and VRD_521_2016 in 1 patient.

Since the early 2000s, unprotected sex in MSM is increasing in many countries. Large-scale PrEP with TDF and FTC has been implemented in France since January 2016 and there are now >3000 MSM taking PrEP. The initial prescription of PrEP was restricted to specialized physicians; however, prescription for maintenance treatment is now available from general practitioners since 1 March 2017.

There has been a large increase in sexually transmitted infections in MSM infected with HIV over the past years, and STIs are also a major problem in MSM taking PrEP.

Our findings and those from other countries suggest that further outbreaks of HAV are likely to occur in MSM. Sustained transmission and outbreaks could be prevented with a level of immunity >70% [7]. Seroprevalence of HAV antibody in MSM in Europe is unknown, but in the adult general population it has been estimated between 20% and 30% in the United States [8] and Europe [9]. In our cohort of MSM with HIV infection (257 patients), HAV antibodies have been found in 76%, with one-quarter of cases secondary to HAV vaccination. HAV immunization is far lower in HIV-negative MSM. For example, in MSM taking PrEP in our hospital (24 patients), 62.5% are seronegative for HAV antibodies.

The availability of the HAV vaccine has been greatly reduced in France and many countries over the past few months due to production issues [10]. This vaccine is no longer available in most French pharmacies and can only be found in scarce pretravel consultations.

Based on our data, because access to the HAV vaccine is so limited, around 24% of MSM infected with HIV and 62% of HIV-negative MSM taking PrEP are likely to be at risk of HAV infection. In this context, avoiding oral anal sex should be recommended for HAV-seronegative MSM. However, no specific health-promotion program has been released to target this issue. There is an urgent need for French health authorities and the pharmaceutical industry to improve access to the HAV vaccine.

Aggarwal, R. and Goel, A. "[Hepatitis A: epidemiology in resource-poor countries.](#)" *Curr Opin Infect Dis* **2015** 28(5): 488-496.

PURPOSE OF REVIEW:

Transmission of hepatitis A virus (HAV) infection is primarily fecal-oral. Symptomatic hepatitis, severe disease, and death are more likely to occur when infection occurs at an older age. Improvements in socioeconomic and hygienic conditions have led to a change in its epidemiology worldwide.

RECENT FINDINGS:

In the last two decades, improved hygiene in several resource-poor countries has led to reduced transmission of HAV, an increase in average age at infection, and, consequently, a paradoxical increase in morbidity and mortality because of hepatitis A. In Argentina, introduction of one dose (instead of the conventional two doses, to reduce costs) of inactivated HAV vaccine at 12-month age in a universal childhood immunization program during such 'epidemiologic transition' has markedly reduced the incidence of symptomatic hepatitis A, and of fulminant hepatitis and liver transplantation caused by HAV infection. The monetary value of medical and nonmedical benefits of this strategy outweighed the expenditure on vaccination. These excellent results were possibly contingent upon a high vaccination coverage.

SUMMARY:

Resource-poor countries should closely monitor the epidemiology of HAV infection and periodically undertake cost-effectiveness analyses of HAV immunization strategies. This should allow timely identification of epidemiologic transition and introduction of preventive strategies before HAV infection becomes a public health problem.

18:00 – 18:10

Presentation 5 : Scientific evidence for the use of one dose

Systematic literature review on efficacy/effectiveness of single dose hepatitis A paediatric vaccination programs

Eveline M. Bunge, PhD, Rosa C. van Hoorn, MSc (Pallas)

From speaker:

From Pubmed search:

Petrecz, M., Acosta, C. J., Klopfer, S. O., Kuter, B. J., Goveia, M. G., Stek, J. E., Schodel, F. P. and Lee, A. W. "[Safety and immunogenicity of VAQTA\(R\) in children 12-to-23 months of age with and without administration of other US pediatric vaccines.](#)" *Hum Vaccin Immunother* **2019** 15(2): 426-432.

