



A Global Hepatitis **A** Meeting

**Has the time come to control
HEPATITIS A globally?**

**MATCHING PREVENTION TO
THE CHANGING EPIDEMIOLOGY**



Miami
Dec 2007

MIAMI, FLORIDA – USA

30 NOVEMBER – 1 DECEMBER 2007

ABSTRACT BOOK

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FOREWORD

It is our great pleasure to welcome you at the global hepatitis A meeting, entitled **“Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology”**. Miami, Florida, US, 30 November to 1 December 2007.

This meeting is a joint initiative of the Centers for Disease Control and Prevention (CDC), the Centre for the Evaluation of Vaccination (CEV) - a WHO collaborating Centre for Prevention and Control of Viral Hepatitis - at the University of Antwerp (UA), the World Health Organization (WHO) and The Pan American Health Organization (PAHO).

This meeting is scheduled at what could be the turning point in the history of hepatitis A virus (HAV) prevention and control. In many parts of the world highly endemic for hepatitis A, most of the population acquired asymptomatic infection at young age providing life-long protection. Thanks to improved standards of living in the last decade, more and more of these populations are no longer becoming infected at a young age and therefore remain susceptible for hepatitis A infection. This leads to repeated outbreaks of disease with considerable morbidity, as currently observed in countries with a transitional hepatitis A epidemiology. As a result of this changing global epidemiology of hepatitis A, policy makers need to reassess the currently established prevention measures and immunization priorities for hepatitis A, against other public health interventions. The changing global epidemiology of hepatitis A should increase attention directed to research, control and prevention of this infectious disease in the coming years. This international meeting offers a perfect opportunity and platform to present data on current research. In addition, a number of countries have already implemented universal hepatitis A vaccination programmes and data on the impact of these strategies will be presented.

This is the first global meeting focusing entirely on hepatitis A as a vaccine preventable disease.

The challenging goals of the conference are to:

- review the changing epidemiology of HAV and its impact on burden of disease and prevention strategies
- share country experiences on the effectiveness of different hepatitis A vaccination strategies
- review diagnostic and surveillance issues
- assess different outbreak control measures
- discuss the economics of universal hepatitis A vaccination in children compared to other health care interventions
- position HAV burden of disease and prevention options vis-à-vis other vaccine-preventable infections
- assess and discuss vaccine efficiency and long term immunogenicity data
- assess the future of global prevention and control of hepatitis A infection.

The outcome of the meeting should assist countries to decide on an optimal prevention strategy including the appropriateness of routine hepatitis A vaccination in their country. To achieve this goal we are bringing together ministry of health representatives, public health officers, epidemiologists, virologists, hepatologists, viral hepatitis experts, (paediatric) infectious disease professionals and travel doctors.

On behalf of the organising and scientific committees, we would like to thank all the participants, poster presenters and speakers for their contribution to the success of this unique meeting. We thank the sponsors for their unrestricted educational grants which made the preparation and organisation of this meeting possible.

During these two days, experts from over 50 countries will discuss about their experiences and exchange lessons learnt. We really hope that this unique opportunity will contribute to the rational control of hepatitis A globally, matching the changing epidemiology.

Pierre Van Damme

On behalf of the organising and scientific committees

Organising committee

- Harold Margolis, International Vaccine Institute, Korea
- Alba Maria Ropero, Pan American Health Organization, USA
- Craig Shapiro, World Health Organization, Switzerland
- Eugene Schiff, University of Miami, USA
- Daniel Shouval, Hadassah-Hebrew University, Israel
- Pierre Van Damme, University of Antwerp, Belgium
- John Ward, Centers for Disease Control and Prevention, USA
- Steven Wiersma, Centers for Disease Control and Prevention, USA

Scientific Committee

- | | |
|---------------------|----------------------|
| ▪ Selim Badur | ▪ Alba Maria Ropero |
| ▪ Beth Bell | ▪ Hermann Schatzmayr |
| ▪ Paolo Bonanni | ▪ Eugene Schiff |
| ▪ Ron Dagan | ▪ Craig Shapiro |
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| ▪ Blaine Hollinger | ▪ John Ward |
| ▪ Wolfgang Jilg | ▪ Steven Wiersma |
| ▪ Harold Margolis | ▪ Zhi-yi Xu |
| ▪ Brian McMahan | ▪ Alessandro Zanetti |
| ▪ Alfonso Mele | |
| ▪ Jeffrey Mphahlele | |
| ▪ Robert Purcell | |

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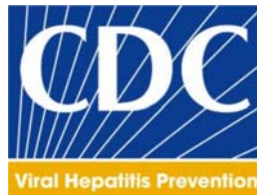
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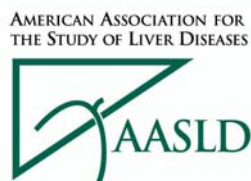


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Endorsement



THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

ROOM PLAN

PROGRAMME OVERVIEW

| | Thursday 29 November | Friday 30 November | Saturday 1 December | |
|-------|-------------------------------|--|--|-------|
| 7:00 | | BREAKFAST REGISTRATION Grand promenade Lobby ballroom | BREAKFAST REGISTRATION Grand promenade Lobby ballroom | 7:00 |
| - | | | | - |
| 8:00 | | | | 8:00 |
| - | | | | - |
| 9:00 | | | | 9:00 |
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| 10:00 | | | | 10:00 |
| - | | | | - |
| 11:00 | | MEETING Mediterranean room | MEETING Mediterranean room | 11:00 |
| - | | | | - |
| 12:00 | | | | 12:00 |
| - | | | | - |
| 13:00 | | | | 13:00 |
| - | | | | - |
| 14:00 | | | | 14:00 |
| - | | | | - |
| 15:00 | | <i>Poster session</i> <i>Grand Promenade</i> | <i>Poster session</i> <i>Grand Promenade</i> | 15:00 |
| - | | | | - |
| 16:00 | | | | 16:00 |
| - | | | | - |
| 17:00 | REGISTRATION | | | 17:00 |
| - | Lobby | | | - |
| 18:00 | | | | 18:00 |
| - | | | | - |
| 19:00 | OPENINGS RECEPTION | Congress Dinner | | 19:00 |
| - | | | | - |
| 20:00 | Pool Deck | Pool Deck | | 20:00 |
| - | | | | - |
| 21:00 | | | | 21:00 |
| - | | | | - |
| 22:00 | | | | 22:00 |

MEETING VENUE

MIAMI BEACH RESORT & SPA
 4833 COLLINGS AVENUE
 MIAMI BEACH, FLORIDA 33140, USA
WWW.MIAMIBEACHRESORTANDSPA.COM



MEETING PROGRAMME

MEETING PROGRAMME

GLOBAL HEPATITIS A MEETING PROGRAMME

Friday, 30 November 2007

8h00 Welcome
Welcome to Miami Eugene Schiff
Welcome to the meeting Pierre Van Damme

| | |
|------------------|--|
| Session 1 | Opening and objectives CHAIRS: EUGENE SCHIFF, ROBERT PURCELL |
|------------------|--|

8h20 Setting the scene talk: Country presentation illustrating the **epidemiology**, the need for an **evidence-based decision making process with regard to control of hepatitis A** and the **relevance of the meeting**: how to match prevention to the changing epidemiology. Argentina

ANGELA GENTILE '30

| | |
|------------------|---|
| Session 2 | Hepatitis A virus infection CHAIRS: EUGENE SCHIFF, ROBERT PURCELL |
|------------------|---|

8h50 Milestones in the discovery of hepatitis A virus

STEPHEN FEINSTONE '20

9h10 Clinical manifestations of hepatitis A

BRIAN MCMAHON '20

| | |
|------------------|--|
| Session 3 | Epidemiology of hepatitis A CHAIRS: ALESSANDRO ZANETTI, DANIEL SHOUVAL |
|------------------|--|

9h30 Surveillance of viral hepatitis A

ANNEMARIE WASLEY '15

9h45 Evolution of global hepatitis A epidemiology

CRAIG SHAPIRO '20

10h05 Measurement of burden of disease of hepatitis A in Europe:
Eurohep.net surveillance project

PAOLO BONANNI '15

10h20 *Coffee break ('20)*

MEETING PROGRAMME

Session 4

Laboratory diagnosis and molecular epidemiology

CHAIRS: ALESSANDRO ZANETTI, DANIEL SHOUVAL

10h40 Current and new diagnostic tools and introduction to molecular epidemiology of hepatitis A HAROLD MARGOLIS '30

11h10 Examples of molecular epidemiological studies

11h10 Hepatitis A outbreak in European travelers returning from Egypt MIRKO FABER '15

11h25 The changing molecular epidemiology of HAV infection in Jerusalem before and after initiation of universal vaccination DANIEL SHOUVAL '15

11h40 Presence of HAV in the environment in Catalonia, Spain ROSINA GIRONES '15

11h55 Lunch (1h35)

Session 5 (A+B)

Country and regional studies of hepatitis A epidemiology

Break out session (A)

CHAIRS: ALBA MARIA ROPERO, JEFFREY MPH AHLELE

13h30 Brazil CLÁUDIA LAMARCA VITRAL ('15)

13h45 Mexico JOSÉ SANTOS ('15)

14h00 Saudi Arabia HAYSAM TUFENKEJI ('15)

14h25 Italy ALFONSO MELE ('15)

14h40 Turkey MERAL CIBLAK ('15)

14h55 South-Africa JEFFREY MPH AHLELE ('15)

Break out session (B)

CHAIRS: BETH BELL, IAN GUST

13h30 China ZHI-YI XU ('15)

13h45 Korea JONG-HYUN KIM ('15)

14h00 Thailand VORANUSH CHONGSRISAWAT ('15)

14h25 India VIDYA ARANKALLE ('15)

14h40 Russia SERGEY MUKOMOLOV ('15)

14h55 Ukraine ANNA MOISEEVA ('15)

15h10 Coffee break ('20)

MEETING PROGRAMME

Session 6

Hepatitis A vaccines

CHAIRS: PIERRE VAN DAMME, RON DAGAN

15h30 History of the vaccine development

IAN GUST '20

15h50 Performance of the available hepatitis A vaccines

KOEN VAN HERCK '20

Session 7

Prevention and control of hepatitis A infections

CHAIRS: PIERRE VAN DAMME, RON DAGAN

16h10 Prevention effectiveness of current immunization strategies as measured by disease/infection reduction

BETH BELL '30

16h40 Epidemiology and prevention strategies for adults at increased risk for Hepatitis A

JOHN WARD '20

17h00 Hepatitis A vaccine versus immune globulin for post-exposure prophylaxis

JOHN VICTOR '15

17h15 Close of the day

MEETING PROGRAMME

Saturday 1 December 2007

Session 7 (continued) Prevention and control of hepatitis A infections

CHAIRS: CRAIG SHAPIRO, STEVEN WIERSMA

8h00 Hepatitis A prevention for travelers

ROBERT STEFFEN '30

Session 8

Vaccine financing and introduction of new vaccines

CHAIRS: CRAIG SHAPIRO, STEVEN WIERSMA

8h30 Economics: Cost-effectiveness of options for Hepatitis A vaccination

PHILIPPE BEUTELS '30

9h00 A mathematical model of hepatitis A transmission in the US indicates value of universal childhood immunization

THIERRY VAN EFFELTERRE '20

9h20 Cost-effectiveness analysis of hepatitis A vaccination in Canada using a dynamic model

CHRIS BAUCH '20

9h40 Introduction of new and underutilized vaccines in Latin America and the Caribbean (LAC)

ALBA MARIA ROPERO '20

10h00 Challenges in introducing new vaccines: GAVI experiences

SUSIE LEE '20

10h20 Coffee break ('20)

Session 9

Country and regional examples of hepatitis A prevention

CHAIRS: PAOLO BONANNI, KOEN VAN HERCK

10h40 Argentina

MARTA VACCHINO ('15)

10h55 The Netherlands

JIM VAN STEENBERGEN ('15)

11h10 Italy, Puglia

ROBERTA PASTORE ('15)

11h25 Israel

RON DAGAN ('15)

11h40 Spain, Catania

ANGELA DOMÍNGUEZ ('15)

11h55 Australia

PHILIPPE BEUTELS ('15)

12h10 Lunch (1h35)

MEETING PROGRAMME

| | | |
|-------|---------|----------------------|
| 13h45 | Chile | KATIA ABARCA ('15) |
| 14h00 | Belarus | ALENA FISENKA ('15) |
| 14h15 | Russia | VASILY AKIMKIN ('15) |
| 14h30 | China | XIAOFENG LIANG ('15) |

Session 10

Oral presentation of selected abstracts

CHAIRS: JOHN WARD, ALFONSO MELE

14h45 8 min presentation of 5 selected abstracts ('45)

15h30 Coffee break ('20)

Session 11

Round table discussion and concluding remarks

CHAIRS: BLAINE HOLLINGER, HAROLD MARGOLIS

15h50 Moderated Q&A session with panel of representatives from countries that made a decision to introduce the vaccine nationwide. What went into making such a decision ('120)

17h50 Close of the meeting



ORAL PRESENTATIONS

SETTING THE SCENE TALK: COUNTRY PRESENTATION ILLUSTRATING THE EPIDEMIOLOGY, THE NEED FOR AN EVIDENCE-BASED DECISION MAKING PROCESS WITH REGARD TO CONTROL OF HEPATITIS A AND THE RELEVANCE OF THE MEETING

ANGELA GENTILE

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Hepatitis A (HA) was an important public health problem in Argentina, being a leading cause of acute liver failure and liver transplant in children.

Universal hepatitis A vaccination was implemented by Argentina's Ministry of Health in June 2005 with a single dose at age 12 months. The decision was made taking into account:

Disease Burden

The 2003 incidence rate was 139/100 000 and the 2004 rate was 172.7/100 000, the Northern and the Western parts of the country were the most affected regions. In Buenos Aires city, with good sanitary conditions, the outbreaks were also important.

Seroprevalence data among children 1-15 years was 54% for the whole country with differences per region and age. Between May 1982-September 2002, 210 patients were recruited with acute hepatic failure (AHF), 87% < 10 yrs and the etiology was HA in 61% of them.

Cost- effectiveness

Compared with no vaccination, the 1-dose schedule would save \$US15.3 millions with regional variations.

Vaccine features

Immunization with hepatitis A vaccine is safe and effective, one dose schedule confer good immunogenicity and effectiveness, perhaps the "work" of the second dose, now, is conferred by wild virus that is still circulating.

Programmatic feasibility

The National Program has a good distribution of vaccines and an adequate cold chain.

Social acceptance and political compromise

The population largely accepts hepatitis A vaccination and the national authorities would have the compromise to provide it regularly.

Argentina considers to survey this one dose schedule, in order to add a second dose if needed .

The main global issue is that Hepatitis A virus (HAV) infection remains the most commonly reported vaccine-preventable disease in many parts of the world despite the availability of vaccines.

MILESTONES IN THE DISCOVERY OF HEPATITIS A VIRUS

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While diseases that may have been hepatitis A have been described in antiquity, the modern era for viral hepatitis began during WWII when the two classic forms of the disease were clearly distinguished. Later, the studies by Saul Krugman resulted in well characterized inocula for both hepatitis A (MS1) and hepatitis B (MS2). During the so-called golden era of virology when many new viruses were being identified in the new cell culture systems, many labs worked on the isolation of these hepatitis viruses. Most of these efforts resulted in identification of extraneous agents or failure to isolate anything. After the discovery of the Australia antigen and its association with hepatitis B and the identification of the Dane particle as the actual hepatitis B virus, there was a renewed interest in finding the hepatitis A virus (HAV). Many of these efforts were misguided by using the same technology that was used to detect HBsAg. These efforts to find the virus or a viral antigen in serum were bound for failure though many interesting particles were described. Hepatitis A virus was not found by serendipity. A few labs understood where the hepatitis A money could be found as the disease was well known to be transmitted by the fecal oral route. Bob Purcell clearly understood where to look. He only needed a young investigator whom he could "persuade" to begin a detailed investigation on the stools of patients with acute hepatitis A. With that, we joined with Al Kapikian who had applied the technique of immune electron microscopy (IEM) to the identification of several difficult to grow human viral pathogens such as corona viruses and finally the Norwalk agent of gastroenteritis. His success suggested the method that we would use to look for HAV. After about a year of looking and evaluating many virus-like particles seen in human stool, we eventually found a particle that reacted specifically with hepatitis A convalescent, but not pre-infection sera. Using IEM as a viral detection system and a serologic assay, we were able to begin establish good animal models, perform sero-epidemiological surveys of populations and to study individual patients and outbreaks of hepatitis as well as to define the period of viral shedding and to begin characterization of the virus. IEM was also the technique used to specifically prove serologically the existence of what was originally termed transfusion associated non-A, non-B hepatitis, now known as hepatitis C. Other milestones in HAV research include tissue culture isolation of HAV, cloning and sequencing the HAV genome and finally, the development of successful vaccines.

CLINICAL MANIFESTATIONS OF HEPATITIS A

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Acute hepatitis A infection results in significant morbidity. The risk of developing clinical symptoms including jaundice increases with increasing age. While the risk of death from acute HAV is < 1%, the risk of mortality is highest in those below age 5 years and especially in those above age 49 years. Variants of acute hepatitis A include Cholestatic hepatitis characterized by prolonged jaundice and pruritus, relapsing hepatitis A and fulminant hepatitis. Fulminant hepatitis occurs in from 10% to 20% of patients hospitalized and is the leading cause of liver transplant due to acute viral hepatitis in the US. Hepatitis A is also an important cause of fulminant hepatitis in developing countries and the introduction of chlorinated water in urban but not rural areas in developing countries has increased the incidence of symptomatic and fulminant hepatitis A in some countries' urban populations. Hospitalization rates vary widely in different countries as does the criteria for admission but in the US about 10% of patients with icteric acute hepatitis A are admitted to the hospital. Other factors that increase the risk for hospitalization, severe illness and fulminant hepatitis besides age below 5 years and above 49 years include: chronic alcohol use, underlying liver disease (alcoholic liver disease, hepatitis B or C and liver disease/cirrhosis of any cause) and acetaminophen use during the prodrome of acute hepatitis A. In conclusion, hepatitis A is a significant cause of symptomatic illness and fulminant hepatitis in developed countries and is increasingly reported in developing countries. Wider use of hepatitis A vaccine would result in the decrease in morbidity and mortality in countries that chose to implement hepatitis A immunization programs.

Different types of surveillance data provide the information needed to decide if and how to use hepatitis A vaccine to reduce transmission and prevent outbreaks. Seroprevalence data which represents the lifetime exposures of individuals to HAV describe the underlying pattern of immunity in the population. Surveillance data measuring acute disease incidence reflects transmission patterns in the community but it does not completely describe population immunity since it does not capture asymptomatic infections which can be the majority of infections in a high endemicity settings. However, in contrast to seroprevalence data, monitoring acute disease incidence detects recent transmission and so is useful for identifying outbreaks and characterizing population groups who are at risk of illness. This presentation will provide examples which illustrate how data on seroprevalence and disease incidence can be used to develop strategies for using hepatitis A vaccine to interrupt HAV transmission and then monitor the impact of those strategies.

EVOLUTION OF GLOBAL HEPATITIS A EPIDEMIOLOGY

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MEASUREMENT OF BURDEN OF DISEASE OF HEPATITIS A IN EUROPE: EUROHEP.NET SURVEILLANCE PROJECT

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European countries use a wide variety of surveillance systems and prevention measures for viral hepatitis. Each system is adapted to the local situation and an overview was never mapped out at European level. The EUROHEP.NET Project is a European Commission-funded feasibility study for a future network on surveillance and prevention of vaccine-preventable hepatitis. We analysed the measurement and reporting of burden of disease for hepatitis A (HA) and B (HB) in the participating countries.

Methods: Twenty-eight countries were invited to participate in this study. An on-line survey was available from the project's website (www.eurohep.net). The questions concerned the organisation of the surveillance system, case definition, burden of disease, epidemiology, and vaccination strategies. The responses on data sources and the numeric data related to burden of disease for HA for the period 1997–2001 were analysed.

Results: Twenty-two countries completed the survey for hepatitis A. Data on total number of hospitalisations and deaths were available from 17 and 18 countries, respectively, although sometimes not complete. Data on hospitalisation days, number of liver transplants and proportion of these due to HAV were often not available.

Conclusion: Surveillance systems on burden of disease for hepatitis A show a wide diversity among the participating countries. The introduction of a standardised system of data collection at the European Union level according to ICD-10 but respecting the local current practices is a primary need, especially for data that should be collected in all countries, like hospitalisation and mortality. A link to surveillance databases is also strongly recommended.

**CURRENT AND NEW DIAGNOSTIC TOOLS AND INTRODUCTION TO MOLECULAR
EPIDEMIOLOGY OF HEPATITIS A**

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HEPATITIS A OUTBREAK IN EUROPEAN TRAVELERS RETURNING FROM EGYPT

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Background: In the summer of 2004 an outbreak of hepatitis A virus (HAV) infections occurred among European guests of a hotel in Hurghada, Egypt. Epidemiological and virological investigations determined the extent of the outbreak, vehicle of infection, and the outbreak strain.

