Summary of the major findings and conclusions of the Global Hepatitis A meeting, Miami December 2007

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Vaccine & Infectious Disease Institute
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Belgium
Global Hepatitis A meeting

- Joint initiative
  - CDC, CEV, WHO, PAHO
- > 250 delegates from 46 countries
- PH representatives, epidemiologists, virologists, hepatologists, viral hepatitis and infectious disease experts, travel medicine doctors, ...

- Abstract book & presentations: www.havmeeting.info

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Global Hepatitis A meeting: objectives

- To review surveillance systems, diagnostic tools, outbreak control, cost-effectiveness of hep A vaccination
- To discuss the changing epidemiology
- To review the hepatitis A immunization programmes
- To review the data needed to assess current hepatitis A prevention strategies
Global Hepatitis A meeting:

• Country presentations on hepA epidemiology:
  - Brazil, Mexico, Saudi Arabia, Italy, Turkey, South-Africa, China, Korea, Thailand, India, Russia, & Ukraine

• Country presentations on prevention
  - Argentina, The Netherlands, Italy (Puglia), Israel, Spain (Calatlonia), Australia, Chile, Belarus, Russia, & China
The epidemiology, the need for an evidence-based decision making process with regard to control of Hepatitis A

Angela Gentile MD

Hospital de Niños R. Gutiérrez

Argentina Pediatrics´ Society
Hepatitis A in Latin America

- Total Population: ≈ 500,000,000.
- Estimated annual incidence rate: 40-50/100,000
- Endemicity: intermediate (South Cone) and high (Tropical countries)
- Estimated cases by year: 350,000-400,000.
- Mortality rate: under 15 yrs. 3,000/year
- Acute liver failure: ~ 0.3-0.4%.

Hepatitis A prevalence in Argentina according to age and socioeconomical level

N: 1500

ALF : Argentina experience

May 1982 - September 2002
N: 210 patients

- **Age**: (mean ± SD): 5.33 years (r: 12 m-17.4 yrs.)
  - 87% < 10 years
  - 63.5% < 5 years

- **Gender**: (masc/ fem): 107/103

The decision was taken considering......

- 1- Disease Burden
- 2- Cost- effectiveness
- 3- Vaccine characteristics
- 4- Programmatic feasibility
- 5- Social acceptance
# National Immunization Schedule

**Argentina, Ministry of Public Health**

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<td>6 meses</td>
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<td>1ª dosis</td>
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<td>18 meses</td>
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<td>4ª dosis</td>
<td>4ª dosis</td>
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<tr>
<td>6 años</td>
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<td>Iniciar o completar esquema [3]</td>
<td>Refuerzo</td>
<td>2ª dosis</td>
<td>Refuerzo</td>
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<tr>
<td>11 años</td>
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<td></td>
<td>Refuerzo [4]</td>
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<tr>
<td>16 años</td>
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<td>Cada 10 años</td>
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<td>Puerperio o post-aborto inmediato</td>
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<td>1 dosis [4]</td>
</tr>
</tbody>
</table>
Argentina: National Immunization coverage in first year of life, 2006

- Sabin: 92%
- Cuádruple: 92%
- Triple Viral: 97%
- BCG: 77%
- Hepatitis B: 84%
- Hepatitis A: 95%
Epidemiologic Shift in Prevalence of Antibodies to Hepatitis A Virus

Improvements in living conditions
Hepatitis A: Transition from High to Intermediate Endemicity
Features

• Lower prevalence among children
  – Increase in average age of infection
  – Increased morbidity

• Outbreak potential
  – Circulating virus
  – Cohorts of susceptible older children, adolescents, and adults

• Variability in incidence
  – Within regions
  – Within countries and cities
    • urban/rural
    • socioeconomic status
Current data limited

- Old
- Missing country, regional data
- Developed-country data used to estimate proportion of acute hepatitis as hepatitis A; age distribution of cases; distribution of severity of cases (including case fatality rate)
Describing the epidemiology of HAV: Prevalence vs. Incidence

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Incidence</th>
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</thead>
<tbody>
<tr>
<td>Assess population immunity and susceptibility</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Monitor trends in incidence of and risk factors for disease</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Assess burden of disease</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Identify and control outbreaks</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Identify infected persons and at-risk contacts for preventive interventions (i.e. post-exposure prophylaxis)</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>
Rationale for Surveillance for Acute Viral Hepatitis A (and other types)

• Quantify burden of disease
• Measure risk of acute hepatitis A in all age groups
• Evaluate risk factors for HAV infection
• Define the need for and identify target groups for vaccination programs
• Measure the impact of vaccination strategies
• Provide basis for further investigations of HAV epidemiology: case/control studies, outbreak investigations
The EUROHEP.NET Project is a European Commission-funded feasibility study for a future network on surveillance and prevention of vaccine-preventable hepatitis

