Current Strategies for Vaccination Against Hepatitis A

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Disclosure - Hepatitis A

• Advisor - Viral Hepatitis Prevention Board
• Advisor - WHO
• Advisor - European Centers for Disease Control
Outline

- Epidemiology
- Hepatitis A vaccines
- Control and prevention strategies
- Global overview of hepatitis A vaccination programs
- Elimination of HAV infection in Israel
- Single dose immunization-Argentina
- Safety
- Summary
Hepatitis A epidemiology shifts with improving hygiene

Seroprevalence of anti-HAV (%)

Increase in susceptibility

Improvement in hygiene

Age (years)
WHO position paper on epidemiology of hepatitis A vaccines – June 2012*

Based on an ongoing reassessment of the global burden of hepatitis A, WHO estimates suggest:

- An increase in the number of acute hepatitis A cases from 177 million in 1990 to 212 million in 2005.
- Deaths due to hepatitis A to increase from 30,283 in 1990 to 35,245 in 2005.
- Increased numbers of cases estimated to occur in the age groups 2–14 years and >30 years.
- Adult infections
  - 75-90% of cases are symptomatic.
  - Historically, fulminant hepatitis is rare (<1%) but rising incidence of fulminant hepatitis in distinct regions?
  - 1.75-2.1% mortality rate after ≥40 years of age.


*Jacobsen KH & Wiersma ST. Vaccine 2010;28:6653
Global risk map of HAV immunity in 2005: Age at midpoint of population immunity to HAV*

Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010;28:6653-
Fig. 6. HAV genotype classification. Phylogenetic analysis of the six currently recognised HAV genotypes. Reproduced with permission from. HAV, hepatitis A virus.
Milestones in development of hepatitis A vaccines*

- **1988** - Propagation of attenuated HAV in culture
- **Early 1990s** - Pivotal efficacy studies in Thailand and the US
- **1996** - ACIP-Introduction of vaccine to selected risk groups
- **1999** - Universal vaccination in selected regions/countries
- **2005** - Single dose immunization
- **2007** - Post exposure prophylaxis
- **2007** - Int. meeting: Global control of HAV infection, Miami *

*Has the time come to control hepatitis A globally? A global hepatitis A meeting 11.09 J Viral Hepatitis 2008;15 suppl 2*
Hepatitis A vaccines

• Inactivated Vaccines

Vs

• Live, attenuated vaccine

• Monovalent Vaccines

Vs

• Combined vaccines
Hepatitis A vaccines

Inactivated, Monovalent or Combined vaccines

✓ Manufactured from attenuated HAV strain
✓ Formaldehyde, inactivated
✓ Contain an adjuvant:
  - aluminum hydroxide
  - formulated in virosomes

Live attenuated vaccines

✓ Inactivated Vs live attenuated vaccines
Differences in:

 ➤ Technology of production
 ➤ Cost
 ➤ Pace of immune response to vaccination
 ➤ Surveillance of safety and tolerability
 ➤ Distribution

† Live attenuated vaccines
  No adjuvant
Inactivated Vs Live Attenuated HAV Vaccines

Table 1. Monovalent formalin-inactivated hepatitis A vaccines.

<table>
<thead>
<tr>
<th>Attenuated HAV strain</th>
<th>Trade name</th>
<th>Adjuvant</th>
<th>HAV antigen Dose/injection</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paediatric</td>
<td>Adult</td>
</tr>
<tr>
<td>HM-175</td>
<td>HAVRIX®</td>
<td>Aluminium hydroxide</td>
<td>720 EU</td>
<td>1440 EU</td>
</tr>
<tr>
<td>CR-326</td>
<td>VAQTA®</td>
<td>Aluminium hydroxide</td>
<td>25 U</td>
<td>50 U</td>
</tr>
<tr>
<td>GBM</td>
<td>AVAXIM®</td>
<td>Aluminium hydroxide</td>
<td>80 U</td>
<td>160 U</td>
</tr>
<tr>
<td>TZ84</td>
<td>HEALIVE®</td>
<td>Aluminium hydroxide</td>
<td>250 U</td>
<td>500U</td>
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<tr>
<td>Lv-8</td>
<td>Weisairuiian®</td>
<td>Aluminium hydroxide</td>
<td>320 EU</td>
<td>640 EU</td>
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<tr>
<td>YN5</td>
<td>Veraxim®</td>
<td>Aluminium hydroxide</td>
<td>800 EU</td>
<td>1600 EU</td>
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<tr>
<td>RG-SB</td>
<td>EPAXAL®</td>
<td>Viromes</td>
<td>24 U</td>
<td>24 U</td>
</tr>
</tbody>
</table>

* Modified and updated from references 75,160

Table 2. Live attenuated hepatitis A vaccines.