Methods: A case-control study was conducted among ill-with-hepatitis-A (cases) and healthy (controls) German hotel guests. On-site investigations (Egyptian authorities) included testing of hotel staff for recent HAV infections and inspections of food suppliers. Virological investigation characterized the outbreak strain.

Findings: The outbreak included 351 primary cases in 9 European countries. Germany was most affected with 271 primary infections. Some secondary infections were noted. Transmission in the hotel occurred at least between June 24 and July 23. In the case control study, unpasteurized orange juice proved to be the only significant risk factor for HAV infection: 82.4% of cases (n=69) drank it, and 63.9% of controls (n=36) (odds ratio=2.6, 95% CI: 1.1-6.6). There was a strong dose-response relationship between days of consumption and disease risk. With respect to all other investigated items, cases and controls were similar. All 13 virus isolates from German cases were identical in the VP1-2A region (genotype 1B). The Egyptian authorities' investigation discovered hygiene problems at the juice supplier's production site independently from the results of the case control study.

Interpretation: This large multinational HAV outbreak was most likely caused by contaminated orange juice. Orange juice had not previously been implicated in other published hepatitis A outbreaks but should be considered a potential hazard in endemic areas. While vaccination against HAV is recommended in Germany and most other European countries for travelers to endemic areas, communication of hepatitis A risk and immunization benefits to package tourists traveling to Egypt and other endemic countries ought to be improved upon.

THE CHANGING MOLECULAR EPIDEMIOLOGY OF HAV INFECTION IN JERUSALEM BEFORE AND AFTER THE INTRODUCTION OF UNIVERSAL VACCINATION

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Universal vaccination against hepatitis A (HAV) was introduced in Israel in July 1999 in 18m old toddlers, with one booster at 24m. Effectiveness of the vaccination program was monitored through active surveillance in the district of Jerusalem and a passive national surveillance system in the entire country. In 2002, the Jerusalem district population consisted of 937,163 residents while the Jerusalem city population consisted of 441,300 Jewish and 203,500 non-Jewish (mainly Moslem Arab) inhabitants. Between 1999 and 2004, a total of 1908 patients were identified in the Jerusalem district with anti-HAV IgM+, acute HAV infection, out of whom 848 underwent HAV-RNA analysis by PCR (using the 325-bp-VP1-2A region). HAV-RNA was detected in 709/848 patients tested (84%). All were of genotype 1 of whom subgenotype 1a was identified in 387 and subgenotype 1b in 322 subjects. 97% of the genotype 1a subjects belong to the Jewish population while 72% of the genotype 1b subjects belong to the non-Jewish population. A Geographic Information System (GIS) program was utilized to map the various HAV clusters and subtypes. Analysis of the GIS data revealed that genotype 1a was almost exclusively (97%) present in the orthodox Jewish communities, characterized by crowding and low socio-economic conditions. Genotype 1b was mainly detected (82%) in localities where the non-Jewish population lived under similar or worse low socio-economic conditions. However, 18% of genotype 1b isolates were obtained from a Jewish secular population residing in the western part of the city. Following the introduction of universal vaccination against HAV in 1999, the annual incidence of acute hepatitis A dropped within three years from 88.4 to 1.8/100,000 in the Jewish population and from 63.8 to 14.8/100,000 in the Non-Jewish population. In 2004, >90% of all acute HAV cases in the city (N=50) belonged to genotype 1b, mainly in the non-Jewish residents. In summary, the distribution of the various HAV clusters reflects the distinct socio-economic, cultural and geographic population patterns in the city of Jerusalem and the impact of universal vaccination.

PRESENCE OF HAV IN THE ENVIRONMENT IN CATALONIA, SPAIN

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The molecular epidemiology of Hepatitis A virus (HAV) has been studied in the area of Barcelona (Catalonia, Spain) by analyzing HAV strains recovered from environmental samples over a 12 years period. Also viral strains from clinical serum samples from acute hepatitis patients were typified over a 5 years period. Since 1999 pre-adolescents are being systematically vaccinated following a pilot program of vaccination against HBV+HAV in Catalonia, northeast of Spain. The study of HAV strains present in urban sewage is proposed as a useful method for the evaluation of the effect of a vaccination program on the prevalence of HAV infections in the population. In a first study a total of 54 samples were collected from 1994 to 2000 and the viral RNA was detected in the 57% of the 1 ml sewage samples tested. Also river water samples presenting fecal contamination showed HAV RNA in about 20-39% of the 4 liter water samples analyzed. HAV RNA was detected in the 57 % of the serum samples from 26 patients with serological diagnostic of HA viral infection. Genotype I was present in 95 % of the environmental and clinical samples with a distribution of nearly 50% of each subgenotype IA and IB. The identified strains were closely related to those described in distant geographical areas suggesting a global distribution of HAV strains.

In a recent study urban sewage samples collected from 2000 to 2007 have been analyzed using identical procedures. In parallel also HEV has been tested. In these samples HAV was detected in 5/18 (28%) in the samples collected over the period of 2000-2005 being the prevalence of HEV in these samples of 39 %. Surprisingly negative results for HAV RNA were obtained in more than 20 sewage samples collected over 2006 and 2007. At the present, HEV is clearly the most prevalent acute hepatitis virus excreted in urban sewage in this region, showing about 33 % of positive samples. Samples from an endemic area and from a region next to Catalonia where the vaccine program has not developed have also been analyzed. The results show the applicability of environmental studies for the analysis of the HA viruses circulating in a population and strongly suggest that the applied vaccination program could be highly efficient reducing the number of infections and the dissemination of HAV in the environment.

EPIDEMIOLOGICAL PATTERN OF HEPATITIS A IN BRAZIL

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Recent studies have shown that hepatitis A virus (HAV) prevalence rates are decreasing in several Latin American countries. Brazil is a very large and heterogeneous country, showing striking regional differences. With regard to sanitary facilities, 81.7% of the districts in the Southeastern region have sewage systems, compared with only 30.2% in the Northeastern region. In order to evaluate the epidemiological pattern of hepatitis A in Brazil, data on HAV seroprevalence available in scientific databases for the different Brazilian regions were consulted. Studies conducted in the northernmost regions of Brazil have indicated that the greatest exposure to HAV infection still occurs early in life. On the other hand, in the Southeastern region, a decline in HAV seroprevalence has been observed resulting in several hepatitis A outbreaks. Epidemiological data obtained from both seroprevalence studies and reported hepatitis A outbreaks indicate that the youngest individuals, especially those under 5 years of age, are mostly unprotected from HAV infection, regardless of their socioeconomic status. Surveillance data about the incidence of hepatitis A in Brazil are lacking. Therefore, in an attempt to generate reliable information on the trends seen in hepatitis A incidence in the country, official government data were used in order to evaluate mortality rates over the last two decades, since fatal cases are generally well investigated and properly diagnosed. Nationwide, hepatitis A mortality rates declined progressively from 1980 to 2002. Since these cases constitute a small, but predictable portion of all acute hepatitis A cases, which are in turn part of the total number of HAV infections, these data suggest that there has been a decline in HAV circulation in all Brazilian regions over the last two decades. Taken together these facts point out that the epidemiological pattern of hepatitis A is changing in Brazil. Besides improvements in sanitary conditions at the poorest Brazilian regions, opting for an immunization policy could be a strategy for controlling HAV infection in the country.

HEPATITIS A EPIDEMIOLOGY IN SAUDI ARABIA

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Saudi Arabia had been considered for many years as one of the highly endemic countries for hepatitis A. Several seroprevalence studies in the 1980's from various regions in the country, which included approximately 18,500 children of 1-18 years of age, showed an anti-HAV prevalence rate of 50-92 percent. In contrast, more recent similar studies from the 1990's to the present in approximately 8,500 children of 1-15 years, showed a rate of 25-30 percent. Review of these two periods demonstrates a significant fall in the seroprevalence rate of HAV antibodies in all regions, except for the one bordering the country of Yemen. Moreover, the highest prevalence rate is found in children from a rural background, while rates in the Beduin and urban children are similar. In all children, the seroprevalence is related to age, being higher in older children, and to socioeconomic status, being highest in the lower groups. It is apparent that the epidemiology of hepatitis A in the country has shifted from high to intermediate endemicity which is concurrent with the social and economic development over the last two decades. This event, compounded with the continuing presence of pockets of high endemicity, the highly mobile population and the influx of foreign workers and pilgrims from developing countries, have all resulted in several reported disease outbreaks in various regions in the country, at a high human and financial expense. Hence, and although hepatitis A vaccine had been used in high risk groups since the year 2000, health authorities have recently approved its introduction into the vaccination schedule for all children in Saudi Arabia, starting January 2008.

INCIDENCE, RISK FACTORS AND CONTROL OF HEPATITIS A IN ITALY

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Introduction: Improvements in the standard of hygiene and sanitation have resulted in a dramatic drop in the level of HAV circulation in Italy, changing the face of the hepatitis A epidemiology. Exposure to HAV is now less common during childhood, with a growing number of young adults susceptible to infection. This increases the probability of HAV infection among older age groups and is occasionally responsible for large outbreaks.

Using data collected by the Italian surveillance system of acute hepatitis (SEIEVA), we have evaluated the incidence and risk factors associated with acute hepatitis A cases, notified from 1991 to 2006, and discussed the appropriate control measures.

Methods: SEIEVA, coordinated by Istituto Superiore di Sanità, was implemented on a volunteer basis in 1985. At present, 62% of the Italian population is covered by SEIEVA which uses a standard questionnaire for data collection. Case definition is based on clinical and serological criteria.

Results: The incidence declined from 4 x 100,000 in 1991 to 1.4 x 100,000 in 2006, with a peak during 1996-97 due to a large outbreak in South Italy. Ingestion of raw shellfish, contact with individuals with hepatitis A, travelling to endemic areas and drinking contaminated water are the most frequent risk factors for all age groups. In 2003 intravenous drug use was the cause of an outbreak, with high fatality rate, in a town of central Italy.

Discussion: In the last decades Italy has become an area of low endemicity for hepatitis A. Infection is now less frequent during childhood and an increasing number of young adults are susceptible to HAV. Paradoxically, the shift of HAV infection to older age groups may increase severity of the disease since it is age-dependent.

Vaccination of individuals at increased risk of infection combined with surveillance of retail outlets of shellfish are efficient control measures.

According to WHO Turkey is intermediately endemic for HAV prevalence. However, a large scale epidemiological study published in 2002 by Kanra et al. suggests that seroprevalence differs from one region to another. In provinces with better socio-economic conditions and better infrastructure seropositivity was lower than those in provinces with low socio-economic conditions and poor infrastructure. For example, seropositivity was significantly lower in Adana (56.7 %) and Edirne (60.7), cities with high level of wealth and high level of education and socio-economic development respectively, than in poor provinces such as Diyarbakır (91.9%), Erzurum (85.1 %) and Samsun (83.6). However, overall seroprevalence in Turkey was 71.3%. According to Kanra et al. 50% of Turkish children become seropositive by 10 years of age. HAV is a vaccine-preventable disease that is continuing to be a problem in Turkey and all over the world. Due to improved sanitary conditions, socio-economic conditions and infrastructure the disease has shifted to the adult population which results in more severe disease. Vaccination of children in intermediately and mildly endemic regions will prevent HAV in adults hence preventing more severe disease conditions. Data supports the need for a routine primary immunization policy in Turkey and development of effective prophylactic programs after possible exposure. Considering the differences in seropositivity between different provinces, immunization policies can be developed based on the needs of the provinces. Currently only private practices can deliver vaccination to their patients. Genetic analysis of HAV has revealed the type 1B as the major genotype in Turkey.

EPIDEMIOLOGY OF HEPATITIS A VIRUS INFECTION IN SOUTH AFRICA

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South Africa is a region of intermediate to high endemicity for HAV infection with pockets of low prevalence, particularly in the upper socio-economic groups (i.e. white South Africans). The majority of black South Africans show prevalence of over 80% by 10 years of age. However, the increasing access to better living conditions for many black South Africans may eventually change the epidemiology of HAV by increasing the number of susceptibles. Data on the precise burden of hepatitis A disease are rare. Adults generally show higher prevalences based on several studies. A recent age specific survey indicated that anti-HAV levels were relatively high (up to 55%) soon after birth, but dropped to lower levels in both lower and upper socio-economic groups. While the upper socio-economic class retained the lower levels of antibodies, with limited increase to 35% by 5 years of age, the lower socio-economic class experienced a dramatic increase, from 48.3% for 3 to 5 year-olds to 86.6% for 11 to 13 year-olds. By 19 years of age, 92% of the lower socio-economic class was protected against HAV infection, compared to only 27% in the upper socio-economic group. Similarly, the prevalence was 100% in antenatal women from the lower socio-economic class compared to only 38.3% of antenatal women in the upper socio-economic group (Schoub et al SAMJ 89: 1074). Additional studies demonstrated that as high as 96% of black health care workers (HCWs) are naturally protected against HAV infection, compared to only 40% of HCWs from the upper socio-economic class. In conclusion, although the upper socio-economic class is particularly vulnerable to HAV infection, the epidemiology is likely to change due to changing socio-economic factors in other population groups. Currently, prospects for universal vaccination against HAV seem far remote in South Africa as a result of competing health priorities, including new childhood vaccines. The vaccine is only recommended for persons at an increased risk of HAV infection. These include but are not limited to HCWs, food handlers, recipients of blood or blood products, susceptible travellers to HAV endemic countries, children in day-care centres and their families, and day-care centre staff.

FACTORS FOR THE SIGNIFICANT DECLINE IN RISK OF HEPATITIS A (HA) IN CHINA, A COUNTRY WITH BOOMING ECONOMY AND RAPIDLY IMPROVING LIFE STYLE

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Background and objectives: The nationwide annual HA incidence rate declined from 50 per 100,000 in 1992 to 5 per 100,000 in 2006, while the cumulative output of live HAV vaccine (H2 strain) doses increased from 2,860,000 to 135,480,000 and GDP per capita from 2,373 Yuan to 12,861 Yuan respectively, during the observed 14 years. Factors for the rate decline were studied.

Methods: Data on HA incidence, vaccine coverage and serological follow-ups were analyzed.

Results: Cyclic epidemics disappeared; children were no longer at higher risk and seasonal peaks flattened in most provinces of China. In rural Hebei, a previous hyper-endemic province, the annualized risk of HAV infection declined from 20% during the 8 years (a single epidemic cycle) before the mass immunization to 0.35% in vaccinated and 2.0 % in unvaccinated children during the 8 years after the mass vaccination. Mass vaccination has led to elimination of HA in several cities and counties. However, the sharp drop in hepatitis A incidence is not attributable to the vaccination alone; it was also correlated with increasing GDP and occurred before the vaccine introduction. In the well-developed area of Shanghai where adults were at higher risk, rates of both hepatitis A and shigellosis among unvaccinated adults were similar, and dropped at the same pace from around 120/100,000 in 1990 to around 40/100,000 in 1998. Lower rates in subjects of all ages for HA (3/100,000) than for shigellosis (20-33/100,000) were not reported till 8-10 years after the vaccine introduction (1994), a time period needed for the immunized school children to grow up. In the under-developed Western provinces, life style remains unchanged, vaccine coverage is low and HA outbreaks are reported from time to time.

Conclusions: Both vaccination and improved living conditions contributed to HAV risk reduction. The booming economy with rapidly changing life style made the chief contribution in the well-developed regions. The eventual eradication of HAV, however, would rely on vaccination.

EPIDEMIOLOGY OF HEPATITIS A IN SOUTH KOREA

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Due to the absence of a reporting system in the past it was impossible to determine the exact disease burden of hepatitis A. In the 1970s, hepatitis A prevalence was so high that hepatitis A patients were approximately about 2-5% of all hospitalized children in South Korea. This situation remained the same till the mid-1980s. Thereafter, the number of cases had significantly decreased until an outbreak occurred in a city in 1996. Since then, the number of the hepatitis A cases gradually increased, and in 2006 1,923 cases were officially reported.

Seroprevalence of anti-HAV IgG had also changed. The seropositive rate for over-ten-year old subjects in the early 1980s was between 85-90%. During the mid-1990s, just before using the hepatitis A vaccine, the seropositive rate between the ages of 0 to 20 years old was under 20%. Since 1997 vaccination of hepatitis A has been increasing and the coverage rate of 1-2 year olds currently is approximately about 40%. Recently one particular study in 2006 displayed the present changing situation - seropositive rates of anti-HAV IgG were 51% in 1-9, 11% in 10s, 16% in 20s, 73% in 30s, 96% in 40s and 100% in over 50 year olds. With changes in seroprevalence, an epidemiological shift has been changing as follows; the age groups of most prevalent hepatitis A patients has changed from 10-20s in the 1990s to 20-30 year olds in recent times.

To decrease the disease burden the policy for universal vaccination of children and the mass catch-up vaccination campaign of high risk groups in adolescents/adults must be considered and adopted in the near future after evaluating the cost-effectiveness of vaccination in South Korea.

Thailand has shifted from a high to an intermediate endemicity country for hepatitis A virus (HAV) infection since the mid-1980s. The falling seroprevalence is due to the socio-economic development and significant improvement in sanitation and personal hygiene. During 2003-2006, The Ministry of Public Health of Thailand has reported 0.58-3.89 per 100,000 per year of HAV cases with case fatality rates ranging from zero to 0.22%. This finding might be underreported as most cases of HAV infection were not tested and there is a high probability of asymptomatic infection in young children. In 2004, a study of the seroprevalence of HAV in 3,997 subjects from four geographically distinct provinces of Thailand was investigated. The prevalence among subjects aged <10, 10-20, 20-30, 30-40, 40-50, 50-60, and >60 years was 5.4%, 11.9%, 35.8%, 59.4%, 70.6%, 74.8%, and 91.4%, respectively. As exposure to HAV declines in childhood, transmission shifts to older age groups and the incidence of symptomatic disease increases. Improved sanitation and hygiene conditions leave large segments of the population susceptible to HAV infection, and outbreaks may result which could lead to intense economic loss. Several epidemics have been present in different parts of the country almost every year. There were outbreaks in the south of Thailand in 2001-2002, in a child care centre in Bangkok in 2002-2003, and in the north of the country in 2005. All of the isolates from those outbreaks were found to be of genotype IA. Molecular study would be useful for clarifying the viral evolution and the epidemiology of a suspicious HAV outbreak in the community. Vaccination, especially in the area under consideration and in identified vulnerable groups, to reduce the incidence of symptomatic disease in those infected need to be carefully considered.

Hepatitis A continues to be a very frequent sporadic infection in India with a population over one billion, over-crowded living conditions and lack of proper sanitation and education. Recent studies conducted in different parts of India document that children from low socio-economic category continue to be almost universally exposed to HAV, mainly through sub-clinical infections. Based on age-stratified population surveys conducted in Pune in 1982, 1992 and 1998, a distinct change in the degree of exposure to HAV was demonstrated only in the population belonging to higher socio-economic status. In fact, lower socio-economic status was independently associated with a 23-fold higher risk of HAV infection. A substantial susceptible pool is generated along with a majority of the population still in the hyperendemic state excreting the virus in faeces. Contamination of water with HAV containing faeces, which seems very likely on account of the prevalent system for sanitation and supply of drinking water, epidemics of hepatitis A seems a distinct possibility. Hepatitis A is the predominant aetiology for both acute-recovering and fulminant hepatitis in children. This decade has witnessed an increasing trend in the number of hepatitis A cases in adults. Importantly, during 2002-04, outbreaks of the disease have been recorded among children from rural and semi-urban areas of the state of Maharashtra, western India. An explosive outbreak among adults from the state of Kerala, southern India, involving 1,137 cases in 2004 and over 450 cases in children and adults during an outbreak of the disease in Shimla, north India in 2007, are noteworthy. The virus is shown almost in every sewage sample. Genotyping of over 500 samples collected during 1981-2007 showed the presence of genotype IIIA.

THE MODERN EPIDEMIOLOGY OF HEPATITIS A IN THE NORTH-WESTERN REGION OF THE RUSSIAN FEDERATION

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The Hepatitis A virus (HAV) infection morbidity confirmed by anti-HAV IgM detection in 80-100% of cases decreased in 6 times in Russian Federation in 2001-2006 compared to 1981-1986. In the North-Western region a similar trend was registered, but morbidity reduction was slower in dynamics. The decrease in number of HAV cases was observed in all age groups, but this change was more significant in children 0-6 years old. The highest HAV incidence rates shifted to older age groups: 11-14, 15-19, 20-29 years old. Limited infection spread during the past 25 years led to changes in HAV herd immunity in the population. Testing of sera of St. Petersburg citizens aged 20-29, 30-39 and 40-49 years for anti-HAV IgG and conducted 4 times in 1986-2005 has shown differences in seropositivity in the population. During the observation period in the group of 20-29 years old anti-HAV IgG rate fell down twice (62% and 30% respectively), but in the group of 40-49 years old the changes were less significant (88% and 70% respectively). It should be noted that the number of mix-hepatitis (HAV + chronic HCV HBV) cases increased in the last years. The share of these cases in the total number of mix-hepatitis patients reached about 10%.