*EUROHEP.NET Team: P. Van Damme, A. Vorsters, K. Van Herck and E. Leuridan (Centre for the Evaluation of Vaccination, WHO Collaborating Centre for Prevention and Control of Viral Hepatitis, Department of Epidemiology and Community Medicine, University of Antwerp, Belgium); M. Kojouharova (National Centre for Infectious and Parasitic Diseases, Sofia, Bulgaria); R. Dagan (Pediatric Infectious Diseases Unit, Soroka University Medical Centre, Beer Sheva, Israel); P. Bonanni, S. Boccalini and A. Bechini (Department of Public Health, University of Florence, Italy); J. Hallauer (Universitätsklinikum Charite´, Berlin, Germany); V. Usonis (Vilnius University Centre of Paediatrics, Lithuania); W. Magdzik, A. Zielinski and M. Czerwinski (Department of Epidemiology, National Institute of Hygiene, Warsaw, Poland).
In summary:

1. All countries have surveillance systems for burden of disease in place but a wide diversity of surveillance systems exists among them due to different local situations.

2. The surveillance data on burden of disease are not collected in a standardized way: different data sources for hospital admission and mortality due to HAV and HBV are in place.

3. In some countries the data on total number of hospital admissions and deaths due to HAV and HBV are not available. Sometimes the data sources are present, but data are not immediately accessible or complete.

4. Data on days of hospitalization, total number of liver transplants and the proportion due to hepatitis A, B and C are not often included in the current surveillance systems of burden of disease.
5. There is not a unique adoption of ICD-10 code to report the diagnosis of hepatitis for hospital admission or death. ICD-10 came into use in WHO Member States since 1994. Many countries had not yet adopted this standard several years later (more countries adopted it since then).

6. In some countries, available data on burden of disease are gathered only for remuneration reasons, not for epidemiological purposes. Sometimes only data from extemporary studies are available, without a routine registration system.

7. In a number of countries, data are collected regionally and there is no centralised national data collection, or their aggregation at the central level is not timely.