<table>
<thead>
<tr>
<th>Attenuated HAV strain</th>
<th>Name</th>
<th>Adjuvant</th>
<th>HAV Antigen Dose/injection</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paediatric</td>
<td>Adult</td>
</tr>
<tr>
<td>H2</td>
<td>Freeze-dried live HAV vaccine</td>
<td>None</td>
<td>0.5 ml (6.5 log CCID&lt;sub&gt;50&lt;/sub&gt;)</td>
<td>1.0 ml (6.5 log CCID&lt;sub&gt;50&lt;/sub&gt;)</td>
</tr>
<tr>
<td>LA-1</td>
<td>HAVAC Freeze-dried live HAV vaccine</td>
<td>None</td>
<td>1.0 ml (6.5 log CCID&lt;sub&gt;50&lt;/sub&gt;)</td>
<td>Changchun Institute of Biologic Products</td>
</tr>
</tbody>
</table>

** Modified from 160

Properties of hepatitis A vaccines

- Highly immunogenic
- Flexible injection schedule
- Excellent safety record
- Long-lasting immunity
- Booster doses not required for immune-competent subjects who received two doses
Post vaccination anti-HAV antibody levels 20 Years

- Anti-HAV antibody GMCs peaked 1 month post-dose 2 in both studies
- GMCs declined sharply during first year after primary vaccination
- Thereafter, low rate of decay in antibody levels
  - ?Plateau reached?
- 20 years post-primary vaccination anti-HAV GMCs persist at 317 mIU/ml and 312 mIU/ml in the seropositive subjects in studies HAV-112 (0, 12) and HAV-123 (0, 6), respectively

Figure provided by Pierre van Damm, Univ of Antwerp, Belgium
Combination Vaccines

- Hepatitis A and B
  - TWINRIX®
- Hepatitis A and typhoid
  - Viatim®
  - Vivaxim®
  - Hepatryx®
Hepatitis A Vaccines
Control and Prevention Strategies

• Immunization of defined risk groups
• Regional mass vaccination of pediatric sub-populations at risk
• Universal vaccination of toddlers
• Single-dose immunization
• Post-exposure prophylaxis and intervention in outbreaks
Hepatitis A Vaccines
Control and Prevention Strategies

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Hepatitis A Vaccines
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Selected regional mass vaccination programs of pediatric subpopulations at risk

• US
  – Alaska
  – American Indians
  – Butte county
• Puglia, Italy
• Catalonia, Spain
• North Queensland, Australia
• Minsk, Belarus
• Shengsi county and Jiaojiang city, Zhejiang province, China (attenuated live vaccine)
Vaccination coverage and incidence of hepatitis A in Puglia region and Italy, 1998-2006*

*Lopalco PL et al. EID 2008;14:256
Belarus 2003: Childhood Hepatitis A Vaccination Program in Minsk

A

Hepatitis A Incidence in 6 Year Old Children and Vaccine Coverage, Minsk, Belarus, 2000-2006

B

Hepatitis A Incidence Rate by Age Group Before and After Vaccination Program Implementation, Minsk, Belarus, 2000-2006

Fisenka EG et al, J Viral Hepatitis 2008; 15 suppl 2:57
China: Hepatitis A Vaccination of Children

- Shengsi County and Jiaojiang City, Zhejiang Province, China
- Begun as demonstration project in 1992
- Initial vaccination of children ages 1-15 years
- Subsequent ongoing vaccination of each new cohort
- Single dose live attenuated vaccine (ZhePu)
- Estimated coverage 85%-91%

Reported Hepatitis A Cases among Children < 16 years and Hepatitis A Vaccine Coverage, Shengsi County and Jiaojiang City, Zhejiang Province, China (1983 to 2002)

Impact of incremental vaccination strategy against hepatitis A in the US

Overall Hepatitis A Incidence* (USA, 1980-2006)

- 1995 vaccine licensure
- 1996 ACIP recommendations
- 1999 ACIP recommendations
- 2006 rate = 1.2

Incidence* of acute hepatitis A, by age group and year following the gradual introduction of mass vaccination in children in the USA, 1990-2007

- One dose vaccine coverage rose from 17% to 47% between 2006-2009 in 12-23m old toddlers (8 sentinel sites).
- Full 2 dose vaccine coverage rose from 1% to 15% (MMWR 29th July, 2010)

MMWR 29th July, 2010
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:
  – 68% reduction
  – $29.1 million (baseline) to $9.3 million (2004)

Updated ACIP Recommendations for Post Exposure Prophylaxis against HAV (abbreviated)

- 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.