Conclusion: The dramatic decrease of HAV immune population in active age cohorts requires the strengthening of preventive measures including, in particular, extension of HAV vaccine administration.

HEPATITIS A SEROPREVALENCE IN DIFFERENT AGE GROUPS IN KIEV CITY, UKRAINE

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Background and Aims: Ukraine is a country with intermediate hepatitis A (HA) endemicity, having a high risk for outbreaks. Vaccination with Avaxim™ (Sanofi Pasteur, France) has been documented to be effective in outbreak control in Ukraine. The inclusion of universal HA immunization of children in the national immunization schedule is planned for 2011. Additional information about HA seroprevalence would therefore be very useful. The objective of the current study was to evaluate HA seroprevalence in different age groups residing in Kiev City, capital of Ukraine.

Methods: A qualitative ELISA kit (Total HAV, Dia-Sorin, Italy) with a sensitivity of 10 mIU/ml was used for detection of anti-HA antibodies in serum from 1000 non-vaccinated subjects in 5 age groups (1-5, 6-11, 12-17, 18-50 and >50 years).

Results: Among children 1-17 years of age, 87.8% were seronegative. Overall, 49.6% of adults were seronegative. Children from 1-5 years of age had the highest seronegativity rate, 91.9%. The number of seronegative children decreased with age, reaching 79.5% in those from 12-17 years. The lowest seronegativity rate, 43.3%, occurred in adults >50 years of age.

Conclusions: The study shows that the seronegativity rate decreased with age, but remained high through adolescence, providing strong support for incorporation of universal hepatitis A vaccination of young children in the Ukraine.

HISTORY OF DEVELOPMENT OF HEPATITIS A VACCINES

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Although the hepatitis A virus was identified in 1973, it took many years and a number of disappointments before several strains were adapted to growth in cell culture. While it was demonstrated that repeated passage of the virus resulted in attenuation and that these attenuated strains were effective in protecting marmosets and juvenile chimpanzees from challenge with wild type virus, most manufacturers elected to develop inactivated vaccines which were equally effective and avoided the potential risk of reversion to virulence.

The events leading to the development of Havrix, the first licenced HA vaccine, will be discussed.

Vaccines against the hepatitis A virus (HAV) have become available since the early 1990s. Among these are 4 formalin-inactivated, cell culture-produced, whole-virus vaccines, which are internationally available. Other hepatitis A vaccines, either inactivated or live attenuated, are produced with a more limited distribution. All vaccines are safe and well tolerated, and induce a rapid, strong and long-lasting immune response in almost all vaccinees. The same is true for existing combination vaccines with a hepatitis A component.

The absolute minimum level of anti-HAV antibodies required to prevent HAV infection has not been defined. Therefore, and in view of the fact that low levels of passively transferred antibodies can prevent clinical disease, all anti-HAV levels above the lower limit of detection are generally considered protective.

Vaccine-induced immunity only takes 2-4 weeks after the first injection to build up, in 95-100% of vaccinees. All widely used vaccines are highly immunogenic and can be used interchangeably.

Studies with different hepatitis A vaccines in Thailand, the United States and in Nicaragua all show a protective efficacy of 100%.

Vaccine-induced antibodies are known to persist for at least 5 years in children and 12 years in adults, and are estimated to persist for much longer (at least 25 years in over 95% of vaccinees). In addition, evidence is accumulating that immune memory will persist even after the loss of detectable anti-HAV levels. Therefore, an International Consensus Group on HAV Immunity in 2002 concluded booster vaccinations to be unnecessary in healthy individuals.

Finally, hepatitis A vaccines have also been shown effective when administered (shortly) after exposure to HAV, and in outbreak situations.

In conclusion, even if some differences do exist between brands in terms of safety or immunogenicity, all available hepatitis A vaccines offer a safe and highly effective means to prevent hepatitis A.

**PREVENTION EFFECTIVENESS OF CURRENT IMMUNIZATION STRATEGIES AS
MEASURED BY DISEASE/INFECTION REDUCTION**

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EPIDEMIOLOGY AND PREVENTION STRATEGIES FOR ADULTS AT INCREASED RISK FOR HEPATITIS A

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The response to hepatitis A virus (HAV) infection is age dependent and adults with hepatitis A have the highest risk of severe illness and death. Populations of adults with certain behavioral and travel characteristics are at increased risk for HAV infection. Cyclic outbreaks of hepatitis A among men who have sex with men are associated with certain sexual practices and other fecal-oral contact. Injection and non-injection drug users are at increased risk as a result of poor hygiene and parenteral exposures. Travelers from low endemic areas to developing countries represent another large risk population and travelers returning from these areas can be a source of transmission to others. Although not at increased risk for infection, HAV infected persons with chronic liver disease are at increased risk for fulminant hepatitis A. Hepatitis A vaccination is recommended for high risk adults but barriers often limit implementation resulting in low vaccination coverage.

As living standards change and vaccination programs are implemented, public health officials can collect acute disease surveillance and other epidemiologic data to identify at risk adult populations and to guide policy development for adult hepatitis A vaccination.

HEPATITIS A VACCINE VERSUS IMMUNE GLOBULIN FOR POST-EXPOSURE PROPHYLAXIS

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Background: Hepatitis A vaccine administered to persons after exposure to the hepatitis A virus has not been compared directly with immune globulin, which is known to be highly effective in preventing hepatitis A when given within 2 weeks after exposure to the virus.

Methods: We randomly assigned household and day-care contacts, 2 to 40 years of age, in Almaty, Kazakhstan, to receive one standard age-appropriate dose of hepatitis A vaccine or immune globulin within 14 days after exposure to patients with hepatitis A. Instances of laboratory-confirmed, symptomatic hepatitis A infection occurring between 15 and 56 days after exposure were then assessed during active follow-up of all susceptible contacts.

Results: Of 4,524 contacts who underwent randomization, 1,414 (31%) were susceptible to hepatitis A virus and 1,090 were eligible for the per-protocol analysis. Among these contacts, 568 received hepatitis A vaccine and 522 received immune globulin. Most contacts were children (average age, 12 years), and most received prophylaxis during the second week after exposure (average interval after exposure, 10 days). The baseline characteristics of the contacts were similar in the two groups. Symptomatic infection with hepatitis A virus was confirmed in 25 contacts receiving vaccine (4.4%) and in 17 contacts receiving immune globulin (3.3%) (relative risk, 1.35; 95% confidence interval, 0.70 to 2.67).

Conclusions: Low rates of hepatitis A in both groups indicate that hepatitis A vaccine and immune globulin provided good protection after exposure. Although the study's prespecified criterion for non-inferiority was met, the slightly higher rates of hepatitis A among vaccine recipients may indicate a true modest difference in efficacy and might be clinically meaningful in some settings. Vaccine has other advantages, including long-term protection, and it may be a reasonable alternative to immune globulin for post-exposure prophylaxis in many situations.

HEPATITIS A PREVENTION FOR TRAVELERS

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Both global travel patterns and epidemiological features of hepatitis A are on the move. In many subtropical and tropical regions, endemicity has decreased, particularly in urban and affluent segments of the society. Consequently, the monthly incidence rate of hepatitis A among travelers from industrialized countries to developing ones has decreased from 1 per 300 to 1 per 3000, but hepatitis A remains a health risk even for those staying in luxury hotels. But also, there is an increasing number of future travelers in countries with middle-income economies visiting destinations with high hepatitis A endemicity. These must become aware of the need for travel health advice. As they may be among those with the lowest anti-HAV rates in their country, they may need hepatitis A immunization.

The World Health Organization (WHO) in its annual brochure "International Travel and Health" (www.who.int/ith) recommends "the (hepatitis A) vaccine should be considered for all travelers to areas with moderate to high risk of infection and those at high risk of acquiring the disease should be strongly encouraged to accept vaccination independently of where they travel". Nevertheless, cross-sectional surveys conducted at various airports have demonstrated a sub-optimal (<50%) compliance with the recommendation.

Recent studies have determined that by age of 35 years in the U.S. almost 40% have a hepatitis A risk factor as per ACIP definition, even more than 60% if these criteria are expanded. In Switzerland — mainly due to travel — this rate exceeds 80%. Thus, considering lifetime exposure to travel risks, also to occupational or behavioral risk factors, universal vaccination against hepatitis A ought to be considered in an increasing number of countries. As immunization against hepatitis B already is a routine procedure as per WHO recommendations, one may decide to use the available combined hepatitis A / hepatitis B vaccine whenever protection against both infections is indicated.

ECONOMICS: COST-EFFECTIVENESS OF OPTIONS FOR HEPATITIS A VACCINATION

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The aim of this presentation is to give an overview of important issues in health economic evaluation applied to vaccines and to discuss results of economic evaluations of options for hepatitis A vaccination.

Many countries have guidelines for performing economic analyses in health care. Whilst these guidelines generally apply, there are a number of important aspects that need to be carefully considered when evaluating a vaccination program. These aspects include perspective, comparator, time span, Quality Adjusted Life Year (QALY) estimates in young children, parameter uncertainty and uncertainty related to the choice of model. A model should be chosen that minimally meets the analytical requirements given the pathogen, the endemic situation and the intervention.

An overview of economic evaluations of hepatitis A vaccination strategies is presented, based on previous reviews and updated searches of the literature.

The various approaches to the methods used for these analyses are discussed, with special attention to choice of model and comparator. General results of the published evaluations are presented by area of endemicity, options for vaccination (broadly distinguishing universal and targeted options), and epidemiological model.

A MATHEMATICAL MODEL OF HEPATITIS A TRANSMISSION IN THE UNITED STATES INDICATES VALUE OF UNIVERSAL CHILDHOOD IMMUNIZATION

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For many vaccine preventable infectious diseases, mathematical transmission models have shown to be very useful to inform the public health community about the population-level impact of different vaccination strategies upon disease incidence.

A few years ago, the recommendations for Hepatitis A (HA) vaccination in the United States were still regionally based. Although HA incidence rates decreased dramatically following the implementation of vaccination, concerns have been raised at that time that the regional approach might not be sufficient to control HA in the United States. In that context, we developed a mathematical model of HA transmission to evaluate the impact of different immunization strategies on future HA incidence in the United States, in particular to compare regional immunization vs. nationwide immunization and to evaluate impact of age at vaccination. The outcomes of the model indicated that nationwide, routine immunization of 1 year-olds in the United States would have a beneficial effect on incidence of HA compared to regional immunization at 2 years of age, while nationwide immunization of 12-years-olds might result in an increase in HA cases within the next decade compared to regional immunization at 2 years of age. The model also indicated important herd protection effects induced by immunization at 1 year of age.

The outcomes of the model were useful to inform the public health community and policy makers in the United States about the importance of extending immunization to the whole country and of vaccinating as early in life as possible.

Such a model could be adapted to the epidemiology of other countries or regions in the world in order to inform the public health community about the best vaccination strategy to be conducted in order to decrease the burden of HA disease.

COST-EFFECTIVENESS ANALYSIS OF HEPATITIS A VACCINATION IN CANADA USING A DYNAMIC MODEL

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Hepatitis A is a low-incidence, low-burden disease in Canada and vaccination is currently targeted towards groups at risk. Cost-effectiveness analyses (CEAs) of universal Hepatitis A (HA) vaccination compared to no vaccination have been carried out for regions with moderate incidence, such as parts of the United States; however, the cost-effectiveness of universal HA vaccination compared to targeted vaccination in a low-incidence context is not currently known. The goal of our study was to identify an optimal universal HA vaccination strategy for Canada, from the viewpoint of cost-effectiveness. We based our CEA on a dynamic (compartmental) model: unlike cohort models traditionally used in cost-effectiveness analyses of vaccination, dynamic models can account for herd immunity and are thus more accurate in principle. Our CEA was structured as a cost-utility analysis with 5% discounting rate on both costs and QALYs, an 80-year timeframe, and both payer and societal perspectives. Under-reporting was accounted for by adjusting differences between seroprevalence data and time series of reported incidence, and declining transmissibility over time due to improving hygiene was also included, allowing a reconstruction of the history of transmissibility over the past century in Canada. Universal HA vaccination with two doses of bivalent HA/HB vaccine in a school-based setting at age 9, with phasing out of the current targeted programme, was most cost-effective, even though the health benefits were modest compared to other schedules. This "9+9" schedule provides mean net benefits of 49.4 QALYs (SD=6.3) from the societal perspective and 3.8 QALYS (SD=3.0) from the payer perspective, at a threshold of \$50,000/QALY.

INTRODUCTION OF NEW AND UNDERUTILIZED VACCINES IN LATIN AMERICA AND THE CARIBBEAN (LAC)

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Immunization programs in the Americas have made remarkable progress against vaccine-preventable disease (VPD), including the eradication of polio, elimination of measles and neonatal tetanus, and control of other VPDs. However, challenges remain including the introduction of new-generation vaccines against priority diseases of children, adolescents, and adults. To guide PAHO's technical cooperation, the Immunization Unit at PAHO has developed a Regional Vision and Strategy that includes PAHO's position on new vaccine introduction.

The availability and relatively higher prices of new vaccines require countries to strengthen their capacities for: (1) making evidenced-based decisions including economic analyses on the sustainable introduction of new vaccines according to national health priorities; (2) enhancing surveillance for new priority diseases; (3) improving vaccine adverse event reporting systems; and (4) securing sustainable financing for new vaccines.

PAHO launched the Pro-Vac initiative, which consists of training, data collection, and development of economic analysis at country level to strengthen national capacity to generate and use economic evidence for decision-making. PAHO also promotes the strengthening of surveillance capacity, standardization and infrastructure, including laboratory networks. Regarding Hepatitis A, this vaccine has been introduced in the public sector in 2 LAC countries and others are planning introducing it in the near future.

Considering the need to increase national immunization budgets to introduce new vaccines, assessing the potential for increasing fiscal space becomes more important. To that end, PAHO has reviewed quality and effectiveness of existing vaccine legislation in LAC. In addition, PAHO's Revolving Fund for vaccine purchase has been a critical regional mechanism to promote price reductions through bulk vaccine purchase vaccines, accelerating the introduction of new and underutilized vaccines in the Americas.

PAHO will continue assisting Member States in making informed decisions regarding sustainable introduction of new vaccines, including Hepatitis A when appropriate.

CHALLENGES IN INTRODUCING NEW VACCINES: GAVI EXPERIENCES

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This session will provide information on GAVI efforts around new vaccine introduction. The presentation will provide background on the GAVI Alliance and highlight activities and efforts around the GAVI Alliance strategic goal to accelerate the uptake and use of underused and new vaccines and associated technologies and improve vaccine supply security.

Discussed will be the various phases of new vaccine introduction, including development, pre-introduction, introduction, and consolidation. Also discussed will be the various activities required for vaccine introduction in each of these phases. This presentation will also provide information on activities currently conducted around these new vaccine introduction efforts by the respective GAVI partners. The presentation will also outline GAVI experiences in challenges and barriers that have been encountered in introducing new vaccines and give an overview of programs and activities that GAVI has supported to address these challenges and barriers. These include, but are not limited to, the Accelerated Development and Introduction Plans for Pneumococcal and Rotavirus, the Hib Initiative, Advanced Market Commitment and plans for an overall vaccine investment strategy.

COUNTRY AND REGIONAL EXAMPLES OF HEPATITIS A PREVENTION: THE CASE OF ARGENTINA

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In Argentina, there was an endemic situation with associated outbreaks; annually reported rates of HAV infection ranged from min. 70.0 to max. 173.8 per 100,000 inhabitants between 1995 and 2005. Age-specific incidence was highest among 5-9 years old, followed closely by those aged 2-4 years. In the same period, there have been outbreaks involving all Argentinean regions.

Since the introduction of universal hepatitis A vaccination with a single dose at 12 months of age as of June 2005, no new major outbreak has occurred, and the incidence rates have decreased, to reach 28.3 per 100,000 in 2006 and 7.76 in 2007 (calculated up to week 39). There also was a reduction of fulminant hepatic failures. Whether this is due to the impact of the targeted immunization program is presently unknown. In 2006, the reported vaccination coverage was 90% or higher in 14 Argentinean jurisdictions and from 60% to 89% in 7 other jurisdictions. Within Argentina, there have been considerable geographic variations in the reported incidence, but all regions showed a decrease from 2006 to 2007.

The Ministry of Health decided to review disease surveillance data before recommending a second dose. Two research protocols were designed aiming (1) to check the persistence of protective antibodies after the application of a single dose of anti HAV vaccine and (2) to evaluate the seroprevalence of total anti HAV antibodies in 2 -3 year-old children after the implementation of the anti HAV vaccination program.

A recent cost-effectiveness study concluded that greater health gains are derived from the first than from the second hepatitis A vaccine dose. However, this analysis supports the cost-effectiveness of providing both first and second doses to children in Argentina. The cost of a single dose approximately represents 25% of the current vaccination budget in Argentina.

COUNTRY AND REGIONAL EXAMPLES OF HEPATITIS A PREVENTION – THE NETHERLANDS

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The annual incidence per 100.000 inhabitants of reported cases of hepatitis A decreased in the Netherlands (16 million inhabitants) in the last decade from 12 to 2 (< 300 cases per year). HAV is imported mainly by children returning from travel to their country of origin (Morocco, Turkey and Surinam). Families with origin in these countries travel home once every three years.

These introductions cause only limited outbreaks due to effective source and contact tracing and ongoing vaccination efforts. Among men who have sex with men (MSM), the other main risk group, ongoing transmission of HAV is seen for several years.

Children with one or both parents originating from HBV-endemic countries are offered free HB-vaccine. A large percentage of these children is susceptible for HAV. Vaccination has a favourable cost-effectiveness, but is not included in the program. In annual pre-travel sessions, organised in collaboration with health insurance companies, HA-vaccination is offered at relatively low cost. The decline in introduction of HAV coincides with the change of protecting travelling children with vaccine in stead of the immune globulin. The epidemiological transition in the source countries might be equally important in explaining the observed reduction in incidence.

Since 2000 MSM are actively approached for free vaccination against hepatitis B and, with payment of an extra 25 euro, the vaccine is changed to the combined hepatitis A and B vaccine.

Each risk group is associated with specific HAV genotypes: genotype 1B mainly from travellers with frequent, seasonal introductions of different strains; genotype 1A from MSM with clusters of identical strains. The 1A clusters are relatively large and remain present for several years. Hepatitis A thus seems endemic among homosexual men.

There are plans to start a national database of HA-viruses that might help in elucidating previously unidentified sources for individual cases (food related) and to evaluate preventive measures.

IMPACT OF HEPATITIS A VACCINATION PROGRAMME IN TODDLERS AND ADOLESCENTS ON THE INCIDENCE OF THE DISEASE, 1998-2006, PUGLIA REGION, ITALY

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Background

In Italy, the annual incidence of hepatitis A (HAV) was <5/100.000 population in the last decades. However the burden of disease was not homogeneously distributed across the national territory. In Puglia region (South-East Italy, about 4,000,000 inhabitants), HAV has been a major public health threat with an enormous impact on the economy of the region. In the period 1989-1995 the average annual incidence of HAV was 25/100.000; a tremendous increase of cases occurred in 1996-1997 due to a large outbreak in the region. In 1998, an immunization programme targeting toddlers and adolescents started at regional level.

Methods

We used routine surveillance data from the Italian Ministry of Health and Epidemiological Office of Puglia Region for the period 1991-2006 to compare HAV incidence in Puglia and in the rest of the country. We used regional administrative data to estimate the vaccine coverage.

Results

Up to 2004 the vaccine coverage was about 20% and 65% among toddlers and 12 years old adolescents respectively. From 1998 to 2006, the HAV annual incidence in Puglia progressively decreased from 22 to 0.7/100.000, while in the rest of Italy it was ranging from 0.5 to 4.5/100.000 without any evident trend. In Puglia the incidence's decrease involved all age groups; the median age of cases shifted from 19 years in 1997 to 25 years in 2006.

Conclusion

It is very likely that the vaccination programme has played an important role to reduce the HAV incidence in Puglia to a level never reported before and even lower than in the rest of Italy. A herd immunity effect might have occurred. However, an urgent catch up vaccination programme should be planned in order to prevent future outbreaks.