8. Blanks or missing data in the answers to the EUROHEP.NET survey, unless otherwise specified, can either be due to non-available/traceable information in the country or to non-availability of such information to the country correspondent at the time of the survey. In the latter case, this does not necessarily mean that the information does not exist.
<table>
<thead>
<tr>
<th>Country</th>
<th>Endemicity Age-specific sero-prevalence</th>
<th>Outbreaks</th>
<th>HepA vacc policy</th>
<th>Coverage</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>High-Intermediate &gt; 90% HAV+ lower s-e class</td>
<td>Outbreaks</td>
<td>Target risk groups</td>
<td></td>
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</tr>
<tr>
<td>Argentina</td>
<td>High-Intermediate Pre: 139/100.000 post: 28.3/100.000</td>
<td>Large outbreaks in 2003-04</td>
<td>Universal hepA vacc in 2005 Single dose</td>
<td>95% Reg. Variations: 60-90%</td>
<td>No new outbreaks &gt;80% reduction in incidence</td>
</tr>
<tr>
<td>Brazil</td>
<td>High-Intermediate 7.5/100.000 but underrep.</td>
<td>Small outbreaks</td>
<td>No vacc policy Improve hygienic conditions</td>
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<tr>
<td>country</td>
<td>Endemicity</td>
<td>outbreaks</td>
<td>HepA vacc policy</td>
<td>coverage</td>
<td>impact</td>
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<tr>
<td>Chile</td>
<td>30-60/100.000 High-intermediate</td>
<td>Increasing number of cyclic outbreaks</td>
<td>Improve hgienic conditions</td>
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<tr>
<td>Mexico</td>
<td>High-Interm. HAV+ &gt; 97% of &gt; 20 y olds Large cohort of pre-school children HAV-</td>
<td>No data</td>
<td></td>
<td></td>
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<tr>
<td>US</td>
<td>Low Pre: 10-15/100.000 Post: 1.2/100.000</td>
<td>Large outbreaks every 10-15 years</td>
<td>’99: universal vacc policy in 17 states 2006: nationwide</td>
<td>Coverage: 13-71%</td>
<td>Decline in hops. (69%), mortality rates (32%)</td>
</tr>
<tr>
<td>country</td>
<td>Endemicity</td>
<td>Age-specific sero-prevalence</td>
<td>outbreaks</td>
<td>HepA vacc policy</td>
<td>coverage</td>
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<tr>
<td>India</td>
<td>High-Intermediate</td>
<td>Sero-survey to be started in 2008 90-100% HAV+ in rural adults</td>
<td>Several large outbreaks</td>
<td>No national imm. policy</td>
<td></td>
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<tr>
<td>Thailand</td>
<td>High-Intermediate</td>
<td>27.4% HAV+, increasing with age</td>
<td>Several outbreaks</td>
<td>Vaccine cost do not justify univ. Imm programme</td>
<td></td>
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<tr>
<td>Belarus</td>
<td>Intermediate</td>
<td>95/100.000 &gt;45y age: 85%</td>
<td>No data</td>
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<tr>
<td>country</td>
<td>Endemicity</td>
<td>Age-specific sero-prevalence</td>
<td>outbreaks</td>
<td>HepA vacc policy</td>
<td>coverage</td>
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<tr>
<td>Israel</td>
<td>Intermediate</td>
<td>50.4/100.000</td>
<td>Pre: 10/y Post: none</td>
<td>1999: toddlers</td>
<td>85-90%</td>
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<tr>
<td>Italy</td>
<td>Low</td>
<td>1995: 4/100.000, 2006: 1.4/100.000</td>
<td>Large outbreak in Puglia (1997)</td>
<td>Risk groups</td>
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<td></td>
<td>Surveillance of shellfish retail</td>
<td>Univ. policy in Puglia (1998)</td>
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<tr>
<td>Spain Catalonía</td>
<td>Intermediate-Low</td>
<td>Pre: 5.51/100.000 Post: 2.98/100.000</td>
<td>No data</td>
<td>1995: risk groups 1998: Univ. Policy: pre-ado’s</td>
<td></td>
</tr>
<tr>
<td>country</td>
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<td>outbreaks</td>
<td>HepA vacc policy</td>
<td>coverage</td>
<td>impact</td>
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<tr>
<td>Russ Fed.</td>
<td>High-intermediate 50-170/100.000 Decreasing immunity in younger pop.</td>
<td>Periodic large outbreaks</td>
<td>No universal policy</td>
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<tr>
<td>Netherlandds</td>
<td>Low 2/100.000 Import MSM transmission</td>
<td>Small n° of outbreaks Import related</td>
<td>Risk group policy Travel-import Related</td>
<td></td>
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</tr>
<tr>
<td>Turkey</td>
<td>Low-Intermediate-High Overall: 71.3% HAV+</td>
<td>No data</td>
<td>Vaccine in private sector</td>
<td></td>
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<tr>
<td>country</td>
<td>Endemicity</td>
<td>outbreaks</td>
<td>HepA vacc policy</td>
<td>coverage</td>
<td>impact</td>
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<tr>
<td>Ukraine</td>
<td>High-intermediate</td>
<td>Several</td>
<td>hepA vacc. Planned to be included in NIP by 2011</td>
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<tr>
<td></td>
<td>Increasing susc. In younger ones</td>
<td>outbreaks</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Saudi Arabia</td>
<td>High-Intermediate 9-14/100.000</td>
<td>Several</td>
<td>2000: risk group –childhood imm in private schools</td>
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<tr>
<td></td>
<td></td>
<td>outbreaks</td>
<td>2008: univ. Policy (18m olds).</td>
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<tr>
<td>Australia</td>
<td>Pre: 31.1-75/100.000 Indigenous pop. Post: 1.8/100.000</td>
<td>Oister-related MSM, IVDU, ...</td>
<td>Risk group 1999: For indigenous children (N-Queensland) 2005: in high incidence states</td>
<td></td>
<td>95% red. in incidence</td>
</tr>
<tr>
<td>Country</td>
<td>Endemicity</td>
<td>Age-specific sero-prevalence</td>
<td>Outbreaks</td>
<td>HepA vacc policy</td>
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<tr>
<td>China</td>
<td>High-intermediate</td>
<td>Pre: &gt; 50/100.000  Post (2005-2006): 5/100.000</td>
<td>Shanghai (1988)</td>
<td>Vacc policy since 1992  Plans to include vacc in routine programme by dec 2007 (18m)</td>
<td></td>
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<tr>
<td>Korea</td>
<td>High-intermediate</td>
<td>9.8/100.000  10-19y &amp; 20-29y are most susceptible</td>
<td>Childhood vacc recommended but not universal</td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>
Uses of Molecular Epidemiology

- Sources of Virus Transmission in outbreaks
  - Food / water / other environmental
  - Risk factors – MSM, IDU
  - Blood / Blood Products
- Transmission Patterns within Populations
- Monitoring Vaccine Effectiveness
- Examples of molecular epidemiological studies were presented:
  - HAV outbreak in European travelers returning from Egypt
  - Used to detect HAV in urban sewage
    - F.u. of epidemiological patterns of excretion of HAV

(routine) monitoring of circulating HAV strains useful to:
  - detect widely dispersed outbreaks and hidden clusters
  - demonstrate links between imported and autochthonous cases
Postexposure policy changes...