Safety and immunogenicity data from 5 clinical trials conducted in the US in children 12-to-23 months old where HAVi was administered alone or concomitantly with other pediatric vaccines (M-M-R®II, Varivax®, TRIPEDIA®, Prevnar®, ProQuad®, PedvaxHIB®, and INFANRIX®) were combined. Among 4,374 participants receiving ≥ 1 dose of HAVi, 4,222 (97%) had safety follow-up and the proportions reporting adverse events (AE) were comparable when administered alone (69.4%) or concomitantly with other pediatric vaccines (71.1%). The most common solicited injection-site AEs were pain/tenderness (Postdose 1: 25.8%; Postdose 2: 26.1%) and redness (Postdose 1: 13.6%; Postdose 2: 15.1%). The most common vaccine-related systemic AEs were fever (≥ 100.4°F, 12.2%) and irritability (8.1%). Serious AEs (SAEs) were observed at a rate of 0.4%; 0.1% were considered vaccine-related. No deaths were reported within 14 days following a dose of HAVi. These integrated analyses also showed that protective antibody concentrations were elicited in 100% of toddlers after two doses and 92% after a single dose, regardless of whether HAVi was given concomitantly with other vaccines or alone. These results demonstrate that HAVi was well-tolerated whether given alone or concomitantly with other vaccines, with a low incidence of vaccine-related SAEs. HAVi was immunogenic in this age group regardless of whether administered with or without other pediatric vaccines and whether 1 or 2 doses were administered. HAVi did not impact the immune response to other vaccines. These data continue to support the routine use of HAVi with other pediatric vaccines in children ≥ 12 months of age.

Zhang, X., An, J., Tu, A., Liang, X., Cui, F., Zheng, H., Tang, Y., Liu, J., Wang, X., Zhang, N., Li, H. "[Comparison of immune persistence among inactivated and live attenuated hepatitis a vaccines 2 years after a single dose.](#)" *Hum Vaccin Immunother* **2016** 12(9): 2322-2326.

OBJECTIVE:

Compare immune persistence from one dose of each of 3 different hepatitis A vaccines when given to school-age children: a domestic, live attenuated hepatitis A vaccine (H2 vaccine); a domestic inactivated hepatitis A vaccine (Healive®); and an imported, inactivated hepatitis A vaccine (Havrix®).

METHODS:

School-age children were randomized into 1 of 4 groups to receive a single dose of a vaccine: H2 vaccine, Healive®, Havrix®, or hepatitis B vaccine [control]. Serum samples were collected 12 and 24 months after vaccination for measurement of anti-HAV IgG using microparticle enzyme immunoassay. Seropositivity was defined as ≥ 20 mUI/ml. We compared groups on seropositivity and geometric mean concentration (GMC).

RESULTS:

Seropositive rates for the H2, Healive®, Havrix®, and control groups were 64%, 94.4%, 73%, and 1.0%, respectively, 12-months post-vaccination; and 63%, 95.6%, 72%, and 1.0%, respectively 24-months post-vaccination. Seropositivity was greater for Healive® than for H2 and Havrix® at 12 months (p-values < 0.001) and 24 months (p-values < 0.0001). Average GMCs for the H2, Healive®, Havrix®, and control groups, in mIU/ml, were 29.7, 81.0, 36.4, and 2.9, respectively at 12 months, and 30.9, 112.2, 44.3, and 2.9, respectively, at 24 months. GMCs were greater for Healive® than for H2 and Havrix® at 12 months (p-values < 0.0001 and < 0.001, respectively) and 24 months (p-values < 0.001). No statistically significant differences in seropositivity or GMC were found within groups between 12 and 24 months.

CONCLUSION:

Immunity persisted 24 months after a single dose of inactivated hepatitis A vaccine and live attenuated hepatitis A vaccine.