COUNTRY EXAMPLE OF HEPATITIS A PREVENTION - ISRAEL

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Israel was considered a country with intermediate endemicity for HAV until 1999. The mean overall incidence in the years 1993-8 was 50.4/100,000. Of the 2 ethnic groups living in Israel, Jews (75% of the population), living in a relatively high social economic status, showed some decline of disease in the last 2 decades, but still had an incidence of 46.8/100,000. Among non-Jews, living in significantly more crowded conditions with a higher birth rate and low average socio-economic status, the mean rate in 1993-8 was 65.1/100,000 with no trend to decline. In 1999, Israel chose to vaccinate toddlers at a 2-dose program (18, 24 months) without a catch-up program. With an average vaccine coverage of 90% for dose 1 and 85% for dose 2, rates dropped to an overall of 2.3 within < 3 years (in 2002) and in 2006 the rate was 1.1, representing a 98% reduction in overall incidence. Israel is now among the countries with the lowest rates worldwide. Disparity between ethnic groups in incidence of HAV disease has almost been completely eliminated. Elementary school and daycare facility outbreaks have not been observed since 2002. Because of the continuous toddler vaccination program, each year an additional sero-positive cohort is added (so far ~ 90% of all children ≤ 10 years of age have received ≥ 1 dose of the vaccine). The Israel paradigm resulted in a unique picture of low HAV morbidity in the presence of increasing sero-positivity as a result of universal toddler-only vaccination. Adoption of toddler HAV universal vaccination should be considered as a policy of choice in all countries in transition from high to intermediate endemicity.

THE EXPERIENCE OF A UNIVERSAL HEPATITIS A VACCINATION PROGRAM IN CATALONIA (SPAIN)

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The availability of an inactivated hepatitis A vaccine of proven immunogenicity and protective efficacy led the Department of Health of the Generalitat of Catalonia to introduce vaccination of risk groups in 1995. This policy had a very limited impact on disease incidence and, at the end of 1998, a program of mass hepatitis A+B vaccination of preadolescents in schools was started. Three doses of hepatitis A+B were administered at 0, 1 and 6 months.

Seven years after the introduction of this vaccination program an evaluation of its effectiveness and the prevented fraction was carried out by means of a longitudinal analysis of cases of hepatitis A reported between 1992 and 2005 to the Department of Health. The age distribution of cases and incidence rates in the periods before (1992-1998) and after (1999-2005) introduction of the vaccination program were compared. Incidence rates were calculated using the census figures for each year and their 95% confidence intervals (CI) were estimated assuming a Poisson distribution. The vaccinated cohorts were composed of children reaching 12 years of age during 1998-2005 and the non-vaccinated cohorts of children that had reached 12 years of age during the previous years.

The incidence rates in the whole population were 5.51 per 100,000 persons-year during 1992-98 and 2.98 during 1999-2005. The 10-19 years age group showed a rate reduction of 72.5% and the reduction was >45% in the 5-9 years and 20-29 years age groups. Hepatitis A cases in the 10-19 years age group accounted for 21.7% of the total in the pre-vaccination period and 8.3% in the post-vaccination period. The effectiveness of the vaccination program was 99.04 (95% CI: 93.11-99.88) and the prevented fraction in the 12-19 years age group was 90.13% (95% CI: 84.47- 90.89).

In conclusion, the universal vaccination program of preadolescents has had an important impact on hepatitis A in Catalonia, not only in vaccinated cohorts but also in non-vaccinated age groups. These results suggest that hepatitis A vaccination confers herd immunity. The indirect protective effect in this study is suggested by the greater reductions in disease incidence in non-vaccinated subjects from the age groups most frequently in contact with vaccinated cohorts.

PREVENTION OF HEPATITIS A IN AUSTRALIA

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Aims: to describe the epidemiology of hepatitis A and preventive strategies for hepatitis A in Australia.

Methods: Analysis and mapping of national notification and hospitalisation data.

Results: The seropositivity and notifications for hepatitis A continue to decrease in Australia. Indigenous Australian children are at far higher risk of clinical hepatitis A than their non-Indigenous counterparts, particularly in the age group 0-4 years. Several deaths from hepatitis A have occurred in recent years in Indigenous children. Rates of hospitalisation (15.5 vs. 0.3 per 100 000), and notification (24.4 vs. 1.8 per 100 000) were higher in Indigenous children aged 0-4 years compared with other children in the same age group. In the age group 5-14 years, the rates were 4.4 per 100 000 (Indigenous) versus 0.6 per 100 000 (non-Indigenous) hospitalisations. This excess morbidity falls sharply with age. Rates were highest in the Northern Territory, South Australia, Western Australia and North Queensland.

Australia currently recommends hepatitis A vaccination for high risk groups only. A geographically targeted, government funded program for Indigenous children commenced in 2005. The rates of disease in Indigenous children have decreased dramatically since this program.

Conclusions: Australia has a targeted hepatitis A program and increasing rates of susceptibility to infection. Indigenous children are at risk of hepatitis A, particularly early in life. Mapping shows that rates were highest in jurisdictions with the largest Indigenous populations. A targeted hepatitis A program for Indigenous children has been very successful in reducing disease incidence and deaths. Further cost-effectiveness analyses will need to inform decisions on universal vaccination.

Chile is a South American country with a population of 15 million; per capita income is USD 4,346; alphabetization rate is 95.2%.

Hepatitis A is under national epidemiological surveillance by clinical notification since 1975. During the last three decades the country had changed from high to intermediate endemicity. Hepatitis A basal rates have oscillated between 30 and 60 cases/100,000 population, with outbreaks occurring every 4-5 years (reaching rates of 80-110 cases/100.000 population).

In 1991 environmental and health education policies were adopted to control cholera; a sharp decline in the incidence of typhoid fever and hepatitis A was observed in the following 2-3 years. Over the next decade typhoid fever has remained at low rates but outbreaks of hepatitis A continue to occur.

Control mechanisms of hepatitis A have relied on both basic sanitation improvements and outbreak control. Sewage water treatment operations started in 2001 and it is expected 95% of contaminated water to be treated by 2010. For outbreak control, secondary prevention was changed from immunoglobulin to vaccine since 2003.

The last national hepatitis A outbreak occurred in 2002-2003 with rates of +70/100.000. During this outbreak, two control strategies were analyzed by the ministry of health and a group of local experts: general sanitary approach and universal immunization. Although universal immunization was recommended by members of Scientific Societies, the Ministry of Health adopted a general sanitary approach. Private use of hepatitis A vaccine has focused in high economic income population.

Current rates are low (6/100.000 in 2006), with persisting local outbreaks mainly in poor northern villages (rates up to 36/100.000).

EFFECTIVENESS OF UNIVERSAL HEPATITIS A IMMUNIZATION OF YOUNG CHILDREN IN MINSK CITY, BELARUS: FOUR-YEAR FOLLOW-UP

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Background and objectives: Belarus began universal hepatitis A vaccination of children 6-7 years of age in Minsk City in 2003. The analysis was conducted to evaluate the short-term impact of this program.

Methods: Vaccination effectiveness was estimated by comparing the incidence of reported hepatitis A cases after 4 years of immunization with incidence when the universal program started. The ratio of vaccine (Avaxim 80™ / Havrix 720™) doses used was 19:1. A sub-study of hepatitis A seroprevalence was conducted in 324 people >18 years of age.

Results: During the period of 2003-2006 hepatitis A incidence in vaccinated children <14 years of age was 20-fold lower than the incidence in unvaccinated children (0.3 cases/10,000 versus 5.98/10,000, odds ratio=0.05, 95% CI 0.012-0.202), indicating a vaccination effectiveness of 95%. The decreased incidence, from 5.5/10,000 in 2001-2002 to 0.5/10,000 in 2006, among children 11-14 years of age can be explained by a herd effect. Routine vaccination has also resulted in a shift of the age pattern of hepatitis A morbidity. The proportion of cases in children under 14 years of age decreased from 33-41% in 2000-2002 to 7% in 2005-2006. In 2007, overall hepatitis A seroprevalence among adults >18 years was 50%. Seroprevalence increased with age ($p=0.0022$): 22%, 43%, 47%, 67% and 85% at 18-24, 25-29, 30-39, 40-44 and >45 years of age, respectively.

Conclusions: Introduction of hepatitis A vaccination in Minsk resulted in sharply reduced incidence in both vaccinated and unvaccinated children. Virus circulation might be further decreased by beginning vaccination at a younger age. Young adults continue to be at risk of hepatitis A infection.

HEPATITIS A UNIVERSAL VACCINATION OF MILITARY PERSONNEL: THE RUSSIAN EXPERIENCE

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Background and objectives: Universal hepatitis A immunization of Russian forces began in 1996. Active surveillance and high vaccination coverage, allow for evaluation of vaccine effectiveness.

Methods: Three vaccines, Avaxim[®] 160, Havrix[®] 1440 and Hep-A-in-Vac[™] have been administered to several hundred thousand recruits. Cases of hepatitis A are routinely reported. Vaccine immunogenicity was evaluated in selected groups of recruits.

Results: Vaccination has resulted in a large decrease in incidence over the last decade. Vaccination during outbreaks in unvaccinated units prevented new cases within 5-28 days with 100% coverage and 18-42 days with 70% coverage, depending on the vaccine. From 2001-2006 only 5 cases of hepatitis A were reported in >60,000 personnel given one Avaxim dose. Three of these were diagnosed within 10 days after vaccination. At 14 days after vaccination, seroconversion rates (≥ 20 mIU/mL) were 98.3%, 94.0%, and 38.9% for Avaxim, Havrix, and Hep-A-in-Vac, respectively. One month after vaccination 100% of subjects who received Avaxim, 96.2% Havrix, and 82.8% Hep-A-in-Vac seroconverted. Immunogenicity was further evaluated in 2006 in 300 personnel in three units, given one Avaxim dose in 2001, 2002 or 2003. Approximately 94% of subjects vaccinated in 2003, 92% in 2002, and 90% in 2001 retained anti-HAV antibody concentrations ≥ 20 mIU/ml.

Conclusions: Single-dose vaccination has been effective in control of hepatitis A in high risk environments. Protection likely persists for 5 years in more than 90% of personnel vaccinated with Avaxim. Avaxim may have immunogenic advantages, related to kinetics of the antibody response.

COUNTRY AND REGIONAL EXAMPLES OF HEPATITIS A PREVENTION – THE CASE OF CHINA

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Hepatitis A is an acute, usually self-limiting infection of the liver caused by hepatitis A virus (HAV). Transmission occurs primarily through the faecal-oral route, and is closely associated with poor sanitary conditions.

The most common modes of transmission in China include ingestion of contaminated food and water by HAV resulting in outbreaks. Some cases may be infected through close personal contact with another infected person. Among children between 5 and 9, the incidence is 13/100,000, the highest in all age groups. Incidence of Hepatitis A is decreasing since 1990, from 52/100,000 to 5/100,000 in 2006. The decline of incidence is shown in all age groups, but most dramatically among children less than 10.

In 2006, 68,667 cases of hepatitis A have been reported by the national notifiable disease reporting system, and the incidence was 5/100,000. The incidence of Hepatitis A was high in children for those provinces with an incidence higher than 10/100,000, and more adult cases occurred in provinces with an incidence less than 5/100,000. In provinces with an incidence between 5/100,000 and 10/100,000, the incidence is almost consistent over all age groups.

Most hepatitis A cases were scattered. Among the reported hepatitis A cases in 2006, 1,296 of 68,667 cases were from 30 recorded outbreaks. Outbreaks occur more often in rural schools with bad water supply and cold food consumption.

Two types of vaccines are available in China, and both can be produced domestically. During 2004/2005, 16 million doses of vaccine have been administered, which covers 1 birth cohort.

Along with the economic development, the environment is becoming cleaner, hence natural infection with HAV will occur less in the general population. In addition, vaccination coverage of hepatitis A is low. Therefore, the population becomes more susceptible to HAV. In order to prevent the transmission of HAV, China will integrate hepatitis A vaccine into routine child immunization in December 2007, and will provide vaccination to all children above 18 months. Besides immunization, the laboratory based surveillance system should be enhanced.



POSTERS

CURRENT PATTERNS OF HEPATITIS A VIRAL INFECTION IN GEORGIA: CHALLENGES TO ELIMINATION

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Topic: Epidemiology of hepatitis A

P1.1

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Background and objectives: Although significant success has been achieved in controlling and preventing infectious diseases, the liver virus diseases present serious concerns to public health. Hepatitis A infection (HAV) predominates following influenza, acute respiratory diseases and diarrhoeal infections of unknown aetiology. This raised an interest to study patterns of the current epidemic process and assess public health interventions to elaborate a rational strategy towards the elimination of the infection.

Methods: Review and analysis of: Surveillance data; sero-survey results on HAV marker, obtained from screening of 630 persons (220 children and 410 adults, selected randomly) using ELISA with Immmono Organics test-system. Analysis of the epidemic process of HAV infection for two periods: 1977-1982 and 1997-2004. Statistical analysis - for significance of the results.

Results: Downward trend has been observed in HAV infection lately although its proportion remains the highest in the total sum of the liver virus infections. Secular trend is still characterized by peaks every 3-4 years. Significant changes have occurred in age structure; proportion of children under 14 decreased from 61.1% to 51.03%. Children-adult ratio declined more than twice. Incidence rates increased in the age groups 15-19 and 20-29. Age-specific high incidence rates correlated with high level of seropositivism to the infection ($r=0.9$). Water was more frequently implicated as a factor.

Conclusion: Serosurvey revealed an intensive spread of HAV infection contrary to the surveillance data; HAV infection is acquiring patterns of an adult infection; Along with vaccination, drinking water quality and improving sanitation should take priority. Recommendation: In HAV high seroprevalence countries it will be prudent to include testing water on viruses in addition to coli-form bacteria into drinking water standards.

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THE EPIDEMIOLOGY OF HEPATITIS A IN FOUR PACIFIC ISLAND NATIONS: IMPLICATIONS FOR VACCINATION POLICY

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Topic: Epidemiology of hepatitis A

P1.2

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Background and Objectives: Studies conducted before 1980 documented that hepatitis A virus (HAV) infection was highly endemic in the Pacific. The epidemiology of HAV in the Pacific may have changed with improvements in water quality and sanitation. This study examines HAV seroprevalence in four Pacific island nations where HAV has historically been endemic.

Methods: We conducted cross-sectional serosurveys during different years in American Samoa (1995-1996), Chuuk (2000) and Pohnpei (2005) in the Federated States of Micronesia (FSM), Palau (2003) and the Republic of the Marshall Islands (RMI) (2007). Antibodies to HAV (anti-HAV) determined the proportion previously infected with HAV. The results, stratified by age, are presented for each country.

Results: In American Samoa, 0.0% of 4-6 year-olds (95% confidence interval (CI)0.0%-3.7%) were anti-HAV positive. In Chuuk, FSM, 8.6% of 1-6 year-olds (95% CI5.7%-11.5%) were anti-HAV-positive compared to 98.3% of ≥ 16 year-olds (95%CI96.6%-100%). In Pohnpei, FSM, 0.8% of 1-9 year-olds (95% CI0.0%-1.6%) were anti-HAV-positive compared to 95.1% of ≥ 16 year-olds (95% CI 92.2%-98.0%). In RMI, 85.7% (95% CI81.9%-89.5%) of 4-9 year-olds were anti-HAV-positive compared to 100% of 16 year-olds. In Palau, 78.9% of 11-13 year-olds were anti-HAV-positive (95% CI72.7%-85.1%).

Conclusions: The low anti-HAV seroprevalence among children from American Samoa and FSM may represent a permanent change from high to intermediate HAV endemicity or reflect an inter-outbreak period. HAV infection appears to remain highly endemic in RMI. Additional studies are recommended among younger age groups in Palau to better describe HAV epidemiology. In considering whether to introduce hepatitis A vaccine programs, individual countries should evaluate the current epidemiology of HAV transmission and the costs and feasibility of adding a vaccine to their routine schedule.

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Topic: Epidemiology of hepatitis A

P1.3

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Background and objectives: Hepatitis A is a benign infection, which in the developing world affects mainly children; the majority of adults are immune by the age of 30. In the last decade or so, a shift in the prevalence pattern of hepatitis A virus (HAV) infection from a low- to a high-age group has appeared in the developed countries.

Methods: In the present study, 162 Syrian of age between 11-30 year-old groups and both sexes equally were tested by enzyme-linked immunosorbent assay technique for the seroprevalence of hepatitis A IgG antibody (anti-HAV IgG).

Results and conclusions: It was observed that anti-HAV IgG was present in 76% Syrian population; with 72% in the 11-20 year age group and 80% in the 21-30 year age group, and 80% in male and 71% in female. These results demonstrate that HAV infection in Syria is mostly acquired during childhood. This is the 2nd study in Syria, in comparing with the 1st one which have been done 5 years ago by dr Antaki and dr Kebbewar and published in Syrian Clinical Laboratory Association journal 2006 No 2 : there is an improvement in the whole ratio (89% to 76%), this shift has been attributed to an improvement in the socio-economic and hygienic conditions.

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HEPATITIS A SEROPREVALENCE IN DIFFERENT AGE GROUPS IN KIEV CITY, UKRAINE

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Topic: Epidemiology of hepatitis A

P1.4

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Background and Aims: Ukraine is a country with intermediate hepatitis A (HA) endemicity, having a high risk for outbreaks. Vaccination with AvaximTM (Sanofi Pasteur, France) has been documented to be effective in outbreak control in Ukraine. Including universal HA immunization of children in the National schedule is planned for 2011. Additional information about prevaccination HA seroprevalence would be very useful. The objective of the current study was to evaluate HA seroprevalence in different age groups residing in Kiev city, capital of Ukraine.

Methods: A qualitative ELISA kit (Total HAV, DiaSorin, Italy) with a sensitivity of 10 mIU/ml was used for detection of anti-HA antibodies in serum from 1000 non-vaccinated subjects in 5 age groups (1-5, 6-11, 12-17, 18-50 and 50 years).

Results: Among children 1-17 years of age, 87.8% were seronegative. Overall, 49.6% of adults were seronegative. Children from 1-5 years of age had the highest seronegativity rate, 91.9%. The number of seronegative children decreased with age, reaching 79.5% in those from 12-17 years. The lowest seronegativity rate, 43.3%, occurred in adults 50 years of age.

Conclusions: The study shows that the seronegativity rate decreased with age, but remained high through adolescence, providing strong support for incorporation of universal hepatitis A vaccination of young children in the Ukraine.

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INCIDENCE AND SEROPREVALENCE OF HEPATITIS A VIRUS INFECTIONS AMONG TAIWANESE LIVING IN TAIPEI METROPOLIS

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Topic: Epidemiology of hepatitis A

P1.5

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Background and objectives: Hepatitis A virus (HAV) infection is a self-limited disease. However, the infection in adults causes significant morbidity, resulting in long absences from work, possible hospitalisation, and occasional mortality resulting from acute fulminant hepatitis. Today, infection rates have declined with marked improvement of hygienic conditions and progress in health education in recent years. The study was performed to determine the incidence and serovalence of HAV infections among Taiwanese living in Taipei Metropolis.

Methods: From 2001 through 2006, 13,190 serum samples have been collected from subjects who have been admitted to Taipei City Hospital and analysed for acute infection marker (HAV IgM). In addition, to evaluate the seroprevalence of HAV infection in Taiwanese, serum samples were obtained from randomly selected subjects among those who have been admitted to hospitals around the Metropolis from July 2006 to July 2007. A total of 1,200 subjects with median age of 45 were enrolled in the study to analyse the anti-HAV immune status (HAV IgG).

Results: As a result, a total of 25 hepatitis A cases were diagnosed among 13,190 Taiwanese during 2001-2006, approximately 4.16 cases per year. The annual incidence rates were 0.21% in 2002, 0.19% in 2003, 0.12% in 2004, 0.19% in 2005, and 0.105% in 2006. All patients were males-females (ratio 1:1.2) with a median age of 43 yr (range, 18-68). The most common symptom was nausea (92%) and older patients had usually serious complications. Furthermore, the overall anti-HAV IgG seropositive rate was determined to be 42% (5041/200).

Conclusions: The yearly HAV infection rate is declining in Taiwanese population (0.1% in 2006) and nearly half of the population does not own protection antibody for HAV infection. The median age of the primary infection in the population is shifted and was older than in previous studies. Given the changing epidemiology of the disease and the associated increase in morbidity, HAV vaccination for Taiwanese could be the best strategy for prevention of HAV infection in this country.

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CLINICAL FEATURES OF SYMPTOMATIC HEPATITIS A IN NORTH AREA OF GYEONGGI-PROVINCE, KOREA, FOR RECENT 9 YEARS

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Topic: Epidemiology of hepatitis A

P1.6

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Background and aims: In South Korea, hepatitis A virus (HAV) infection in children decreased recently because of hygiene improvement. As opposed to this, symptomatic hepatitis A (SHA) in adults increased. A national outbreak of SHA occurred in 1998. We investigated the clinical features of SHA in the north area of Gyeonggi-province, Korea from 1998 to 2006.

Methods: A total of 166 patients with SHA who showed IgM anti-HAV antibody from January 1998 to December 2006 in single hospital located in the target area were analyzed.