- In much of Europe and Canada, hepatitis A vaccine becomes recommended after exposure, but recommendations vary:
  - In countries where immune globulin was not used
  - In some countries vaccine is recommended over IG
  - In the UK, vaccine is recommend if it can be given early while IG is considered preferable later/for those with higher risk of serious outcome.
Study in Kazakhstan compared the efficacies of hepatitis A vaccine and IG in the prevention of laboratory-confirmed symptomatic hepatitis A when given within 14 days of exposure to a symptomatic index case of hepatitis A.

Study concluded: hepA vacc. had high efficacy, similar to that of IgG.
For healthy persons age ≥ 12 months to 40 years, hepatitis A vaccine is preferred to IG.

For persons > 40 years, IG is preferred. (Vaccine can be used if IG cannot be obtained.)

For children age < 12 months, immunocompromised persons, persons with chronic liver disease, and persons for whom vaccine is contraindicated, IG should be used.
Conclusions: HEpatitis FLoridA

- Highly immunogenic
  - Non-response in > 99%
  - Rapid seroconversion
  - Long-term antibody persistence
- Excellent safety profile
- Freedom to choose
  - Coadministration / combination vaccines
  - Flexible vaccination schedule
  - Interchangeability
- Long-lasting protection
  - Beyond antibody persistence (life-long)
  - Proven effectiveness, even post-exposure
- After single dose? How long protected?

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## Selected Countries with Routine Childhood Hepatitis A Vaccination Programs; 2007

<table>
<thead>
<tr>
<th>Country</th>
<th>Target Ages</th>
<th>Year Begun</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhejiang Province, China</td>
<td>1-15 years</td>
<td>1992</td>
<td>Single dose live attenuated vaccine</td>
</tr>
<tr>
<td>North Queensland, Australia</td>
<td>18 months; catch-up to age 6 years</td>
<td>1999</td>
<td>Indigenous population</td>
</tr>
<tr>
<td>United States</td>
<td>2-18 (regional)</td>
<td>1999</td>
<td>2006 - national (12 months)</td>
</tr>
<tr>
<td>Catalonia, Spain</td>
<td>12 years</td>
<td>1998</td>
<td>A/B vaccine</td>
</tr>
<tr>
<td>Puglia Region, Italy</td>
<td>15 months; 12 years</td>
<td>1997</td>
<td>A/B vaccine for adolescents</td>
</tr>
<tr>
<td>Israel</td>
<td>18 months</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>12 months</td>
<td>2005</td>
<td>Single dose</td>
</tr>
</tbody>
</table>
Hepatitis A Incidence, by Age and Population Group, Israel, 1993-2004

1-4 years

Vaccination Program

5-9 years

Vaccination Program

10-14 years

Vaccination Program

15-44 years

Vaccination Program

Source: Dagan et al, JAMA 2005
Medstat MarketScan Database

Comparing baseline (1996-97) to 2004, statistically significant declines:

- Hospitalizations – 69%
- Ambulatory visits – 42%

Adjusted to US population, medical expenditures for hospitalizations and ambulatory visits declined:

- $29.1 million (baseline) to $9.3 million (2004)
  – 68% reduction

Conclusions

- Hepatitis A is a significant cause of morbidity in the world
- Mortality due to hepatitis A is low but is the leading cause of liver transplant for acute viral hepatitis:
  - Surprising rates of fulminant hepatitis A in younger ones (e.g. in Korea, Brazil, Argentina)
- Lack of recent country data!
- Need for improved surveillance – standardized systems of data collection and case definition
  - To produce accurate BOD data
  - To document the increased nº of susceptibles
  - Through low cost methods (cross sectional data, ...)

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Conclusions

- The changing epidemiology is visualizing the clinical features of the disease and its consequences.
- Investment in improved sanitation, makes high endemicity countries move to intermediate situation, ... this should go hand in hand with the implementation of universal hepatitis A immunization programmes.
conclusions

• Data on circulating strains need to be shared globally and within the regions.
• Vaccination of travellers need to be stressed (prevention of HAV importation).
• Low endemicity country: most HE analysis have shown hep A risk group vaccination to be cost-effective.
• Low endemicity country: routine vaccination studies have been inconclusive.
• However, recent analysis have shown more favourable results:
  - With reduced vaccine costs.
  - Using dynamic models taking the indirect effect of herd immunity into consideration.
Conclusions

- Consensus reached on a stepwise strategy at country-level:
  - Invest in accurate surveillance
    - Document level of endemicity/outbreaks/...
  - Secure political support
  - Conduct HE analysis
- The need to control HAV globally was emphasized
- The need to place HAV disease in the context of global health priority was stressed
Future

- Revisit the WHO position paper
- Put HAV on the international agenda
- Next edition of a similar meeting over 1 or 2 years
  - Update the situation
  - Review what has been achieved in the meantime