Hepatitis A Vaccines
Control and Prevention Strategies

• Immunization of defined risk groups
• Regional mass vaccination of pediatric subpopulations at risk
• Universal vaccination of toddlers
• Single-dose immunization
• Post-exposure prophylaxis and intervention in outbreaks
Factors affecting vaccination strategy

- Disease burden and level of endemicity
- Socio-economic development and sanitation
- Risk of outbreaks
- Vaccine costs and cost-effectiveness
- Acceptance by the population
Highlights of HAV Epidemiology in Israel

**Background**
- Heterogeneous population (contact between high and low socioeconomic risk groups)
- Highest attack rate in children **5-9 years old**
- Maternal anti-HAV IgG is usually cleared in babies by the age of 18 months
- Hepatitis A is rarely observed < age of 18m
- Toddlers seem to be the main vehicle for HAV transmission (pilot study results)

Jews vs Non-Jews in Israel - Relevance to HAV Epidemiology

The non-Jewish population in Israel as compared to the Jewish population:

- Lower socioeconomic status
- Higher birthrate (37.6 vs 18.5 per 1,000)
- More crowded living conditions (2.99 vs 2.18 per household)
- Lower hygienic infra-structure
Incidence of Viral Hepatitis in Israel
1963-1996 by Population

- Non-Jewish population
- Jewish population
Israel: Childhood Hepatitis A Vaccination Program

- July 1999
- Vaccination of all 18 month old children
- Vaccine provided free of charge, as part of regular immunization program
- Estimated first dose coverage in vaccinated cohorts – 90%; second dose – 85%

Source: Dagan et al, JAMA 2005
Incidence of Hepatitis in Israel 1996-2016

Annual incidence rates of hepatitis A/100,000 population, by specific age and ethnicity, 1993-2012
Geographic Information System (GIS)

A system of **hardware** and **software** linking **mapped objects** to **collected** information (i.e. epidemiologic data)
Number of Acute Hepatitis A Cases in the Jerusalem District*

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
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<tbody>
<tr>
<td>1999</td>
<td>671</td>
</tr>
<tr>
<td>2000</td>
<td>654</td>
</tr>
<tr>
<td>2001</td>
<td>420</td>
</tr>
<tr>
<td>2002</td>
<td>46</td>
</tr>
<tr>
<td>2003</td>
<td>67</td>
</tr>
<tr>
<td>2004</td>
<td>50</td>
</tr>
<tr>
<td>total</td>
<td>1908</td>
</tr>
</tbody>
</table>

*Through active surveillance in a population of ~900,000
HAV Genotype Distribution in Sub-populations - Jerusalem

Jewish population (N=466)
- 1b (19%)
- 1a (81%)

Non-Jewish population (N=243)
- 1b (96%)
- 1a (4%)

Shouval D et al. submitted
- Control of HAV infection in Jerusalem
- Follow-up on GIS
Countries Using HepA Vaccine in National Immunization Schedule, 2010

No (182 countries or 94%)

Yes (11 countries or 6% - Argentina, Bahrain, China, Greece, Israel, and Kazakhstan, Panama, Qatar, Saudi Arabia, Uruguay, USA)

Source: WHO/IVB database, 193 WHO Member States.
27 October 2011
Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines - A systematic review

The WHO recommends integration of universal mass vaccination (UMV) against HAV in national immunization schedules for children aged ≥1 year, if justified on the basis of acute HAV incidence, declining endemicity from high to intermediate and cost-effectiveness. This recommendation has been implemented in several countries.

-Review of 27 studies (Argentina, Belgium, China, Greece, Israel, Panama, the United States and Uruguay).

• All except one study showed a marked decline in the incidence of hepatitis A post introduction of UMV.
• The incidence in non-vaccinated age groups decreased as well, suggesting herd immunity but also rising susceptibility.
• Long-term anti-HAV antibody persistence was documented up to 17 y after a 2-dose primary vaccination.

Conclusion: introduction of UMV in countries with intermediate endemicity for HAV infection led to a considerable decrease in the incidence of hepatitis A in vaccinated and in non-vaccinated age groups alike

Hepatitis A Vaccines
Control and Prevention Strategies

• Immunization of defined risk groups
• Regional mass vaccination of pediatric subpopulations at risk
• Universal vaccination of toddlers
• Single-dose immunization
• Post-exposure prophylaxis and intervention in outbreaks
Fulminant hepatitis A in children

Number of reports is rising?