Outbreak management with one dose

Sabria, A., Gregori, J., Garcia-Cehic, D., Guix, S., Pumarola, T., Manzanares-Laya, S., Cayla, J. A., Bosch, A., Quer, J. and Pinto, R. M. "[Evidence for positive selection of hepatitis A virus antigenic variants in vaccinated men-having-sex-with men patients: Implications for immunization policies.](#)" *EBioMedicine* **2019** 39: 348-357.

Background: A huge outbreak in the men-having-sex-with-men (MSM) has hit Europe during the years 2016-2018. Outbreak control has been hampered by vaccine shortages in many countries, and to minimize their impact, reduction of antigen doses has been implemented. However, these measures may have consequences on the evolution of hepatitis A virus (HAV), leading to the emergence of antigenic variants. Cases in vaccinated MSM patients have been detected in Barcelona, opening the possibility to study HAV evolution under immune pressure.

Methods: We performed deep-sequencing analysis of ten overlapping fragments covering the complete capsid coding region of HAV. A total of 14578255 reads were obtained and used for the analysis of virus evolution in vaccinated versus non-vaccinated patients. We estimated maximum and minimum mutation frequencies, and Shannon entropy in the quasispecies of each patient. Non-synonymous (NSyn) mutations affecting residues exposed in the capsid surface were located, with respect to epitopes, using the recently described crystal structure of HAV, as an indication of its potential role in escaping to the effect of vaccines.

Findings: HAV evolution at the quasispecies level, in non-vaccinated and vaccinated patients, revealed higher diversity in epitope-coding regions of the vaccinated group. Although amino acid replacements occurring in and around the epitopes were observed in both groups, their abundance was significantly higher in the quasispecies of vaccinated patients, indicating ongoing processes of fixation.

Interpretation: Our data suggest positive selection of antigenic variants in some vaccinated patients, raising concerns for new vaccination policies directed to the MSM group.

Neukam, K., Delgado Fernandez, M., Hernandez Quero, J., Rivero-Juarez, A., Llaves-Flores, S., Jimenez Onate, F., Gutierrez-Valencia, A., Espinosa, N., Viciano, P. and Lopez-Cortes, L. F. "[Brief Report: Response to Hepatitis A Virus Vaccine in HIV-Infected Patients Within a Retrospective, Multicentric Cohort: Facing Hepatitis A Outbreaks in the Clinical Practice.](#)" *J Acquir Immune Defic Syndr* **2019** 81(1): e1-e5.

BACKGROUND:

Various recent outbreaks of hepatitis A virus (HAV) have been described in men who have sex with men despite the availability of an effective vaccine. This study aimed to determine the current rates of seroconversion after receiving HAV vaccine (HAV-V) in HIV-infected patients under real-life conditions.

SETTING:

Patients were selected from a Southern Spanish multicentric cohort of HIV-infected subjects.

METHODS:

Retrospective analysis of all patients who received 2 doses (standard scheme) from April 2008 to May 2016 or from June 2016 to February 2018 facing an HAV outbreak with shortage of HAV-V, 1 single dose of HAV-V. Response to HAV-V was defined as positive anti-HAV IgG between 1 and 12 months after the last vaccination dose.

RESULTS:

A total of 522 patients were included, mainly men who have sex with men (86.2%). In the standard-dose group, 303/343 [88.3%; 95% confidence interval (CI): 84.5 to 91.5] patients showed seroconversion as compared with 149/179 (83.2%; 95% CI: 76.9 to 88.4) of the single-dose group (P = 0.107). Undetectable baseline HIV-RNA (adjusted odds ratio: 4.86; 95% CI: 1.86 to 12.75; P = 0.001) and a CD4 T-cell count $\geq 350/\mu\text{L}$ (adjusted odds ratio, 3.96; 95% CI: 1.26 to 12.49; P = 0.019) were independently associated with response to both regimens. A higher CD4/CD8 ratio was also associated with response after a single dose.