Results: Male and female ratio was 1.35:1. Mean age was 25 years (range 5-61). Distribution of SHA according to age showed high frequencies in 3rd and 4th decade of age, 69 (41.6%) and 46 (27.7%) cases, respectively. Annual frequency was 20, 16, 22, 5, 11, 7, 16, 33, and 56 cases from 1998 to 2006, respectively. Chief complains were gastrointestinal symptoms (27.1%), fever with chill (27.1%), fatigue (18.7%), jaundice (15.7%), and etc. Mean hospital stay was 9.9 days (range 2-38). The highest ALT and total bilirubin (TB) (meanSE) was 2343161 IUL and 5.90.2 mgdL, respectively. Twenty-eight cases (16.9%) were children (under 15 years). Compared to children, adult patients showed a significant elevation of ALT and TB. There was no severe complication such as encephalopathy, ascites or death.

Conclusion: After the outbreak of SHA in 1998, annual frequency of SHA decreased in 1999~2003, and then increased from 2004 with an abrupt increase of SHA in 2006 in north area of Gyeonggi-province, Korea. Frequencies of SHA in the 3rd and 4th decade of age were so high, that preventive methods against HAV for these high-risk groups must be investigated in South Korea.

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HEPATITIS A VIRUS INFECTION AMONG MEXICAN YOUNG POPULATION. NATIONAL HEALTH AND NUTRITION SURVEY 2006

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Topic: Epidemiology of hepatitis A

P1.7

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Background and objectives: Hepatitis A virus (HAV) remains as a very common infectious agent in Mexico. This survey aimed to measure the seroprevalence of HAV and to describe some socio-demographic features of infection in children and adolescents throughout Mexico.

Methods: This was a probabilistic population-based study nested in the Mexican National Health and Nutrition Survey 2006. Following parental consent, children aged 1-9 and adolescents 10-19 years old were randomly selected from August 2005 until June 2006. In total 7,176 serum samples were ELISA tested for HAV antibodies. Data about age, gender, geographic region of residence and greater Mexico City, urban or rural settings were obtained.

Results: Anti-HAV among children was 56.8% and for adolescents 75.6%; there were no gender differences. HAV seroprevalences by age group were: 47.7% (1-4 years); 67.4% (5-14 years) and 79% (15-19 years). With regard to geographic region, the South showed the highest prevalence both in children (68.8%) and adolescents (87.8%) in comparison to the North and Central region (lowest prevalence). The setting provided by greater Mexico City presented the lowest prevalence among children (41.1%) and adolescents (61.3%) as compared to other urban and the rural (highest prevalence) settings.

Conclusions: Results obtained are mostly comparable to data gathered during the National Health Survey 2000. One important exception is that children seem to have increased their infection rate from 43% to 57%. As of year 2006, it is possible to estimate that 11,487,796 children and 17,287,421 adolescents have been infected by HAV. This public health problem known to be related to poor sanitary and social conditions of certain population groups, and which is vaccine preventable, requires to be addressed by the Mexican health authorities in order to minimize HAV transmission.

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DISCORDANCE BETWEEN IGM ANTI-HAV POSITIVE RESULTS AND THE CLINICAL AND BIOLOGICAL CHARACTERISTICS OF NOTIFIED HEPATITIS A CASES, FRANCE, 2006

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Topic: Epidemiology of hepatitis A

P1.8

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Background and objectives: In France, cases of hepatitis A, defined by serum anti-HAV IgM positivity, have been mandatory reported since November 2005. Recent publications suggest that false anti-HAV IgM(+) results are more likely in older people. Our objective was to compare clinical and biological characteristics of older and younger cases notified in 2006 to investigate this hypothesis.

Methods: Data collected by mandatory notification include sex, age, ALT (value, laboratory reference), IgM test kit (brand name, sample optical density, threshold), ratios (sample optical density, threshold), clinical signs and exposures. The characteristics of older (50 years) and younger (18-50 years) cases were compared.

Results and conclusion: In 2006, 1,336 cases were notified (incidence rate 2.1100,000); 704 (53%) were 18 years old, 500 (37%) 18-50 years and 132 (10%) 50 years. Cases of 50 years were more likely to be women (51% vs 34%, p10-3), and less likely to have a jaundice (59% vs 79%, p10-3), to have cases among close contacts (8% vs 32%, p10-3) and to have travelled outside mainland France (29% vs 41%, p0.02) than 18-50 years old. Thirty-eight percent of the 50 years had ALT values 10 times the reference value vs 12% of the 18-50 years (p10-3). Ratios were ≤ 3.65 vs 5.18 in 50% of the 50 years and of the 18-50 years respectively. The clinical and biological characteristics of the 50 years cases are indirectly indicative that false positives may be more common in older than younger cases. A specific IgG avidity test developed by the French National Reference Center for hepatitis A will be used to further test this hypothesis. It may then be used to improve diagnosis among older cases and avoid unnecessary control measures.

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SHIFTING EPIDEMIOLOGY OF HEPATITIS A IN BRAZIL: SHOULD WE THINK ABOUT IMMUNIZATION POLICY?

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Topic: Epidemiology of hepatitis A

P1.9

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Background and objectives: Recent studies have shown that hepatitis A virus (HAV) prevalence rates are decreasing in several Latin American countries. Herein, data on HAV seroprevalence and mortality rates over the last two decades available in scientific databases and official government data for the several Brazilian regions were evaluated. Studies conducted in the Northernmost regions of Brazil have indicated that, although improved hygiene has led to a reduction in childhood exposure to HAV, the greatest exposure still occurs early in life. On the other hand, in the Southeastern region, where improvements in sanitary conditions have been largely implemented mainly in urban areas, a decline in HAV seroprevalence has been observed resulting in several hepatitis A outbreaks. Epidemiological data obtained from both seroprevalence studies and reported hepatitis A outbreaks indicate that the youngest individuals, especially those under 5 years of age, are mostly unprotected from HAV infection, regardless of their socioeconomic status. A decline in the anti-HAV prevalence could also be observed among young adults in a study that we conducted in the State of Rio de Janeiro throughout the last two decades with health care students.

Method: In April 2007, serum specimens were collected and tested for anti-HAV by ELISA method. The results were compared to those obtained in 1996 and 1986 from students of the same age and attending the same university.

Results: HAV seroprevalence decreased from 54,3% (samples collected in 1986) to 9,2% (samples collect in 2007), which indicates a decrease in the exposure to HAV infection. Surveillance data about the incidence of hepatitis A in Brazil are lacking, Therefore, in an attempt to generate reliable information on the trends seen in hepatitis A incidence in Brazil, we analyzed only the rate of hepatitis A mortality since fatal cases are generally well investigated and properly diagnosed. Nationwide, hepatitis A mortality rates declined progressively from 1980 to 2002.

Conclusion: Taken together these facts point out the urgent need for further discussion about the implementation of preventive measures through vaccination programs for controlling hepatitis A in Brazil.

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EPIDEMIOLOGY OF HEPATITIS A AND OUTBREAK INTERVENTION THROUGH ACTIVE IMMUNIZATION IN BOGOTÁ, COLOMBIA

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Topic: Epidemiology of hepatitis A

P1.10

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Background: Seroprevalence studies evidence Bogota as a region in transition to intermediate endemicity. Frequent outbreaks compromising scholarship population and adolescents, and acute liver failure cases confirm these findings.

Objective: descriptive epidemiology and report of outbreaks intervention by vaccination.

Methods: Surveillance program of the Public Health Department, 2000-2006. Frequency distribution, incidences by age, sex and residence. Characterization of outbreaks and intervention by vaccination.

Results: Global incidence rates, Bogota, Colombia, 2000-2006: Years 2000 2001 2002 2003 2004 2005 2006. Cases: 2015 1888 2924 3028 2722 3181 3077. Incidence: 31.5 290 47.8 44.3 39.0 47.5 45.2. No of outbreaks/year: 8 64 63 74 95 103. Total cases/outbreak: 166 275 275 346 548 471. Incidence for the period is 40.5 X 100.000, children 1-14 years concentrate 68% of cases: 1-4: 15%; 5-9: 31%; 10-14: 22%; 15 years: 32% Incidence is higher in children 5-9 yrs. Outbreaks were reported in schools (54%) and family clusters (46%). Geo-reference analysis demonstrated that south-east areas of the city were mostly affected, with incidences from 61-95 X 100.000.

Conclusions: Bogota reported 18.836 cases of hepatitis A from 2000-2006, true number could be 75.3444 cases. Incidence is higher in children 5-9 yrs. Localities with high incidences were concentrated in populations with low socioeconomic standards and unsafe drinking water. Outbreak intervention has successfully controlled hepatitis A in school settings, reaching 80% vaccination coverage with one dose of hepatitis A vaccine. Vaccination campaigns have been considered for these localities, where hepatitis A has a high social cost due to children's and parents' absenteeism, school desertion, loss of parents labour days, closing of schools for several months, and reduced feeding portions for absent children.

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SEROPREVALENCE OF HEPATITIS A VIRUS IN COLOMBIAN CHILDREN 1-15 YEARS OLD

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Topic: Epidemiology of hepatitis A

P1.11

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Background and objectives: Seroprevalence of hepatitis A in children 1-15 yrs will demonstrate the pattern of infection and contribute to vaccination policies. The objective is to estimate the seroprevalence of anti-hepatitis A antibodies in children 1-15 years in a representative sample of Colombian children.

Methods: This is a hospital-based seroepidemiological transversal survey on children 1-15 years old. National population sample was estimated in 2.262 children, from Bogotá, Medellín, Cali, Bucaramanga, and Barranquilla. Sera were collected from children 1-4 years, 5-9 years and 10-15 years of age. Hepatitis A antibodies were detected using standard immunoenzimatic assay. Statistical analysis calculated the seroprevalence of anti-hepatitis A antibodies in selected age groups.

Results: Preliminary report includes 782 samples from Bogotá (436), Cali (262), Medellín (84). Global seroprevalence was estimated in 21.4% for children under 15 yrs.

Prevalence by age groups: 1-4 years: 8.1%; 5-9 years: 22.4%; 10-15 years: 29.4%

Geographic distribution of hepatitis A seroprevalence:

| Cities/age groups | 1-4 years | 5-9 years | 10-15 years | Global prevalence |
|-------------------|-----------|-----------|-------------|-------------------|
| Bogotá | 7.3% | 20.2% | 25.4% | 19.7% |
| Cali | 4.4% | 19.6% | 35.6% | 20.9% |
| Medellín | 17.1% | 52.0% | 33.3% | 32.1% |

Conclusions: Preliminary seroprevalence rates demonstrate that 78.6% of children under 15 years of age are susceptible to hepatitis A virus infection. Bogotá shows a low prevalence of Hepatitis A antibodies even in the group 10-15 yrs. In contrast Cali increases the exposure to hepatitis A infection in this specific group up to 35.6%. Medellín has higher rates of hepatitis A infection. These results classify Colombia as an intermediate endemicity country, with frequent outbreaks in school children and clinical disease in adolescents and young adults. National vaccination programs are recommended as the best intervention to control hepatitis A in Colombia.

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EPIDEMIOLOGY OF HEPATITIS A VIRUS INFECTION IN SOUTH AFRICA

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Topic: Epidemiology of hepatitis A

P1.12

Although South Africa is a region of intermediate to high endemicity for HAV infection, there are pockets of low prevalence, particularly in the upper socio-economic groups (mainly the white population). The majority of black South Africans show prevalence of over 80% by 10 years of age. However, the increasing access to better living conditions for many black South Africans may eventually change the epidemiology of HAV by increasing the number of susceptibles. Data on the precise burden of hepatitis A disease are rare. Adults generally show higher prevalences based on several studies. A recent age specific survey indicated that anti-HAV levels were relatively high (up to 55%) soon after birth, but dropped to lower levels in both lower and upper socio-economic groups. While the upper socio-economic class retained the lower levels of antibodies, with limited increase to 35% by 5 years of age, the lower socio-economic class experienced a dramatic increase, from 48.3% for 3 to 5 year-olds to 86.6% for 11 to 13 year-olds. By 19 years of age, 92% of the lower socio-economic class was protected against HAV infection, compared to only 27% in the upper socio-economic group. Similarly, the prevalence was 100% in antenatal women from the lower socio-economic class compared to only 38.3% of antenatal women in the upper socio-economic group (Schoub et al SAMJ 89: 1074). Additional studies demonstrated that as high as 96% of black health care workers (HCWs) are naturally protected against HAV infection, compared to only 40% of HCWs from the upper socio-economic class. In conclusion, although the upper socio economic class is particularly vulnerable to HAV infection, the epidemiology is likely to change due to changing socio-economic factors in other population groups. Currently, prospects for universal vaccination against HAV seem far remote in South Africa as a result of competing health priorities, including new childhood vaccines. The vaccine is only recommended for persons at an increased risk of HAV infection. These include HCWs, food handlers, recipients of blood or blood products, susceptible travellers to HAV endemic countries, children in day-care centres and their families, and day-care centre staff.

DIFFERENCES IN THE PREVALENCE OF ANTIBODIES AGAINST HEPATITIS A VIRUS (HAV) BETWEEN CHILDREN AND ADOLESCENTS OF CURITIBA AND ITS METROPOLITAN REGION

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Topic: Epidemiology of hepatitis A

P1.13

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Background and objectives: The rapid growth of large urban centers is changing the epidemiology of Hepatitis A in these areas. Objectives: to estimate the seroprevalence of anti-HAV antibodies in children aged 1 -14 years and to identify the most susceptible populations.

Method: A transversal epidemiological study conducted in the city of Curitiba and its metropolitan region (Brazil). Data on subjects living conditions were collected by a socioeconomic situation questionnaire. Laboratory analysis consisted of qualitative measurement of total anti-HAV antibody levels in serum samples. Statistical analysis was descriptive with χ^2 tests: 5% accuracy and 95% CI.

Results: 460 children from Curitiba and 441 from its metropolitan region were enrolled. The overall prevalence of anti-HAV antibodies was 19.8%. Children from the metropolitan region came from poorer families, in areas poorly served by sewerage systems and had less well educated parents. A statistically meaningful difference was observed in the prevalence of antibodies according to the stratification by minimum wages. It was higher in the population with an income below 3 wages ($p < 0.05$). The prevalence of anti-HAV antibodies in the 10-14 years age group was also statistically higher among children from the metropolitan region (36.1%) compared to those from the city of Curitiba (24.3%), $p < 0.05$.

Conclusion: These results confirm previous studies which show different hepatitis A prevalence rates can occur between adjacent regions and these differences can be linked to inequitable socioeconomic conditions. This knowledge justifies the investment in control measures, including improved sanitation and early vaccination.

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Topic: Epidemiology of hepatitis A

P1.14

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Background: Hepatitis A virus (HAV) is present worldwide and is endemic in many regions. The level of endemicity, measured by the prevalence of specific antibodies against hepatitis A virus (HAV) by age group, varies with sanitary and socioeconomic conditions of the population. With the rapid growth of large urban centers its prevalence is changing in these areas. Knowledge about the real burden of the disease and the under-notification rate is essential for developing a public vaccination policy.

Objective: To evaluate the burden of hepatitis A (HA) in Parana state and to estimate the correction coefficient of under-notification in Parana.

Methods: Maluf E et al seroprevalence, epidemiological surveillance official data and data available in the literature were used to determine the burden of HA disease and the correction coefficient of under-notification.

Results: Based on the population of 2,799,289 people under 15 years of Parana, we expect to have 14,063 symptomatic cases of hepatitis A per year. From this we can expect: 84,378 medical visits; 421,890 lab tests; 703 hospitalizations; 1,406 relapses; 14 fulminant hepatic failures; 6 transplants; 1 case of retransplantation; 3 fulminant hepatic failures with no transplantation and 84,378 days of absenteeism. The estimated correction coefficient of under-notification was 14.6.
Conclusions: The burden of hepatitis A is substantial in Parana state and the correction coefficient of under-notification was similar to the one described in the international literature. The hepatitis A vaccination would certainly reduce the burden of this illness in Parana.

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Topic: Epidemiology of hepatitis A

P1.15

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Background and objectives: Hepatitis A is considered an endemic infection in Morocco, which is considered as a zone of intermediate endemicity. However, Hepatitis A vaccine (available since 2003) is not yet routinely administered. Hepatitis A generates a non negligible morbidity and mortality. The purpose of this study is to describe epidemiological features of severe viral hepatitis (SVHA) A in CHIR hospital Casablanca in Morocco during seven years.

Methods: It is a retrospective study conducted between (2000 - 2007) at the infectious disease department of the children's hospital of Casablanca. The criteria of inclusion were a positive anti HVA IgM or a compatible clinical presentation with high hepatic enzymes (6 to 10 x normal) and at least one criteria of severity. Records of hospitalized patients with SVHA diagnosis were retrieved from registers and electronic databases.

Results: Since July 2000 to July 2007, 120 cases of (SVHA) were recorded. The mean age of our patients was 7 years old, 52% were female. Similar rates in the patients entourage were detected in 17% of the cases. VHA was confirmed in 82,5%. The mean of clinical history was 15 days; hospitalisation length was 11 days, jaundice was recorded in 94%, bleeding symptoms in 23%, hepatomegaly in 35%, oedema in 12.5%, and encephalopathy in 23%. The hepatitis infection was fulminant in 17% and severe in 53%. Thrombocytopenia was recorded in 3% (4 cases), anemia in 11% (13 cases). Evolution: prolonged forms (1 month) were seen in 12 cases, the relapse of hepatitis in 5 cases, death was recorded in 12 cases (10%).

Conclusion: HAV infection is a significant cause of morbidity and mortality among children in Morocco. The disease is mostly prevalent in preschool and school-aged children. A considerable number of patients tend to have a complicated course and prolonged hospitalization. In view of these data, hepatitis A vaccine should be considered as a part of routine childhood immunization.

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THE MODERN EPIDEMIOLOGY OF HEPATITIS A IN THE NORTH-WESTERN REGION OF THE RUSSIAN FEDERATION

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Topic: Epidemiology of hepatitis A

P1.16

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The Hepatitis A virus (HAV) infection morbidity confirmed by anti-HAV IgM detection in 80-100% of cases decreased in 6 times in Russian Federation in 2001-2006 compared to 1981-1986. In the North-Western region a similar trend was registered, but morbidity reduction was slower in dynamics. The decrease in number of HAV cases was observed in all age groups, but this change was more significant in children 0-6 years old. The highest HAV incidence rates shifted to older age groups: 11-14, 15-19, 20-29 years old. Limited infection spread during the past 25 years led to changes in HAV herd immunity in the population. Testing of sera of St. Petersburg citizens aged 20-29, 30-39 and 40-49 years for anti-HAV IgG and conducted 4 times in 1986-2005 has shown differences in seropositivity in the population. During the observation period in the group of 20-29 years old anti-HAV IgG rate fell down twice (62% and 30% respectively), but in the group of 40-49 years old the changes were less significant (88% and 70% respectively). It should be noted that the number of mix-hepatitis (HAV + chronic HCV HBV) cases increased in the last years. The share of these cases in the total number of mix-hepatitis patients reached about 10%.

Conclusion: The dramatic decrease of HAV immune population in active age cohorts requires the strengthening of preventive measures including, in particular, extension of HAV vaccine administration.

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Topic: Epidemiology of hepatitis A

P1.17

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Background and objectives: Hepatitis A is a vaccine preventable disease with changing epidemiology. In Greece, the vaccine has been available and recommended but no universal mass vaccination has been implemented as yet. Seroepidemiology of hepatitis A in children 0-14 years old living in Greece was studied.

Methods: We collected 100 sera per year of age, stratified by geographic region. Demographic data and documented hepatitis A vaccine history was entered into a specially designed anonymous database. Sera were tested for the presence of anti-HAV IgG antibodies (AXSYM, Abbott Laboratories).

Results: Data from 1,393 children were analyzed. Although the vaccine is not reimbursed, 25.7% of children were fully immunized. Children from immigrant families (11.42%) and children living in rural areas (21.55%) were less likely to be immunized. Among fully vaccinated children, 89.9% (323359) were immune. In unvaccinated children over 12 months of age, the rate of natural immunity was 17.07% (149873). Un-immunized immigrant children had a significant higher seroprevalence (26.3% versus 14.9%, OR2.04). Interestingly, living in rural areas was not associated with higher rates of natural infection.

Conclusions: Although there is an identifiable selection bias in our sample collection since sera were collected from Public Paediatric Clinics and since we had a high percentage of immigrant children in the study cohort, the implementation of universal vaccination against hepatitis A in Greece should be discussed, given that according to our results 17% of unvaccinated children have serologic evidence of past natural infection.

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Topic: Epidemiology of hepatitis A

P1.18

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Background and objective: More than 100 million Chinese children have received hepatitis A (HA) vaccines and the nationwide annual incidence rate of HA declined from higher than 50 per 100,000 before 1992 to lower than 5 per 100,000 during the past 3 years. Causes for the decline and changing HA epidemiology were studied.

Methods: Data on HA incidence, vaccine coverage and serological follow-up were analyzed.