- Turkey 4 cases (6/04-11/06)
- UK 9 cases (1991-2000)
- Argentina 128 cases (5/82-9/02)
  41 cases (9/03-1/06)
- Brazil 13 cases (1998-2007)
- Korea 35 cases (2003-2008)

Reports are retrospective and released by individual centers

Argentina: Childhood Hepatitis A Vaccination Program

- Universal single-dose hepatitis A immunization program
- June 2005
- Children aged 12 months
- Most vaccines provided free of charge
- Vaccine coverage 95% in 2006
- 80% decrease in incidence from 70.5-173.8/100,000 to 10.2/100,000

Vacchino NM et al, J Viral Hepatitis 2008;15: suppl 1.2:47
Rapid Seroconversion Following a Single Dose of an HAV Vaccine

Shouval D et al. Vaccine 1993;11:suppl 1 9S
Fig. 8. Impact of the single-dose immunisation strategy against hepatitis A in Argentina. (Reproduced with permission from\textsuperscript{177}).

Lemon SM, Ott JJ, Van Damme P, Shouval D. J Hepatology 2017
Hepatitis A Vaccines
Control and Prevention Strategies

• Immunization of defined risk groups
• Regional mass vaccination of pediatric subpopulations at risk
• Universal vaccination of toddlers
• Single-dose immunization
• Post-exposure prophylaxis and intervention in outbreaks
Hepatitis A vaccine versus immune globulin for post-exposure prophylaxis

- 1090 household and day-care contacts, 2-40y old of index cases randomized to receive an hAV vaccine or IG
- Transmission of HAV confirmed by anti-HAV IgM occurred in 4.4% of vaccine and 3.3% IG recipients (RR 1.35; 95% CI: 0.70-2.67)

Victor JC et al. NEJM 2007;357:1685
Hepatitis A virus infection is a self limited disease but it still causes significant morbidity in young and older adults, associated with temporary disability and cost.

Large populations of adolescents and young adults in countries with intermediate endemicity (and in transition”) who escaped HAV infection in their early childhood are at risk for contracting clinical hepatitis A due to the current shift in susceptibility. This trend may lead to potential outbreaks.

Immunization of defined risk groups has a limited impact on overall burden of infection.

Universal immunization against hepatitis A to babies is highly effective in controlling transmission to children and provides herd immunity to unvaccinated adults.

Booster dose(s) are not required after successful immunization.

Post exposure prophylaxis using an hepatitis A vaccine within 14 days of exposure, is effective with an important advantage of providing much longer protection against hepatitis A as compared to immune globulin.
Two outbreaks of HAV

- IVDA
- MSM

Evidence for Hepatitis A Virus Endemic Circulation in Israel Despite Universal Toddler Vaccination Since 1999 and Low Clinical Incidence in All Age Groups

Yosef Manor, Matthew Lewis, Daniela Ram, Nili Daudi, Orna Mor, Michal Savion, Zipi Kra-Oz, Yonat Shemer Avni, Rivka Sheffer, Daniel Shouval, and Ella Mendelson.
Outbreak of HAV in the Tel Aviv District 2012-2013

N=75

20% IVDA
HAV clinical cases, 2017

• Number of reported cases: 81
• Median age: 34y (range 3-56y)
• Male/Female: 69/24 (85.2% M)
Sewage derived environmental surveillance

• A useful tool for population-based monitoring of microbial and viral activities.

• In Israel, a national program for surveillance of the poliovirus in sewage has been ongoing since 1988. It led to the identification of wild poliovirus in 2013, which activated a major emergency response by the Public Health Services.

• Similar surveillance is currently employed for HAV

Manor Y et al.. *J Infect Dis.* 2016
Sampling of Urban Sewage

Shafdan STF

500 ml sample (filter & centrifuge) to 15 m

Extract NA from 1 ml

Real-Time PCR (TQM)

HAV negative

HAV positive

sequence
147 sewage samples were collected monthly from 14 facilities around the country. 31% (45/147) of sewage samples were HAV positive, with a high prevalence (63%, 26/41) in facilities in the Tel-Aviv area.
Phylogenetic tree showing the Israeli (black and green) and the reference (red) strains belonging to genotypes IA, IB, III, and IV, as indicated in each reference strain name. Black letters indicate serum samples, and green i indicate environmental samples.
Summary

• The HAV 1a outbreak in MSM in Israel is m.p. imported, from European countrise. HAV 1B in IVDA is mainly derived from the Gaza strip and possibly Jordan West bank.

• Despite the efficient universal mass vaccination program which lead to a dramatic fall in the annual HAV incidence (from 33-70 cases to 2,5 cases/100,000), HAV can still be transmitted to susceptible/high-risk adult population, raising the issue of catch-up vaccination.

• The role of environmental sampling in disease surveillance is demonstrated.
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Thank You
References

The Immunological Basis for Immunization Series, Module 18, Hepatitis A. Immunization, Vaccines and Biologicals, May 1, 2011. [Link](http://whqlibdoc.who.int/publications/2011/9789241501422_eng.pdf)