CONCLUSIONS:

HIV-infected patients should be encouraged to undergo HAV-V with 2 standard doses 6 months apart; a single dose achieves a high rate of seroconversion in those patients with favorable response factors and may be enough to limit future outbreaks in case of HAV-V shortage until supply is reestablished.

Campos-Outcalt, D. "[CDC provides advice on recent hepatitis A outbreaks.](#)" *J Fam Pract* **2018** 67(1): 30-32.

The epidemiology of hepatitis A virus disease has changed. Since July 2016, there have been 5 large outbreaks of infection involving more than 1600 cases, with affected states requiring assistance from the Centers for Disease Control and Prevention. Two of these outbreaks were foodborne, and 3 involved person-to-person transmission. This article reviews the extent of the outbreaks, what's behind the outbreaks, and outbreak-specific vaccine recommendations.

Parron, I., Planas, C., Godoy, P., Manzaneres-Laya, S., Martinez, A., Sala, M. R., Minguell, S., Torner, N., Jane, M. and Dominguez, A. [Effectiveness of hepatitis A vaccination as post-exposure prophylaxis.](#) *Hum Vaccin Immunother* **2017** 13(2): 423-427.

Hepatitis A (HA) has been a vaccine-preventable disease since 1995. In Catalonia, a universal combined hepatitis A+B vaccination program of preadolescents was initiated at the end of 1998. However, outbreaks are reported each year and post-exposure prophylaxis (PEP) with hepatitis A virus (HAV) vaccine or immunoglobulin (IG) is recommended to avoid cases.

The aim of this study was to assess the effectiveness of HAV vaccine and IG in preventing hepatitis A cases in susceptible exposed people.

A retrospective cohort study of contacts of HA cases involved in outbreaks reported in Catalonia between January 2006 and December 2012 was made. The rate ratios and 95% confidence intervals (CI) of HA in susceptible contacts receiving HAV or IG versus those without PEP were calculated.

There were 3550 exposed persons in the outbreaks studied: 2381 received one dose of HAV vaccine (Hepatitis A or hepatitis A+B), 190 received IG, and 611 received no PEP. 368 exposed subjects received one dose of HAV vaccine and IG simultaneously and were excluded from the study. The effectiveness of PEP was 97.6% (95% CI 96.2–98.6) for HAV vaccine and 98.3% (95% CI 91.3–99.9) for IG; the differences were not statistically significant (p = 0.36).

The elevated effectiveness of HAV vaccination for PEP in HA outbreaks, similar to that of IG, and the long-term protection of active immunization, supports the preferential use of vaccination to avoid secondary cases.

Whelan, J., Sonder, G. and van den Hoek, A. "[Declining incidence of hepatitis A in Amsterdam \(The Netherlands\), 1996-2011: second generation migrants still an important risk group for virus importation.](#)" *Vaccine* **2013** 31(14): 1806-1811

Background: The Netherlands is a very low endemic country for hepatitis A virus infections (HAV, notification rate of $< 1/100,000$). Historically in Amsterdam, a large proportion of infections are imported from Turkey and Morocco in children returning

from summer holiday. Annually since 1998, the public health service of Amsterdam has targeted these children for HAV vaccination before the summer. As the population of non-western immigrants and their descendents increases, we describe recent trends in HAV in ethnic groups in Amsterdam (1996-2011), identifying current risk groups and recommending targeted prevention through vaccination.