Results: Cyclic epidemics disappeared; children were no longer at higher risk and seasonal peaks flattened in most provinces of China. In rural Hebei, the annualized risk of HAV infection declined from 20% during the 8 years (a single epidemic cycle) before the mass immunization to 0.35% in vaccinated and 2.0 % in unvaccinated children during the 8 years after the mass vaccination. Mass vaccination has led to elimination of HA in a few counties and cities. However, the sharp drop in hepatitis A incidence is not attributable to the mass vaccination alone. In the well developed areas, such as Shanghai, hepatitis A and shigellosis, both enteric diseases, dropped dramatically from around 120 and 130 per 100,000 respectively in 1990 to around 3 and 33 per 100,000 in 2005. The drop of the 2 diseases was correlated with the rapid increase of GDP. The impact of HAV vaccination was observed only recently when the previously immunized children have grown up to replace the young adults of the population.

Conclusions: The contribution of the childhood HAV vaccination to the rate decline has been so far secondary. The eventual eradication of HAV would rely on vaccination.

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Topic: Epidemiology of hepatitis A

P1.19

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Background and objectives: Venezuela has been considered a as a high endemicity country for Hepatitis A (VHA) and children and adolescents are frequently affected. This study will obtain epidemiological indicators to describe the trends of hepatitis A in Venezuela.

Methods: Recollection of Venezuelan official yearly registry of morbidity and mortality compiled by Ministry of Health from 1990-2005. Descriptive statistics applied; frequency distribution, calculated crude and specific rates, graphics and correlation coefficients. Data was classified and analyzed by age, sex and residence.

Results: Morbidity rates (specific laboratory confirmed VHA) is very high in Venezuela (25,3 x 100.000), and has not time trend. Incidences are higher in children 5-9 years, (54,1 x 100.000), followed by children 1-4 (43,5 x 100.000) and 10-14 (30,6 x 100.000). Registry reports that most hepatitis is unspecified (around 78%). Rates in unspecific viral hepatitis are higher as well in children 5-14 years old (193.5 x 100.000). There is a strong correlation (r 0,997; p 0,000), mirror image between curves of VHA and unspecific viral hepatitis by age groups. Therefore incidence rates of hepatitis A could be as high as 111 x 100.000 for Venezuela. VHA is considered the cause of about 14% of all deaths caused by hepatitis virus.

Conclusions: VHA affects mainly children under 15 yrs, therefore VHA is in transition to intermediate endemicity. Preliminary seroepidemiological survey results show that contact with HAV is becoming lower in children less than 15 yrs, particularly in high and medium income populations. Universal vaccination should be implemented to reduce morbidity, complications and high costs derived from clinical infections and frequent outbreaks of hepatitis A in Venezuela.

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THE SHIFTING EPIDEMIOLOGY OF HEPATITIS A FOLLOWING ROUTINE CHILDHOOD IMMUNIZATION PROGRAM IN ISRAEL

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Topic: *Epidemiology of hepatitis A*

P1.20

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Background: Until recent years, Israel was considered a country with intermediate hepatitis A virus endemicity with an annual reported incidence rates of approx. 50 per 100,000 population.

Objectives: In 1999 Israel became the first country to introduce immunization against hepatitis A into its national childhood vaccination program. The study objectives were to assess the uptake of hepatitis A vaccine following the new policy and to examine the incidence of hepatitis A and the number of prevented cases.

Methods: Data on incidence of hepatitis A and vaccination rates were obtained from a large health maintenance organization in Israel covering 1.6 million members. We identified all members that were diagnosed by a primary care physician as suffering from hepatitis A, had a positive hepatitis A virus-IgM test result, or were hospitalized due to hepatitis A between 1998 and 2004.

Results: The results indicate that 5 years following its inclusion into the national childhood immunization program, vaccination coverage levels with at least one dose of hepatitis A vaccine for children aged under 5 years and 5-14 years were 87% and 51%, respectively. During this period the annual incidence rates declined by 88% from 142.4 to 17.3 per 100,000. The most significant reduction in morbidity was observed among children.

Conclusions: In endemic areas, vaccination of infants and children against hepatitis A may be efficient to greatly reduce the total burden of the disease.

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HAV EPIDEMICS IN ROMA POPULATION OF TWO PREFECTURES IN NE GREECE

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Topic: Epidemiology of hepatitis A

P1.21

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Background and objectives: HAV is the first causative agent for acute hepatitis worldwide. Greece is included in the list of low endemicity countries regardless of existing groups, like ROMA, with high impact. In Greece a big reduction of the impact of hepatitis A infection was observed during the period 1980-1995, and today most cases are sporadic. Over the last years 210-250 cases of hepatitis A annually have been reported, and the illness is presented with the form of sporadic cases or epidemics. The present study focused on a reported outbreak of hepatitis A in two prefectures, Xanthi and Evros, NE Greece from July till September. A case study was performed.

Methods: An outbreak investigation questionnaire was developed to gather information on patients' gender, age, symptoms, dates of onset symptoms, laboratory tests and hospitalization. After 15 days, cases of HAV in the neighbouring prefecture of Alexandroupolis were reported and a similar questionnaire was developed to collect information on the relatedness of the cases. Serum samples from patients were collected for laboratory investigation. RNA from serum samples was extracted using the QIAamp Viral RNA kit according to the manufacturers' protocol, and tested in RT-PCR reaction. Positive samples for HAV were confirmed by sequencing of the PCR product. Also two water samples were tested for HAV.

Results and Conclusions: Forty-one cases from two prefectures were reported from July till September. 80.5 % of the patients were up to 10 years old. 48.8 % of the patients were male and 51.2% were female. 80.5% of the cases were from Xanthi prefecture from where the initial cases were reported. All the cases reported in Evros prefecture, were related to cases from Xanthi prefecture. Also, 65.9% of the cases had a clear relationship. 75.6% of the cases were hospitalised. Vaccination of the populations by the Health Departments of both prefectures as well as sanitation measures were performed and the epidemic was controlled.

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Topic: Epidemiology of hepatitis A

P1.22

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Background and objectives: Ecuador is considered a country with a high endemicity for Hepatitis A (VHA). However school age children, adolescents and young adults are frequently affected by important outbreaks. This study describes the epidemiological trends of hepatitis A in Ecuador.

Methods: Recollection and analysis of official yearly registry of morbidity compiled by Epidemiological Surveillance Group of Ministry of Health from 1994-2006. Descriptive statistics applied. Information is analyzed by incidence and total cases by sub-regions and provinces.

Results: country incidence rates vary in this period from 41.42 to 73.5 x 100.000, and do not evidence a time tendency. Oriente sub-region reported the highest incidences (64.8-139.15 x 100.000), followed by Sierra (37.4-74.58 x 100.000), Costa (26.5-74.84 x 100.000) and Insular (4.85-38.83 x 100.000). High incidence rates (some years at a rate 200x100.000) by provinces are reported in Oro, Orellana, Zamora, Sucumbios, Pastaza, Napo, Morona, Loja, and Los Ros among others. Epidemic years 2000 and 2001 reported the highest number of cases and incidence rates, 9.294 and 8.104 cases, and 73.5 and 64.9 x 100.000, respectively. A total of 130.284 clinical cases were reported for this period, but the real number could be as high as 520.136 cases.

Conclusions: Important variations in incidence rates were shown between sub-regions in Ecuador. High HAV circulation and clinical cases were reported in Oriente. According to CDC criteria for vaccination, universal vaccination should be established in countries with incidence rates 20 x 100.000. Further characterization requires precise incidence rates by age, and age distribution of clinical cases. Seroepidemiological studies will contribute to the definition of the endemicity level in Ecuador, in order to introduce universal vaccination in EPI programs.

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PREVALENCE OF HAV TOTAL IN HCV INFECTED PATIENTS ATTENDING A PUBLIC HOSPITAL IN PETRÓPOLIS, RIO DE JANEIRO, BRAZIL

KYCIA MARIA DO Ó
FUNDAÇÃO OSWALDO CRUZ
BRAZIL

Topic: Epidemiology of hepatitis A

P1.23

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Hepatitis A virus (HAV), a hepatovirus of the Picornaviridae family with a worldwide distribution, can cause an infection disease with mainly faecal-oral transmission, through ingestion of contaminated water and food or through person to person contact. In Brazil this infection has an endemic pattern with epidemic outbreaks that can present as major public health problem depending on local sanitary conditions. The infection is shifted to a higher age group, if they haven't been in contact with the virus during their childhood. In Brazil, few information is available on the true incidence and prevalence of HAV total in HCV infected individuals. In the present study we analyze IgG antiHAV marker in HCV positive population: 293 adults attending public health units and tested at Reference Laboratory of the state of Rio de Janeiro - Laboratrio Central Noel Nutels (Lacen) - during the period 2004-2007. All patients are 2-85 years old. Samples were processed through immunoenzymatic assay (AXSSYM SYSTEM ABBOTT) for the detection of IgGHAV specific antibody. Preliminary data showed that 30.3% (89 patients) are HAV IgG positive. Although hepatitis A prevalence is diminishing in Brazil due to improvements in basic sanitation conditions, Anti HAV total antibodies prevalence shows that HAV prevalence is relatively stable in HCV carriers.

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LONG-TERM EFFICACY OF LIVE ATTENUATED HEPATITIS A VACCINE: RESULTS AFTER 15 YEARS OF OBSERVATION

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Topic: Hepatitis A vaccines

P2.1

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Background and Objects: Live attenuated hepatitis A vaccine (H2 strain) is now widely applied in prevention of hepatitis A in China, India, and other endemic countries. Its safety and immunogenicity has been proven in many research reports. It is essential to evaluate the vaccine's long-term efficacy. This study reported the results after 15 years observation.

Methods: A total of 220 children with negative anti-HAV antibody (aged 1-3y) were taken for following assay to observe seroconversion and GMT level after inoculation at 2m, 12m, 6yrs, 10yrs and 15yrs. Another survey that was sampled in different age groups (3y, 6y, 9y, 15y, 18y, 25y, and 35y) compared anti-HA antibody positive rate before and after inoculation at 10yrs. Epidemiological observations were taken for 15 years to evaluate the relationship between vaccine coverage and hepatitis A morbidity. Serum was detected by ELISA (Calibrated by WHO international reference) and ABBOTT AxSYM HAVAB mEIA.

Results: Seroconversion in following assay after inoculation 2m and 15yrs was 98.6% and 81.3% separately. Under 18yrs children before and after vaccination 10yrs, the anti-HA antibody positive rate was significantly different, from 7.69% to 70.45% (in 3yrs group) and from 52.58% to 71.78% (in 18yrs group). Epidemiological efficacy: when vaccine coverage rose from 57% to 74% in children (aged 1 to 15 yrs), there was no HA epidemics. When vaccine coverage reached 85%, there were no HA cases. Finally, as vaccine coverage remained between 85% and 91%, there were no HA cases in the group population (1-15yrs) for 10 years.

Conclusions: Live attenuated hepatitis A vaccine (H2 strain) has an obvious long-term efficacy in prevention and control of HA epidemics.

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A LONG-TERM STUDY COMPARING THE IMMUNOGENICITY OF TWO PEDIATRIC HEPATITIS A VACCINATION REGIMENS IN ONE-YEAR-OLD CHILDREN FROM MENDOZA, ARGENTINA

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Topic: Hepatitis A vaccines

P2.2

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Background: In 2005, Argentina introduced inactivated hepatitis A vaccine into its national childhood vaccination program, with a single dose given at 12 months. Although this strategy may be effective, confirmation is needed since it is not yet known how long one dose maintains protection in children. While 100% seroconversion and protective anti-HAV antibodies levels lasting 6 years are expected following a 0, 6-month, two dose schedule, antibody levels in children receiving a single dose may be lower over time and protection rates below those following two doses.

Objective: Long-term follow-up of 600 subjects over six years has been established to compare the efficacy and long-term immunogenicity of the official, single dose regimen with two doses in one-year-old children. The results should provide valuable information to public health bodies to optimise the protection of children offered by routine immunization against hepatitis A virus (HAV) and its potentially serious consequences. Methods HAV immunogenicity will be monitored during six years in two groups of 300 children aged one year: Group 1 receiving a single dose of hepatitis A vaccine (Avaxim 80, Sanofi Pasteur) at month 0 (0m) and Group 2 receiving two doses at 0m and 6m. Blood samples are taken 4 weeks after each vaccination and annually for six years. Anti-HAV IgG levels are measured by ELISA with titres ≥ 20 mIU/mL considered protective.

Results: To date, 480 subjects (240 in Group 1 and 240 in Group 2) have received the first vaccination. Data analysed so far show 100 % seroprotection after one dose of vaccine.

Conclusions: The long-term effectiveness of a single hepatitis A vaccination in routine childhood immunization schedules needs to be confirmed.

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IMPACT OF ONE DOSE HEPATITIS A UNIVERSAL VACCINATION ON THE BURDEN OF DISEASE IN CHILDREN OF MENDOZA PROVINCE, ARGENTINA

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Topic: Hepatitis A vaccines

P2.3

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Background: Hepatitis A is the most frequent cause of viral hepatitis in the world and also one of the most common immuno-preventable illnesses. The local epidemiological surveillance reveals that the rate of notification of HAV lightly surpassed the country rate (average 175100000). In September 2004, the local health authorities decided to incorporate universal hepatitis A vaccination in children of one year of age in Mendoza province. The implemented plan of a single dose vaccination at 12 months of life is the same one applied in the whole country by the National Ministry of Health and Environment (Act n° 653) as of June 2005. **Objective:** To assess the modification in the epidemiology of hepatitis A after universal vaccination based on the incidence of hepatitis A.

Methods: Data of incidence from 5 years before and 2 years after vaccination were analyzed and related to the vaccination uptake, the number of outbreaks occurring after the start of the new vaccination policy and the necessity for liver transplants.

Results: The effectiveness of a one dose vaccination after two years in the province reached 80%, being historical compared to the last 5 years before the start of vaccination. The outbreaks were reduced during 2005 and there were no outbreaks during 2006. Finally, there were no liver transplants in children caused by hepatitis A over the last two years.

Conclusions: The impact of a one dose hepatitis A vaccine in our province has been highly beneficial, dropping the incidence of illness to historical low rates and removing the cases of fulminant hepatitis A in our child population.

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IMPACT OF UNIVERSAL IMMUNIZATION AGAINST HEPATITIS A IN CHILDREN HOSPITALS IN ARGENTINA

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Topic: Hepatitis A vaccines

P2.4

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Background: Hepatitis A Virus (HAV) infection remains the most frequently reported vaccine-preventable disease worldwide. Fulminant hepatic Failure (FHF) by HAV is the most severe complication. In Argentina, official reported data had revealed an increase of HAV incidence rate in 2003-2004. Thus HAV vaccination was included as universal immunization (UI) with one dose at 12 month of age in July 2005.

Objectives: This study was designed to measure the impact of UI on the incidence of HAV and its complications.

Methods: Hospital records of hepatitis cases clinically diagnosed or serologically confirmed as HAV were reviewed and collected retrospectively from ambulatory and hospitalized children from five hospitals in the interior cities of the country. Data about FHF and Liver transplant (LT) due to HAV was also collected. The study period included data collection before UI, January 2002-December 2005, and after UI, January 2006-December 2007, to measure the impact.

Results: Before UI 4,397 cases of HAV from the ambulatory setting, and 217 cases of children hospitalized were collected, mostly clinically diagnosed. Also 14 FHF were collected, 92% were by HAV; 50% of them died and 5 patients required LT. After UI started 325 ambulatory cases and 23 hospitalized cases were recorded without any case of FHF. None presented complications. None of the patients of both periods had been vaccinated. Children in the second period were older than in the first one (p0.001).

Conclusions: UI reduced 80% of the cases of both ambulatory and hospitalized HAV cases; but a greater and most important reduction of FHF was observed.

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EXPERIENCE WITH THE PAEDIATRIC FORMULATION (0.25 mL) OF AN ALUMINIUM-FREE HEPATITIS A VACCINE: RESULTS FROM THREE RANDOMISED, CONTROLLED CLINICAL TRIALS

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Topic: Hepatitis A vaccines

P2.5

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Dagan R et al. *Pediatr. Infect. Dis. J.* 2007; 26: 787-93
Van Der Wielen M et al. *Pediatr. Infect. Dis. J.* 2007; 26: 705-10

Background: The availability of paediatric formulations will facilitate the introduction of universal mass vaccination against hepatitis A.

Objective: To present the clinical experience with the 0.25mL paediatric dose of the aluminium-free, hepatitis A vaccine Epaxal in terms of immunogenicity and safety in comparison to an aluminium-adsorbed vaccine.

Methods: In three studies in Israel (A), Belgium (B) and Chile (C) a total of 803 children were enrolled. In study A toddlers (aged 12-15 months) were given Epaxal 0.25mL alone (n105) or concomitantly with the routine childhood vaccines DTPaHibIPV+MMR+OPV (n109) [1]. In studies B [2] and C children aged 1-16 years were given Epaxal 0.25mL (n123; n 69) or Epaxal 0.5mL (n123; n67). Groups with an aluminium-adsorbed hepatitis A vaccine (Havrix Junior) were included in all three studies (n108; n62; n37). Vaccines were administered according to the schedule 0 and 6 months. Sero-protection rates (≥ 20 mIU/mL) were assessed for non-inferiority. Incidences of local solicited and unsolicited systemic adverse events were recorded.

Results: In the first 2 studies non-inferiority in terms of sero-protection at month 1 could be shown for the co-administration group as compared to Epaxal 0.25mL alone (study A), as well as for Epaxal 0.25mL in comparison to Epaxal 0.5mL (study B). After the first dose, Epaxal 0.25mL was in studies A and B significantly more immunogenic (seroprotection rate and antibody concentrations) than Havrix Junior. Both hepatitis A vaccines were generally well tolerated; however, in study B the incidence of injection site reactions were 2.5 and 1.5 times lower for Epaxal 0.25mL than for Havrix Junior after dose 1 and 2, respectively. For the third, still ongoing study (C) interim results (n173) will be presented.

Conclusions: Both vaccine types were immunogenic and well tolerated. After the first dose Epaxal 0.25mL was more immunogenic than Havrix Junior. All children were sero-protected after 2 doses. Epaxal 0.25mL compared favourably to Havrix Junior regarding local reactogenicity.

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SAFETY AND IMMUNOGENICITY OF A NEW INACTIVATED HEPATITIS A VACCINE (VERO CELL): A RANDOMIZED CONTROLLED TRIAL

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Topic: Hepatitis A vaccines

P2.6

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Objective: To assess the safety and immunogenicity of a new inactivated hepatitis A vaccine (Vero cell).

Methods: 1507 subjects were selected in Gongcheng county of Guangxi Zhuang Autonomous Region, and the clinical trial was carried out according to the random, double-blind and parallel principle from January to August, 2005. After vaccination by 0,6 schedule, adverse events in the subjects were observed, the seroconversion rate and geometric mean titre (GMT) were tested by the competitive inhibition ELISA.

Results: After vaccination, the systemic and local reaction rates of adults were 8.80% and 2.67% respectively, which was not a statistically significant difference compared to control group, 12.41% and 4.41%; while the rates of children were 10.60% and 2.28% respectively, also not a statistically significant difference compared to the control group, 10.71% and 2.86%. One month after a first dose of vaccination, the seroconversion rates of children and adults were 88.2% and 93.8% respectively, and one month after the second dose of vaccination, the rates all reached 100.0%, the GMTs of children and adults were 16447 mIU/ml and 8555 mIU/ml, which was a statistically significant difference compared to the control group, 1946mIU/ml and 5881mIU/ml, respectively.

Conclusion: The new inactivated hepatitis A vaccine (Vero cell) has the same result in safety compared to the imported hepatitis A vaccine, and the seroconversion was 100% by 0,6 schedule, with a high antibody titre.

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HEPATITIS A SEROPREVALENCE IN DIFFERENT GEOGRAPHICAL REGIONS IN TURKEY: DIFFERENT VACCINATION NEEDS IN DIFFERENT AREAS IN THE SAME COUNTRY

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Topic: Hepatitis A vaccines

P2.7

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Background: Hepatitis A is a worldwide vaccine-preventable infection. Recommendation on vaccination depends on the endemicity of the disease. The World Health Organization recommends universal hepatitis A vaccination in areas of intermediate endemicity. Consequently, most countries adopt a vaccination policy according to the overall endemicity for the whole country. However, the endemicity of this infection varies among various regions within most countries because of differences in sanitary conditions and hygiene.

Objective: To detect the current seroprevalence of hepatitis A infection in geographical regions with different socioeconomical and sanitary conditions and discuss the need for universal hepatitis A vaccination in Turkey.

Methods: A sample of 1,173 persons between the ages of 0 to 91 years from 9 randomly selected centers in 5 different geographical areas of Turkey were tested for the level of anti-HAV IgG antibodies by using ELISA.