Methods: We studied all cases of (non-homosexually acquired) HAV infection notified in the Amsterdam region (1996-2011, n=819) by ethnic group and generation (first/second generation migrants: FGM and SGM respectively). Incidence rates were estimated as the average number of cases per 100,000/year. Using Poisson regression, we calculated incidence rate ratios (IRR) by ethnic group and generation adjusted for age and calendar year, and modeled seasonal variation using a smoothed time series. Results: Incidence of HAV in Amsterdam dropped from 24.8/100,000 population in 1996 (178 cases) to 1.0/100,000 in 2011 (8 cases). Since 2005, 56% of cases are imported, the majority (62%) in second generation migrant (SGM) children of Moroccan, or other non-western ethnic backgrounds. The adjusted IRR in SGM relative to the ethnic Dutch population was 3.7 (95% CI: 2.3-6.1) in Moroccan SGM, 4.3 (95%CI: 2.6-7.2) in SGM of other non-western backgrounds and 1.9 (95%CI: 0.8-4.1) in Turkish SGM.

Conclusion: Though incidence of HAV in Amsterdam has declined substantially since 1996, it is still higher in SGM children of Moroccan & other non-western ethnic backgrounds. In line with WHO recommendations of June 2012, introduction of single-dose HAV vaccination, targeted at SGM children from HAV endemic countries, could be considered within the routine childhood vaccination schedule.

Selnikova O, Moisseeva A, Zadorozhnaja V, Dokachenko A, Kachur N, Gavrik S. [Hepatitis A vaccination effectiveness during an outbreak in the Ukraine](#). *Vaccine*. **2008**;26:3135–7.

No abstract available.

Shen YG, Gu XJ, Zhou JH. [Protective effect of inactivated hepatitis A vaccine against the outbreak of hepatitis A in an open rural community](#). *World J Gastroenterol*.

2008;14:2771–5.

Aim: To evaluate the protective effect of inactivated hepatitis A vaccine (Healive) against hepatitis A outbreak in an emergency vaccination campaign.

Methods: During an outbreak of hepatitis A in Honghe Town, Xiuzhou District, Jiaxing City, Zhejiang Province, two nonrandomized controlled trials were conducted in September 2006. The first trial was to vaccinate 108 anti-HAV negative individuals with close contacts of the patients from September with 1 dose of an inactivated hepatitis A vaccine, Healive. The control group comprised of 115 individuals with close contacts of the patients before September. The second trial was to vaccinate 3365 primary and secondary school students who volunteered to receive a dose of Healive and 2572 students who did not receive Healive serving as its controls. An epidemiological survey was conducted to evaluate the protective efficacy of the vaccine.

Results: A total of 136 hepatitis A cases were reported during an outbreak that started in June, peaked in August and September, and ended after December of 2006. After a massive vaccination of school children in September, the number of cases declined significantly. No hepatitis A was detected in the 108 vaccinated individuals with close contacts of patients, whereas 4 cases of hepatitis A were found in the controls. The infection rate of hepatitis A was not significantly different in the individuals with close contacts of patients whether or not they received the vaccine ($P = 0.122$). No hepatitis A was detected in the 3365 students who received the vaccine, four cases of hepatitis A were found in the controls. The infection rate of students with or without vaccination was significantly different in the students who received the vaccine (0/3365 vs 4/2572, $P = 0.035$). The protective efficacy of the vaccine was 100%.

Conclusion: Inactivated hepatitis A vaccine demonstrates a good protective effect against an outbreak of hepatitis A.

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](#). *Eur J Clin Microbiol Infect Dis*. **2001**;20:185–7.

The epidemiology and control of hepatitis A virus was investigated during an outbreak of hepatitis A in a village in Israel. Postexposure administration of immune globulin to contacts was ineffective in controlling the outbreak. However, within 2 weeks of starting a mass immunization campaign with hepatitis A vaccine, the incidence of hepatitis A declined dramatically; the last case occurred 6 weeks after the immunization program began. The study demonstrated that while postexposure administration of immune globulin may diminish but not entirely arrest transmission of hepatitis A virus, active hepatitis A vaccination is a safe and effective intervention that can be used safely in hepatitis A virus antibody-positive children.

Immunogenicity in special populations

Garcia Garrido, H. M., Veurink, A. M., Leeflang, M., Spijker, R., Goorhuis, A. and Grobusch, M. P. "[Hepatitis A vaccine immunogenicity in patients using immunosuppressive drugs: A systematic review and meta-analysis.](#)" *Travel Med Infect Dis* **2019**: 101479.