Results: The overall prevalence of anti-HAV antibodies was 64.4 % while the rate of seropositivity was over 80 % in subjects 5-9 years of age group and 90 % after 14 years of age in Southeastern and Eastern regions., Seroprevalence was 50 % in those 5 to 9 years of age in Central and Western regions and remained 80 % in the latter areas.

Conclusion: HAV seropositivity is different among various geographical regions in Turkey. Immigration from areas of high to intermediate endemicity is a risk factor for children who live in intermediate regions. Visits of children living in intermediate areas to their home towns in areas of high endemicity, are also a risk factor for infection. Universal vaccination of children must be considered for all children living in intermediate regions of the country.

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COMPARISON OF IMMUNOGENICITY OF LIVE ATTENUATED HEPATITIS A VACCINE AND INACTIVATED VACCINE

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Topic: Hepatitis A vaccines

P2.8

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Objective: To compare immune efficacy of live attenuated hepatitis A vaccine with that of inactivated vaccine.

Methods: 217 children aged 6 ~12 with negative anti-HAV IgG at the enrolment from Liucheng county of Guangxi Zhuang Autonomous Region were randomized to 4 groups. Groups B and C received the LA-1 strain, a live attenuated HAV vaccine (106.75 TCID₅₀, Changchun Institute of Biology Products) according to schedules of 0-6 months and 0-12 months respectively. 106.0 TCID₅₀ live attenuated HAV vaccine was administered to group D, and inactivated hepatitis A vaccine (HavrixTM, 720EI.U, SKB) to group E both at 0-6 month. Follow-up blood samples were taken at month 6,12,24 after the first dose and 1 month after the second dose for all groups with additional samples at month 1 for Group D and E. All samples were tested for anti-HAV IgG using Imx mEIA kit (Abbott Lab.).

Results: During follow-up, in both schedules, live attenuated vaccine had similar effective seroconversion rates and antibody titres as inactivated vaccine at all points of time except for that of the 0-6 months schedule at 1 month after the booster. In group D with lower dose live attenuated vaccine, the anti-HAV positive rate and level were lower than those in the other groups.

Conclusion: A high dose of attenuated live HAV vaccine with a booster dose was similar to the inactivated vaccine in immunity effect, demonstrating a good immunogenicity and memory. Booster dose will ensure long-term protection against HAV.

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EVALUATION ON SAFETY AND IMMUNOGENICITY OF A COMBINED HEPATITIS A AND B VACCINE IN CHILDREN AND YOUNG ADULTS

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Topic: Hepatitis A vaccines

P2.9

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Objective: To evaluate the safety and immunogenicity of a combined hepatitis A and B vaccine, manufactured by Tangshan Yuan Biological Products Co., Ltd.

Methods: 137 healthy children and 127 young adults with HbsAg, anti-HBs, anti-HBc and anti-HAV negative selected from Tianyang county of Guangxi Zhuang Autonomous Region were randomly divided into 6 groups. 127 children (group AB) and 137 young adults (group AB) received 5g0.5ml and 10g1.0ml of a home-made combined hepatitis A and B vaccine, and 55 children (group B) and 55 young adults (group B) received 5g0.5ml and 10g1.0ml of hepatitis B vaccine (Beijing Tiantan Biological Products Co., Ltd) by 0,1,6 months schedule. 86 children (group A) and 137 young adults (group A) received 2500.5ml and 5001.0ml of inactivated hepatitis A vaccine (Tangshan Yuan Biological Products Co., Ltd) by 0,6 months schedule. The local and systemic side-effects were recorded the first 72 hours after each vaccination, and the seroconversion of anti-HAV IgG and anti-HBs were tested at months 2 and 7 after the first dose of vaccination.

Results: The local and systemic side-effects were not observed in all participants within 72 hours after the first dose of vaccination. Seven months after the first dose of vaccination, the seroconversion rates and GMTs of anti-HAV IgG and anti-HBs were 100%, 96.8% and 29144mIU/ml and 102mIU/ml in children AB group and 100%, 98.8% and 21891mIU/ml and 12mIU/ml in adults AB group, respectively. The seroconversion rates and GMTs of anti-HAV IgG and anti-HBs of combined hepatitis A and B vaccine were significantly higher than that of the single hepatitis A and hepatitis B vaccines.

Conclusion: The home-made combined hepatitis A and B vaccine is safe and highly immunogenic in children and young adults.

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Topic: Hepatitis A vaccines

P2.10

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Hepatitis A represents an important public health problem in Brazil, accounting for more than 50% of all clinical hepatitis cases. Seroepidemiological studies carried out in Brazilian population groups have been showing a possible change in the epidemiological pattern of hepatitis A in the country. The increasing number of susceptible individuals for hepatitis A virus (HAV) infection resulted in the occurrence of several hepatitis A outbreaks, especially in metropolitan regions. Under these circumstances, the adoption of vaccination programs would represent an ideal measure for hepatitis A prevention. Unfortunately, the cost of vaccination remains high, preventing its wider use in developing countries. A nationally-produced and affordable HAV vaccine could facilitate the implementation of a national immunization program. Several laboratories have produced candidate killed virus vaccines. In commercial vaccines, HAV is purified and concentrated by sterile filtration, ultra filtration and column chromatography. Sterile virus is inactivated with formaldehyde for 15 days at 37° C. The Institute of Technology on Immunobiologicals, Bio-Manguinhos, is involved in the development and production of vaccines to meet public health demands. We have approached the development of an inactivated vaccine using the Brazilian HAV strain (HAF-203). Our results have shown that HAF 203 strain replicates in Vero cells establishing a persistent infection without cytopathic effect. Viral replication was confirmed by the detection of the negative-strand RNA intermediate, using strand-specific RT-PCR. The next step will be the optimization of virus yields in Vero cells defining the process for virus concentration and purification. Vero is a continuous, adherent cell line, which has been recommended by the World Health Organization. Commercial processes using this cell line are based on its culture on micro carriers in stirred systems.

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OPTIMIZATION OF EXTRACTION AND RECOVERY OF BRAZILIAN HEPATITIS A VIRUS STRAIN FROM FRHK-4 AND VERO CELL CULTURE VALUATED BY REAL TIME PCR AND IN SITU

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Topic: Hepatitis A vaccines

P2.11

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Hepatitis A is an important public health problem in Brazil accounting for a large number of acute hepatitis cases. HAV seroprevalence rates have decreased in several Brazilian regions, leading to increasing number of susceptible individuals to HAV infection, especially children. The cost of vaccination remains high mainly due to the low replication cycle of HAV and low infection titers in most cell culture systems. Large scale preparations of virus require selection of an efficient process of virus extraction from cells, once the major of viral particles remain intracellular or strictly cell-bound, and concentration of large volumes. Development of methods that optimize virus recovery with low cost, reduced time-consuming and high yields virus, capable of inducing an immune response is necessary to scale-up HAV antigen production. The Institute of Technology on Immunobiologicals, Bio-Manguinhos, is involved in the development and production of vaccines to meet public health demands. We have approached the development of an inactivated vaccine using the Brazilian HAV strain (HAF-203). In this work we investigated different methods of HAV extraction from FRhK4 and Vero cells, and different strategies of HAV concentration. The cells were grown in stationary flasks and until confluent monolayer was formed we inoculated with HAV. In the fourth day the virus was extract using four different methods. Allowing extraction, the samples were concentrated by three distinct methods and the results were evaluated by real time PCR and and in situ Enzyme Immunoassay (EIA), these techniques were very sensitive and reproducible for HAV extract monitoring.

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Topic: Hepatitis A virus infection

P3.1

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Background: In 2006, a waterborne outbreak of hepatitis A involving 194 cases occurred in South-western Bulgaria, near Sofia. From 12 July to 21 August 2006, 194 suspected cases of hepatitis A were reported in the municipality of Svoge (Sofia region). Of these, 48 were employees in a food factory.

Objectives: Here we report the clinical, epidemiological and serological data of hospitalized patients in the Infectious Diseases Department at St. Anna University Hospital, Sofia.

Methods: The serological marker for acute hepatitis A antiHAVIgM was determined by ELISA method using commercial immunoenzymatic assay (DiaSorin, Italy). Liver function tests were performed by routine methods.

Results and conclusion: The source of the outbreak and its subsequent spread are most likely associated with the contamination of the drinking water supply pipes with wastewater during a breakage, which occurred on 1 July 2006. A total of 124 patients (pts) aged 3-60 (mean 39) were enrolled in the present study. The male to female ratio was 6361. All the pts were with clinical picture compatible with acute viral hepatitis, 16 without jaundice. The course of the disease was mild in 58121 (47,94%) cases, moderate in 41121(33,88%) and severe in 22121(18,18%). A hundred and five (84,68%) pts were found to be positive for antiHAVIgM. The remaining 19 were negative for antiHAVIgM, but positive for antiHAV total. Seven pts of 9 with negative antiHAVIgM tested had seroconverted when second serum samples were collected 7 days later. They had a uncomplicated course with full recovery; there were no apparent cellular or humoral immune defects. It is suggested therefore, that in suspected cases of hepatitis A with a negative antiHAVIgM, a second serum sample should be obtained a few days after the first.

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HEPATITIS A FULMINANT HEPATIC FAILURE: FOLLOW-UP OF PAEDIATRIC PATIENTS IN SOUTHERN BRAZIL

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Topic: Hepatitis A virus infection

P3.2

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Background and objectives: Acute liver failure (ALF) caused by hepatitis A virus (HAV) is a rare yet devastating condition with high mortality rates. Although efficacious vaccines are licensed in many countries, their use has sometimes been limited by cost considerations. In Brazil there is not a national routine HAV immunization policy. The aim was to follow-up paediatric patients with HAV ALF hospitalized in a liver transplant unit over the last 10 years.

Methods: a retrospective analysis was made of 33 children and adolescents with ALF who had been treated in a liver transplant unit. Ages varied between 2 months and 15 years (median 6,2 +- 5,3 years) and 21 (64%) were males. ALF was defined as biochemical evidence of liver injury, without previous known liver disease and uncorrectable coagulopathy (Prothrombin time (PT) 15 sec or INR 1,5 with encephalopathy (EN) or PT 20 sec or INR 2.0 without EN). Thirteen patients were IgM anti-HAV positive (39.4%). Eleven cases (33%) were of indeterminate aetiology.

Results: the 13 children with HAV ALF were between 17 months and 15,6 years old (median 5,8 +- 4,6 years) and 8 were males (61.5%). All were on the list for urgent liver transplants: 5 died waiting for an organ (38.5%). Only one patient recovered spontaneously. Seven patients received a liver transplant; 3 died in the post-op period and 1 died 45 days after surgery. Three children are alive: 5, 2 and 1 years after the transplant.

Conclusions: HAV was the most frequent cause of ALF with a high rate of mortality. These results suggest universal vaccination against HAV could be a good strategy in this part of the world.

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DETECTION OF IgG ANTI-HAV IN SALIVA OBTAINED FROM VACCINEES

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Topic: Laboratory diagnosis and molecular epidemiology

P4.1

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Background: Saliva can be used as an alternative to serum for diagnostic and epidemiological testing. One major drawback to using saliva is that among vaccinees there is relatively lower concentration in serum and saliva compared to naturally infected individuals.

Objectives: To develop a more sensitive and non-invasive EIA from vaccinees and natural infections by determining the sensitivity and specificity in matched salivaserum samples.

Method: 78 saliva samples obtained from naturally infected adults and 208 saliva samples collected from 105 American Indian infants were assayed for IgG anti-HAV using an IgG capture ELISA format.

Results: The new saliva based capture ELISA showed 100% sensitivity and 97.5% specificity using saliva samples from naturally infected individuals. The sensitivity was lower (79.1%) when testing saliva samples from vaccinees; however, some vaccinees received only a single dose which may explain the lower concentration in serum. The sensitivity values obtained using saliva was shown to be directly proportional to the concentration in serum: 37.0% for saliva with a paired serum concentration between 30-100 mIU/ml (n27), 59.2% for concentration between 100-200 mIU/ml (n49), 83.3% for concentration between 200-300 mIU/ml (n36), and 99% in vaccinees where the antibody concentration in paired sera was 300 mIU/ml and higher (n95).

Conclusion: The sensitivity of the capture EIA format for the detection of IgG anti HAV in saliva depends upon the IgG concentration in serum and varies from an average of 79.1% among vaccinees (some of whom received only a single dose) to 100% among naturally infected individuals.

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Topic: Laboratory diagnosis and molecular epidemiology

P4.2

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Background and objectives: Anti-HAV IgM is the golden standard for acute hepatitis A diagnosis. However, positive IgM are also reported in persons without acute hepatitis A due to polyclonal activation of memory B cells. The frequency of this phenomenon can reach 30% in older subjects due to non-targeted IgM testing. We developed an avidity test for HAV IgG antibodies with the following interpretation rules: avidities over 70% are considered as past infections and avidities less than 50% are considered as acute infections. Our objective was to assess the validity of this rule on results collected prospectively since 2004.

Methods: From January 2004 to August 2007, 247 out of 608 IgM positive sera received at our centre were analyzed for both anti-HAV avidity and HAV viremia by RT-PCR targeting VP1 region. HAV infection was considered active if HAV RNA was detected.

Results Avidities over 70% were found for 95 patients with a mean age of 53,6+-24 years. Of them 6 were HAV RNA positive (6,3%) and presented relapsing or protracted forms of acute infection. Avidities less than 50% were found in 122 patients with a mean age of 30,3 +- 17 years. Of them, 111 were HAV RNA positive (91%). Avidities ranging from 50 to 70% were observed in 30 cases with HAV RNA detectable in 16 (53,3%). The mean age of these 30 patients was 31 +- 27 years. If 70% is chosen as a threshold, the specificity of the avidity assay for the diagnosis of polyclonal activation is 95,5% and its positive predictive value is 93,7%.

Conclusions: Anti-HAV avidity could help epidemiologists to exclude patients without acute hepatitis A and better surround outbreaks.

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Topic: Laboratory diagnosis and molecular epidemiology

P4.3

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Background and objectives: Up to these later years, most of HAV genotypes found in Western Europe were IA and IB. Genotype IIIA was observed sporadically in France in patients having travelled to endemic areas. Since 2005 this genotype is becoming more prevalent. The safety of blood products relies on nucleic acid assays. Performances of the LightCycler HAV quantification kit (Roche Diagnostics) and the Artus HCV LC RT-PCR Kit (QIAgen), for detection and quantification of HAV were evaluated.

Methods: HAV quantification performances were compared with 49 sera out of the 288 received by our Centre in 2006 for the surveillance of strains circulation. Samples were stored at -80C until extraction. HAV genotype was determined by sequencing and phylogenetic analysis of a 508 base-pair fragment encompassing the VP12A junction. Genotype IA was present in 10 samples, IB in 14 and IIIA in 23. Quantification was performed according to the manufacturer instructions with 5l of extracted RNA.

Results: None of the 23 genotype IIIA samples was detected by the Roche assay. The Artus assay detected all IIIA samples; mean viremia of IIIA samples was 3,14 +- 0,86 log copies/ml. The Roche assay detected all type I samples while the Artus assay missed 3 samples. Quantification results correlated well ($r=0.82$, with a 95% CI 0,62-0,92) but there was an important mean difference of 0,7 log copies/ml obtained in the Bland and Altman model indicating that the Artus assay was less sensitive with mean detected viral loads of 3,68+-1,2 log copies/ml and 3,00 +- 1,5 log copies/ml, respectively.

Conclusion: Amplification and quantification tests have to be adapted to the changing epidemiology of HAV.

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HEPATITIS A VIRUS DETECTION IN A RIVER FROM BUENOS AIRES, ARGENTINA

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Topic: Laboratory diagnosis and molecular epidemiology

P4.4

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Background: Argentina has implemented a vaccination program against HAV in one-year-old children since June 2005, which is expected to diminish household transmission. However, contaminated food and water transmission might still take place.

Objective: To demonstrate the presence of HAV RNA in river water.

Methods: Forty-nine water samples were collected monthly from October 2004 to September 2005 in three different locations at the Riachuelo River in Buenos Aires city. HAV RNA was detected by RT-PCR using primers targeting the VP 3 C terminal region. Purified PCR products were sequenced in an automatic sequencer.

Results: HAV RNA was detected in 23 samples (49%) and the genomic sequences confirmed the specificity of the amplification products.

Conclusions: The Riachuelo-Matanza basin is a 2,240 km² area (including the south of Buenos Aires city and fifteen districts of Buenos Aires province) affected by intensive and extensive agricultural activities, and bearing almost 3,000,000 inhabitants (services of drinking water only reach 65% of the population and 45% of houses have sewer facilities). Our results showed the presence of HAV RNA in the river water. Contaminated water frequently floods houses, streets and lands, thus representing a public health problem. HAV has shown a long-term stability in various humid or aqueous environments. Sanitary improvements are necessary to avoid sporadic cases or outbreaks in susceptible older groups.

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MOLECULAR EPIDEMIOLOGY OF HEPATITIS A VIRUS IN BRAZIL, OVER A PERIOD OF SEVEN YEARS (1999-2006)

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Topic: Laboratory diagnosis and molecular epidemiology

P4.5

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Background and objectives: Hepatitis A virus (HAV) seroprevalence rates are decreasing in Brazil and a shift from high to medium endemicity has been observed. Despite the availability of safe and immunogenic vaccines, hepatitis A is a cause of significant morbidity, since universal vaccination has not been implemented. Molecular epidemiology studies constitute a useful tool for an active surveillance program.

Methods: The VP12A genomic region of 542 HAV isolates, collected over a seven year-period (1999 to 2006), was sequenced for genotyping. Three hundred and fifty nine (66%) isolates were from serum samples from sporadic cases, 153 (28%) serum samples were collected during outbreaks, and 30 (6%) were from environmental samples.

Results: All isolates belonged to genotype I; 423 (78%) were from subgenotype IA and 117 (22%) from subgenotype IB. Subgenotype IA isolates were significantly more frequent among sporadic cases (92%) than during outbreaks (49%) or among environmental samples (67%). Co-circulation of subgenotypes IA and IB was observed in each year of the period. The genotype IB was more common in outbreaks (51%).

Conclusion: This study providing the baseline for molecular epidemiology of HAV in Brazil may help in documenting the hepatitis elimination program.

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DETECTION OF HEPATITIS A VIRUS RNA IN SALIVA SAMPLES DURING AN OUTBREAK IN A CHILD CARE CENTER IN RIO DE JANEIRO BRAZIL

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Topic: Laboratory diagnosis and molecular epidemiology

P4.6

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Background and objectives: Hepatitis A infection is a significant health problem mainly in day care centers, causing outbreaks that can be propagated to community. To facilitate the detection and investigation of outbreaks, it would be reasonable to make use of fluids that are less invasive and easier to collect, such as saliva. However, for prospective studies involving hepatitis A virus (HAV) RNA detection, a standard methodology must be developed. The objectives of this study were to standardize molecular assay for HAV RNA detection in saliva samples and to evaluate its use for diagnosis and molecular studies of hepatitis A outbreaks.

Methods: In this study, nested RT-PCR and real-time PCR were optimized and evaluated for HAV detection and quantification, using saliva from healthy volunteers (n 20) and paired serum/saliva samples from individuals involved in a hepatitis A outbreak that occurred in a public child care center of Rio de Janeiro, Brazil (n 78). The saliva samples were collected using OraSure™ collector. The sensitivity of the assays was 6×10^3 copies/mL in RT-PCR and 140 copies/mL in real time PCR.

Results: Nested RT-PCR detected HAV RNA in 50% of saliva and in 42% of serum samples from acute individuals, as well as in 12% of all samples from susceptible cases. Through real-time PCR, among acute individuals, HAV RNA was detected in 61% and 71% of saliva and serum samples, respectively. Among susceptible subjects, the virus was detected in 17% and 12 % of saliva and serum samples, respectively. Mean viral loads were 1.7 3.24×10^3 copies/ml (in saliva) and 2.8 6.46×10^3 copies/ml (in serum).

Conclusion: This study indicates that saliva is a practical and efficient alternative to diagnostic and molecular studies of hepatitis A in outbreaks.

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MOLECULAR SURVEILLANCE OF HEPATITIS A VIRUS IN THE UNITED STATES: SENTINEL COUNTIES STUDY OF ACUTE VIRAL HEPATITIS, 1996-2006

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Topic: Laboratory diagnosis and molecular epidemiology

P4.7

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Background and Objectives: To define population-based genetic and molecular epidemiologic characteristics of hepatitis A virus (HAV) circulating in the United States. This study updates a previous analysis of specimens collected during 1996-1997.

Methods: HAV genetic relatedness of cases reported from the Sentinel Counties Study of Acute Viral Hepatitis during 1996-2006 was determined by analysis of a 315-nucleotide segment in the VP1P2B region of the viral genome following amplification by reverse-transcriptase PCR.

Results: Of 1512 cases, 1229 (81%) were HAV RNA-seropositive. The majority (97%) of specimens included HAV belonging to genotype IA, and the remainder to IB or IIIA. Of 407 UNSPs (defined as those carried by unique nucleotide sequences pattern), 288 (23%) were found in only one specimen; there were 119 UNSPs isolated from the remaining 941 specimens. 757 of the HAV RNA-seropositive cases (62%) were infected by 40 dominant UNSPs (defined as those carried by 5 cases). 25 UNSPs circulated for 3 years. Three major genotype IA phylogenetic clusters (US-IA1, 2 and 3) were identified, accounting for 95% of sequences. 39% of all RNA-seropositive cases were infected by US-IA1, 26% by US-IA2 and 30% by US-IA3. US-1A2 strains were particularly dominant in Multnomah County before 2002, and US-1A3 strains in Denver before 2000. Patients infected during travel to Mexico predominated among US-1A1 strains, injection drug users among US-1A2 strains, and men who have sex with men among US-1A3 strains.

Conclusions: Molecular surveillance and genetic relatedness analysis provide insights into the distribution of distinct HAV variants and predominant specific transmission routes.

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Topic: Laboratory diagnosis and molecular epidemiology

P4.8

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Background and objectives: HAV continues to be the main etiological agent of acute hepatitis throughout the world despite the availability of vaccination as a preventative measure (Flehmig, Lancet 1989, Flehmig, NEJM 2000). There are global differences in HAV prevalence and outcome. Up to now, no unequivocal results are available to support any association between the pathogenicity of the virus and the genotype or specific sequences in the HAV genome. It is of fundamental importance for data relating to the prevalence of the infectious agents to be regularly updated: recommendations pertaining to vaccinations are established on such information. In analogy to other viral diseases, in which specific genotypes are associated with a higher virulence, it is relevant for hepatitis A strains and their circulation to be analyzed in greater detail. To date, sequence analysis of the VP1-2A region is used to genotype HAV isolates, which allows the classification of HAV into seven different genotypes. Realtime RT-PCR analyses of the 5NCR showed higher sensitivity compared to RT-PCR analyses in the VP1-2A region. We therefore performed and compared genotyping using amplicons from both genome regions.

Methods: RT-PCR was performed of 50 HAV isolates from both genome regions. The amplicons were subjected to sequence analyses followed by phylogenetic analyses (Clustal).

Results: The phylogenetic analyses revealed identical results, i.e. all isolates were classified into the same genotype, but out of the 50 serum samples 32% were positive with RT-PCR from VP1-2A, whereas RT-PCR in the 5NCR yielded 74% positive samples.

Conclusion: The greater sensitivity of the 5NCR RT-PCR has therefore significant advantage over the VP1-2A RT-PCR and we recommend for further phylogenetic analysis the 5NCR.

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Topic: Laboratory diagnosis and molecular epidemiology

P4.9

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Background: Hepatitis A virus (HAV) is the commonest etiological agent associated with acute liver disease worldwide, and is also a major public health problem in many developing countries. Sequence analysis of selected genome regions has shown that HAV presents a moderate nucleic acid divergence, allowing the identification of several genetic variants. However, the genetic variation along the entire HAV genome is largely unknown.

Objective: To develop a protocol to amplify and sequence the entire length of the HAV genome.

Methods: First-round PCR involves using a primer set encompassing the extreme 5- and 3-ends of the cDNA of the genome. Subsequently, a set of 15 primer pairs are used to define the sequences of the overlapping sub-genomic regions. Serum samples from 12 acute cases of hepatitis A linked to a common source of infection were studied.

Results: Preliminary results show that the isolates exist as very closely related variants with little nucleotide variation. Studies are being conducted to confirm the sequence heterogeneity, determine the mechanisms by which variations occur, and investigate whether the nucleotide changes identified may be useful to predict routes of transmission and characteristics of hosts infected.

Conclusions: HAV whole-genome analysis might be essential to fully characterize individual isolates and establish relatedness among isolates, helping to predict mode of transmission in different epidemiologic settings.

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NEW ENZYME IMMUNOASSAY FOR THE DETECTION OF IGM ANTIBODIES AGAINST HEPATITIS A VIRUS

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Topic: Laboratory diagnosis and molecular epidemiology

P4.10

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Background and Objective: Hepatitis A remains a worldwide health problem not only in developing countries, but also in industrialized ones. Diagnosis of acute Hepatitis A is based on the detection of IgM antibodies against HAV in patients who present clinical features of hepatitis. The purpose of this study was to assess the performance of the MONOLISA Anti-HAV IgM EIA assay from Bio-Rad in comparison to the FDA approved ETI-HA-IgMK PLUS assay from Diasorin.

Methods: A multicenter clinical study was conducted at two sites (Hospital Paul Brousse, France, and Parma Hospital, Italy) in the European population. Additionally, samples from the US population were tested in Bio-Rad, France.

Results: 929 European adult and paediatric subjects were enrolled in the study including patients with acute (84) and recovered (151) hepatitis A infection, patients with signs or symptoms of hepatitis (253), patients who were at high risk for hepatitis (62), asymptomatic hospitalized patients (345) and healthcare workers (34). 404 samples were collected from the US population and consisted of 174 subjects with signs or symptoms of hepatitis and 230 subjects from the high risk group for hepatitis A. Including the combined US and European sites, the positive percent agreement with the reference Diasorin assay was 100% (8686). The negative percent agreement was 99.12% (12331244).

Conclusion: MONOLISATM Anti-HAV IgM EIA assay is a safe and effective tool for the in vitro qualitative determination of anti-HAV IgM antibodies in human (adult and paediatric) serum and plasma. This kit may be used as a laboratory diagnosis of acute or recent hepatitis A infection, in conjunction with other serological or clinical information. This assay is FDA cleared.

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NEW ENZYME IMMUNOASSAY FOR THE DETECTION OF TOTAL ANTIBODIES AGAINST HEPATITIS A VIRUS

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Topic: Laboratory diagnosis and molecular epidemiology

P4.11

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Background and Objective: Hepatitis A remains a worldwide health problem not only in developing countries, but also in industrialized ones. The purpose of this study was to assess the performance of the MONOLISA Anti-HAV EIA assay from Bio-Rad in comparison to the FDA approved ETI-AB-HAVK PLUS from DiaSorin.

Methods: A multicenter clinical study was conducted at two sites (Paul Brousse Hospital, France and Parma Hospital, Italy) in the European population. Additionally, samples from the US population were tested in Bio-Rad, France.

Results: 928 European adult and paediatric subjects were enrolled in the study, including patients with acute (84) and recovered (151) hepatitis A infection, patients with signs or symptoms of hepatitis (252), patients who were at high risk for hepatitis (62), asymptomatic hospitalized patients (345) and healthcare workers (34). The 404 specimens from the US population consisted of 174 subjects with signs or symptoms of hepatitis and 230 subjects from the high risk group for hepatitis A. Overall, the positive percent agreement with the reference DiaSorin assay was 99.5% (931936). The negative percent agreement was 96.2% (378393). A study of subjects vaccinated with one of three different vaccines that are currently licensed in the US was performed. MONOLISATM Anti-HAV EIA was in overall agreement with the reference assay for 2122 (95.5%) pre-vaccination samples, and for 3334 (97.1%) of post-vaccination samples.

Conclusion: MONOLISATM Anti-HAV EIA is a safe and effective tool for the in vitro qualitative determination of anti-HAV total antibodies. It may be used as an aid to the diagnosis of acute or past HAV infection or in the identification of HAV susceptible individuals for vaccination. This assay is FDA cleared.

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A LONG-TERM PROSPECTIVE STUDY ON HEPATITIS A MOLECULAR EPIDEMIOLOGY IN ST PETERSBURG, RUSSIA

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Topic: Laboratory diagnosis and molecular epidemiology

P4.12

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Objective and method: Molecular epidemiology of the Hepatitis A virus (HAV) strains in St. Petersburg was studied during 1997-2006. Hepatitis A virus RNAs were isolated from clinical samples and subsequently RT_PCR and sequencing were carried out.

Results: The results show that the IA subtype was the most common during the follow-up period: 90% of the isolated HAV strains belonged to that subtype. It is important to note that the viruses isolated in 1997-1998 and in 2003-2006 in St. Petersburg (low HAV incidence rates) are not grouped with the viruses circulated in 2000-2001 (highest HAV incidence rate). Keeping in mind that HAV IA strains are usually very conservative it is possible that the HAV outbreak in 2000-2001 in the city was connected with the introduction of a new, more aggressive HAV IA strain. Moreover, in 2001 the subgenotype IIIA was isolated for the first time in several patients in St. Petersburg. In that year and in 2000 the highest incidence rates of hepatitis A were officially reported by the St. Petersburg City Surveillance Center for the period 1997-2006. It should be emphasized that in most cases of HAV IIIA (isolated in St. Petersburg in 2001) the patients were intravenous drug users. The appearance of the subgenotype IIIA in circulation as well as the high HAV incidence rate support speculation that during 2001 in St. Petersburg an unrecognized HAV IIIA outbreak occurred in the community of intravenous drug users.

Conclusion: The permanent monitoring of the HAV strains circulating in a region could be very useful for detecting changes in the spread of the virus as an aid to taking preventive measures in time.

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HEPATITIS A UNIVERSAL VACCINATION OF MILITARY PERSONNEL: THE RUSSIAN EXPERIENCE

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Topic: Prevention and control of hepatitis A infections

P5.1

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Background and objectives: Universal hepatitis A immunization of Russian forces began in 1996. Active surveillance and high vaccination coverage allow for evaluation of vaccine effectiveness.

Methods: Three vaccines, Avaxim 160, Havrix 1440 and Hep-A-in-VacTM have been administered to several hundred thousand recruits. Cases of hepatitis A are routinely reported. Vaccine immunogenicity was evaluated in selected groups of recruits.

Results: Vaccination has resulted in a large decrease in incidence over the last decade. Vaccination during outbreaks in unvaccinated units prevented new cases within 5-28 days with 100% coverage and 18-42 days with 70% coverage, depending on the vaccine. From 2001-2006 only 5 cases of hepatitis A were reported in 60,000 personnel given one Avaxim dose. Three of these were diagnosed within 10 days after vaccination. At 14 days after vaccination, seroconversion rates (≥ 20 mIU/mL) were 98.3%, 94.0%, and 38.9% for Avaxim, Havrix, and Hep-A-in-Vac, respectively. One month after vaccination 100% of subjects who received Avaxim, 96.2% Havrix, and 82.8% Hep-A-in-Vac seroconverted. Immunogenicity was further evaluated in 2006 in 300 personnel in three units, given one Avaxim dose in 2001, 2002 or 2003. Approximately 94% of subjects vaccinated in 2003, 92% in 2002, and 90% in 2001 retained anti-HAV antibody concentrations ≥ 20 mIU/mL.

Conclusions: Single-dose vaccination has been effective in control of hepatitis A in high risk environments. Protection likely persists for 5 years in more than 90% of personnel vaccinated with Avaxim. Avaxim may have immunogenic advantages, related to kinetics of the antibody response.

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EFFECTIVENESS OF UNIVERSAL HEPATITIS A IMMUNIZATION OF YOUNG CHILDREN IN MINSK CITY, BELARUS: FOUR-YEAR FOLLOW-UP

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Topic: Prevention and control of hepatitis A infections

P5.2

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Background and objectives: Belarus began universal hepatitis A vaccination of children 6-7 years of age in Minsk City in 2003. The analysis was conducted to evaluate the short-term impact of this program.

Methods: Vaccination effectiveness was estimated by comparing the incidence of reported hepatitis A cases after 4 years of immunization with incidence when the universal program started. The ratio of vaccine (Avaxim 80 Havrix 720) doses used was 19:1. A sub-study of hepatitis A seroprevalence was conducted in 324 people 18 years of age.

Results: During the period of 2003-2006 hepatitis A incidence in vaccinated children 14 years of age was 20-fold lower than the incidence in unvaccinated children (0.3 cases 10,000 versus 5.98/10,000, odds ratio 0.05, 95% CI 0.012-0.202), indicating a vaccination effectiveness of 95%. The decreased incidence, from 5.5/10,000 in 2001-2002 to 0.5/10,000 in 2006, among children 11-14 years of age can be explained by a herd effect. Routine vaccination has also resulted in a shift of the age pattern of hepatitis A morbidity. The proportion of cases in children under 14 years of age decreased from 33-41% in 2000-2002 to 7% in 2005-2006. In 2007, overall hepatitis A seroprevalence among adults 18 years was 50%. Seroprevalence increased with age ($p < 0.0022$): 22%, 43%, 47%, 67% and 85% at 18-24, 25-29, 30-39, 40-44 and 45 years of age, respectively.

Conclusions: Introduction of hepatitis A vaccination in Minsk resulted in sharply reduced incidence in both vaccinated and unvaccinated children. Virus circulation might be further decreased by beginning vaccination at a younger age. Young adults continue to be at risk of hepatitis A infection.

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IMPACT OF HEPATITIS A AS UNIVERSAL VACCINATION ON THE INCIDENCE OF FULMINANT HEPATIC FAILURE IN FOUR LIVER TRANSPLANT CENTERS IN ARGENTINA

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Topic: Prevention and control of hepatitis A infections

P5.3

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Introduction: Hepatitis A (HA) is the most frequent liver disease affecting children. Although it is a vaccine preventable disease, it still causes morbidity and mortality in case of fulminant hepatic failure (FHF). In Argentina, the number of cases and deaths is higher if FHF is caused by HA, than indeterminate failure. HA vaccine was included as universal immunization (UI) since July 2005.

Objective: The aim of this study was to analyze the impact of universal vaccination on the incidence of FHF caused by HA.

Methods: Retrospective and multicenter studies that analyze the number of cases and the outcome of FHF due to HA, before and after the UI in four Liver Transplant Centers in Argentina. **Results:** From March 1993 to September 2007, 406 patients with diagnosis of FHF were hospitalized. Out of them, 209 cases were due to HA, 40 had a good evolution not needing liver transplantation, 38 patients died without LTx and 128 were transplanted. Before starting the UI, 188 pts were admitted during 148 months; after UI, there were just 18 pts in the period from August 05–July 06. From August 06 to August 07, only 3 patients with FHF caused by HA were hospitalized. None of the patients in the last periods have been vaccinated.

Conclusion: In a preliminary analysis, the number of pts with FHF due to HA in Argentina strongly decreased as from the first year of UI. The analysis shows that the HA vaccine not only reduces the number of cases but also reduces the most important severe complications.

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LONG-TERM IMMUNITY OF AN INACTIVATED HEPATITIS A PAEDIATRIC VACCINE IN ARGENTINIAN CHILDREN FROM AN INTERMEDIATE-HIGH ENDEMICITY AREA

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Topic: Prevention and control of hepatitis A infections

P5.4

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Background: In the last five years Argentina was considered a high-intermediate endemicity country for hepatitis A. Hepatitis A vaccines have been demonstrated to be safe and highly immunogenic in children. Inactivated vaccines are now available in many countries, however, few studies have been conducted to demonstrate the long-term persistence of anti-HAV antibodies in children. Objective: to evaluate the long-term (10 years) immunity following two doses schedule with an inactivated HAV (Avaxim 80U) in children 1 to 4 years old.

Material and Methods: from children who had completed the primary immunization schedule a blood sample was obtained to measure serum concentration of anti-HAV antibodies. Quantification of anti-HAV antibodies was done using a fluorescent enzyme immunoassay (Vidas AntiHAV) by Biomerieux.

Results: In 1997 a total of 103 initially seronegative children completed the two doses schedule HAV, 6 month apart. One month after booster dose, the anti-HAV serum concentration was: Geometric Mean titre 6743 mIU/mL (95% CI: 5805 7833); seroconversion rate was 100%. In addition, 7 initially seropositive children completed the immunization obtaining higher titres of anti-HAV antibodies one month after booster dose. In 2007, 44103 (42.7%) children, have completed the follow-up. Age: 156.3 (11.7) months; female: 2544 (56.8%). The current serum level concentration was: Mean 396.30 mIU/mL (95% CI: 279.66 512.93). One of 44 (2.3%) children was negative (less than 15 mIU/mL). Also 47 (57.1%) of initially seropositive children were controlled. Age: 158.5 (22.9) months; 44 male; anti-HAV titres: 2663.8 mIU/mL (95% CI: -2035.3 7362.8).

Conclusions: The long-term anti-HAV immunity after ten years two doses immunization schedule using an inactivated hepatitis A vaccine 80U showed seroprotection level in 97.7% of children in an intermediate-high endemicity area.

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⁽³⁾ Sanofi Pasteur, Buenos Aires, Argentina

POTENTIAL CONFLICT OF INTEREST

The organising committee would like to make aware all participants of any affiliation or financial interest that may affect the speaker's presentation. Therefore all speakers participating in this meeting have been asked to disclose to the program audience any real or apparent conflict(s) of interest that may have direct bearing on the subject of the meeting. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers or other corporations whose products or services are related to the subject matter of the presentation topic. The intent of this is not to prevent a speaker with a potential conflict of interest from making a presentation. Its merely intended that potential conflict should be identified openly so that the listener may form his own judgment about the presentation with the full disclosure of the facts.

| | Speaker | Potential Conflict of Interest |
|-------------------|------------------------------------|--|
| Session 1 | Session 1 | |
| | Angela Gentile | Not reported |
| session 2 | Session 2 | |
| | Stephen Feinstone Brian McMahon | Not reported My spouse has 100 shares of GlaxoSmithKline common stock in her Individual Retirement Fund. GSK is one manufacturer of hepatitis A vaccine |
| Session 3 | Session 3 | |
| | Annemarie Wasley Craig Shapiro | Not reported Not reported |
| | Paolo Bonanni | Occasional sponsorship of studies on vaccination strategies and pharmaco-economic aspects of vaccination by vaccine producers. Participation to international and national boards or to consultancies on vaccination sponsored by vaccine producers. Participation as an invited speaker to meetings on vaccination sponsored by vaccine producers |
| Session 4 | Session 4 | |
| | Harold Margolis Mirko Faber | Not reported None |
| | Daniel Shouval | Not reported |
| | Rosina Girones | There is no potential conflict of interest; the research presented has been developed through projects funded by the Spanish Government through open research programs |
| Session 5A | Session 5A | |
| | Cláudia Lamarca Vitral | None |
| | José Santos | Not reported |
| | Haysam Tufenkeji | Not reported |
| | Alfonso Mele | None |
| | Meral Ciblak | Not reported |
| | Jeffrey Mphahlele | None |

| | | |
|------------|------------------------|---|
| Session 5B | Session 5B | |
| | Zhi-yi Xu | None |
| | Jong-Hyun Kim | None |
| | Voranush Chongsrisawat | None |
| | Vidya Arankalle | None |
| | Sergey Mukomolov | Not reported |
| | Anna Moiseeva | The trial was performed with unrestricted grant of Sanofi Pasteur |
| Session 6 | Session 6 | |
| | Ian Gust | The NIH licenced its IP on HAV to SBB and receives royalties from the sales of HAVRIX of which I have received a minor share. |
| | Koen Van Herck | As a co-investigator, I have been involved in several vaccine trials with hepatitis A vaccines from different manufacturers |
| Session 7 | Session 7 | |
| | Beth Bell | Not reported |
| | John Ward | Not reported |
| | JC Victor | None |
| | Robert Steffen | RS has accepted fee for speaking, organizing and chairing education, consulting and/or serving on advisory boards, also reimbursement for attending meetings and funds for research from Astral, Baxter, Berna Biotech/Crucell, GlaxoSmithKline, Novartis Vaccine, Optimer, Roche, Salix, Sanofi Pasteur MSD and/or SBL Vaccin. |
| Session 8 | Session 8 | |
| | Philippe Beutels | None |
| | Thierry Van Effelterre | Thierry Van Effelterre is employee of GlaxoSmithKline Biologicals. |
| | Chris Bauch | This research was funded by an industry-partnered grant from the Canadian Institutes of Health Research, in connection with GlaxoSmithKline Canada. C.T. Bauch and A. Anonychuk were external consultants for GlaxoSmithKline. B. Pham was an employee of GlaxoSmithKline. |
| | Alba Maria Ropero | Not reported |
| | Susie Lee | None |
| Session 9 | Session 9 | |
| | Marta Vacchino | None |
| | Jim Van Steenbergen | None |
| | Roberta Pastore | Not reported |
| | Ron Dagan | None |
| | Angela Domínguez | None |
| | Philippe Beutels | Not reported |
| | Katia Abarca | Dr. Abarca has received research support for hepatitis A vaccine trials from GSK, Sanofi-Pasteur and Berna Biotech; has been paid speaker for GSK and Merck; and has participated in expert panel for GSK and Merck for an unrelated vaccine |
| | Alena Fisenka | None |
| | Vasily Akimkin | We have an unrestricted grant for serological studies from Sanofi Pasteur |
| | Xiaofeng Liang | None |

Information on this meeting can be accessed at www.havmeeting.info
All presentations will be made available on this website pending author's consent

Organising Secretariat:

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