INTRODUCTION:

Inactivated hepatitis A (HepA) vaccines are very immunogenic in healthy individuals; however, it remains unclear how different immunosuppressive regimens affect HepA vaccine immunogenicity. Our objective was to summarise the current evidence on immunogenicity of HepA vaccination in patients using immunosuppressive drugs.

METHODS:

We systematically searched the literature for studies on immunogenicity of inactivated HepA vaccines in adults using immunosuppressive drugs. Studies reporting seroconversion rates (SCR) 4-8 weeks after 1 and 2 doses of HepA vaccine in organ transplant recipients and patients with chronic inflammatory conditions were included in a meta-analysis.

RESULTS:

We included 17 studies, comprising 1,332 individuals. In healthy controls (2 studies), SCRs were 90-94% after the first dose and 100% after the second dose. In organ transplant recipients, SCRs ranged from 0 to 67% after the first dose of vaccine and 0-97% after the second dose. In patients with chronic inflammatory conditions, SCRs ranged from 6% to 100% after the first dose and from 48 to 100% after the second dose of vaccine. Patients using a TNF-alpha inhibitor versus conventional immunomodulators (e.g. methotrexate, azathioprine, corticosteroids) were more likely to seroconvert after the first dose of vaccine (OR12.1 [2.14-68.2]) but not after the second dose of vaccine (OR 0.78 [0.21-2.92]) in a meta-analysis.

CONCLUSION:

Studies evaluating HepA vaccine immunogenicity in immunosuppressive agents are heterogeneous. Overall, there is an impaired immune response following HepA vaccination in patients using immunosuppressive drugs, especially after only one dose of vaccine and in organ transplant recipients. HepA vaccination should therefore be considered before immunosuppressive therapy. Future research should focus on alternative vaccination regimens and long-term immunogenicity.

Dazley, J., Sison, R., Jimenez, H. and Slim, J. "[Hepatitis A Vaccine Response in Human Immunodeficiency Virus-infected Patients: The Interchangeability of Single Dose versus Double: A Prospective Look.](#)" *J Glob Infect Dis* **2016** 8(4): 161-162. (USA)

Hepatitis A virus (HAV) infection is problematic in HIV-infected patients. Comparison of single-antigen hepatitis A (HAVRIX) or double-antigen combined hepatitis A and hepatitis B (TWINRIX) vaccines showed better results in HIV-positive patients who received TWINRIX than those who received HAVRIX, depending on CD4 count. There is literature that indicates that the seroconversion rate is dependent on dose,[1,2] which is our focus. We report the rate of seroconversion in HIV patients of various levels of immunocompromised state in those given different doses of vaccine. This was a prospective, randomized, nonblinded, single-center study at an urban ambulatory care HIV clinic directed at giving primary and HIV-specific care. Patients were included in the study if they had either a single or double dose of hepatitis vaccine. Antibodies for HAV were measured pre- and post-vaccination using the Vitros ECI immunodiagnostic

system through the Laboratory Corporation of America (LabCorp). A positive test includes an antibody cutoff of <0.80 for anti-HAV total antibodies and a no detection of anti-HAV IgM at a cutoff of <0.80. Fisher's exact test was used for categorical variables in relation to antibody response after vaccination. Logistic regression was used for continuous variables in relation to antibody response. Of 1217 screened patients who received the hepatitis A vaccine, 40 were included, among them, 23 were male (57.5%) and 26 (65%) were African-American. Thirty-six (90%) patients had CD4 counts higher than 200 cells/mm³. Twenty-five (62.5%) patients had an HIV-1 viral load lower than 200 copies/mL. The median age was 47 years. Half of the patients received a single dose, while the other half received a double dose of the hepatitis A vaccine. Patients were included if they completed a series of hepatitis A vaccine after having a negative hepatitis A antibody. Table 1 outlines the results of the univariable analysis, in relation to the dependent variable (positive antibody response). Only age showed statistical significance, with younger age associated to antibody response after vaccination. In our experience, one or two doses appeared to provide comparable rates of immunogenicity. Virologic suppression and the CD4 count at the time of vaccination did not contribute to seroconversion rates. We previously observed that patients who receive a single dose even with high CD4 counts do not show higher rates of seroconversion, as with more recent studies.[3,4] In contrast to the previous studies, we did not observe that women show higher rates of seroconversion when given standard doses of the hepatitis A vaccine and, in our cohort, half of the participants responded to vaccination.[5,6] The main limitation of our study is the small sample size. While there may be no difference in the immune response of the HIV-positive patients who received either the single or the double dose, differences may become evident in studies with large sample size, enabling a comparison of patient groups with different CD4 counts, different contributing comorbidities, and levels of immunocompromise. Due to the small sample size, larger prospective, multi-center studies are needed to generate more reliable and convincing results.

Askling, H. H., Rombo, L., van Vollenhoven, R., Hallen, I., Thorner, A., Nordin, M., Herzog, C. and Kantele, A. "[Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study.](#)" *Travel Med Infect Dis* **2014** 12(2): 134-142.

BACKGROUND:

Hepatitis A vaccine is the most frequently used travel vaccine, yet data are scarce about its ability to induce protection in patients with concurrent immunosuppressive treatment. We assessed the immunogenicity of this vaccine in rheumatoid arthritis (RA) patients treated with tumour necrosis factor-inhibitors (TNFi) and/or methotrexate (MTX).

METHODS:

Hepatitis A vaccine was administered to non-immune RA patients at 0 and 6 months. Hepatitis A virus (HAV) antibodies were assessed at 0, 1, 6, 7, 12, and 24 months with a quantitative Chemiluminescent Microparticle Immuno Assay (CMIA) for HAV-IgG. Samples from month 1, 6, and 7 were, in addition, analysed with a microparticle EIA (MEIA) for anti-HAV IgM + IgG.

RESULTS:

The final study population consisted of 53 patients treated with TNFi (n = 15), TNFi + MTX (n = 21) or MTX (n = 17). One and six months after the first dose, 10% and 33% of the patients had attained seroprotection. One and six months after the second dose 83% and 72% were seroprotected. At month 24, 86% of the vaccinees showed protective levels.

CONCLUSIONS:

Two doses of hepatitis A vaccine at a 6-month interval provided protection for most immunosuppressed RA patients. A single dose does not seem to afford sufficient protection to this group of patients.

Jimenez, H. R., Hallit, R. R., Debari, V. A. and Slim, J. "[Hepatitis A vaccine response in HIV-infected patients: are TWINRIX and HAVRIX interchangeable?](#)" *Vaccine* **2013** 31(9): 1328-1333.

Introduction: Hepatitis A virus (HAV) infection remains a health risk for human immunodeficiency virus (HIV)-infected persons. Seroconversion rates among HAV vaccinated HIV-infected patients have been shown to be reduced compared to the general population. Current guidelines regard HAV vaccines as interchangeable, however there no published data comparing their efficacy in HIV patients. Our study evaluated the impact of different factors, including type of vaccination, on the immunologic response to hepatitis A vaccination in HIV-infected patients in the HAART era.

Methods: This was a retrospective review of 226 HIV-infected patients at our clinic in Newark, NJ. Patients were eligible if at least one dose HAVRIX (1440 ELISA units) or TWINRIX (720 ELISA units) was administered and had anti-HAV antibody data pre- and post-vaccination. Numerous variables were evaluated for their effect on seroconversion.

Results: Seroconversion developed in 53.5% of the population. Responders had higher baseline median CD4 counts (446 versus 362 cells/mm³; P=0.004) and lower median HIV RNA levels (475 copies/mL versus 5615 copies/mL; P=0.018) than non-responders. Patients with CD4 counts >350 cell/mm³ were more likely to respond than those with CD4 counts <200 cell/mm³, 60% and 35%, respectively (P=0.0498). Responders were also more likely to be virologically suppressed (48% versus 32%; P=0.0024). TWINRIX recipients had a 7-fold increased probability of seroconversion when virologically suppressed and less likely to respond if the vaccination series was not completed (OR 0.42; 95% CI 0.18-0.96).

Discussion: Seroconversion rates to HAV vaccination are significantly impaired among HIV-infected patients. CD4 cell count and virologic suppression at vaccination impact response. Seroconversion among TWINRIX recipients appeared to be more sensitive to these factors and vaccine series completion in comparison to those administered HAVRIX. Among HIV-patients requiring hepatitis a and b vaccination, the advantage of TWINRIX over HAVRIX as a combination product should be reevaluated.

Mena, G., Garcia-Basteiro, A. L., Lluvia, A., Diez, C., Costa, J., Gatell, J. M., Garcia, F. and Bayas, J. M. "[Factors associated with the immune response to hepatitis A vaccination in HIV-infected patients in the era of highly active antiretroviral therapy.](#)" *Vaccine* **2013** 31(36): 3668-3674. Preventive Medicine and Epidemiology Unit, Hospital Clinic, Barcelona, Spain. guille.menapinilla@gmail.com

Erratum in
Vaccine. 2015 Mar 3;33(10):1297.

A

INTRODUCTION:

HIV seropositivity is considered a risk factor for complications in hepatitis A virus (HAV) infection. HAV vaccination schedules are widely implemented in HIV-infected patients, but the immune response remains impaired.

METHODS:

We analysed the response to vaccination (antiHAV titres ≥ 20 IU/l) in 282 HIV-infected patients included in a standard (1440 Elisa Units (EU) at 0, 6 months) or rapidly accelerated schedule (720 EU at 0, 7, 21 days and 6 months) between 1997 and 2009. Factors associated with the response to vaccination were analysed using logistic regression.

RESULTS:

The overall response rate was 73.4%. Male sex (OR: 0.16, 95% CI 0.05-0.51) and hepatitis C virus co-infection (OR: 0.30, 95% CI 0.14-0.74) were associated with a lower probability of response. Protective antibody response was associated with a higher CD4/CD8 ratio (OR: 3.69, 95% CI 1.3-10.5) and having received two doses of standard schedule (compared with patients receiving only one dose of the same schedule) (OR: 2.51, 95% CI 1.22-5.15). Three doses of the rapidly accelerated schedule were not more effective than a single dose of 1440 EU (OR: 1.32, 95% CI 0.48-3.63).

CONCLUSION:

The low responses observed in patients receiving a single dose suggest the need to emphasize adherence to vaccination protocols to avoid failure. The CD4/CD8 ratio may be considered as an immune status marker which could help to better choose the moment of vaccination. Our findings underscore the importance of identifying strategies that optimize the timing and effectiveness of hepatitis A vaccination in HIV-infected patients and of the need for further studies on individual factors such as sex and hepatitis C co-infection that may affect the response to vaccination. Likewise, the sub-optimal effectiveness of three doses of 720 EU in the rapidly accelerated schedule, if confirmed in future studies, might lead to a revision of the current schedule recommended for HIV-infected travellers.

18h10-18H20 **Questions concerning presentation**

Session 3 : Groups discussion

Chairs:

18:20- 19:45 Statements to be discussed during the groups discussion.

- 1. *Is there enough scientific evidence to support one dose hepatitis A vaccination***
- 2. *Can one dose be recommended in outbreak managements***
- 3. *Better one than no dose?***
- 4. *Do we need a booster after one dose hepatitis A vaccination***

19:45 – 20:00 Closing of the meeting

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