«20 Years of successful Hepatitis A vaccines and Future perspectives»

Hugues H Bogaerts MD FFPM
Global Vaccine Consultant

EASL, St Petersburg
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Twenty-seven diseases are now vaccine preventable

“Vaccines are one of the greatest achievements of biomedical science and public health”

MMWR 1999; 48(12):243-248
Impact of Vaccination: Some Examples

- **Polio - worldwide**
  - Reported cases (000s)
  - EPI implemented

- **Diphtheria - England & Wales**
  - Vaccine introduced
  - 1940, 1950, 1960

- **Measles - US**
  - Vaccine introduced
The example of Hepatitis A vaccination

Hepatitis A Incidence, United States, 1980-2002 *

- 1995 vaccine licensure
- 1996 ACIP recommendations
- 1999 ACIP recommendations
- 2002 rate* = 2.9

*2002 rate provisional

“The best weapon against viral diseases, in spite of several efficacious antivirals, is still vaccination.”

Stanley Plotkin, 2008
Epidemiological risk groups for acute hepatitis A virus infection in the western hemisphere (reported cases in the USA; 2007)*

- unknown (67.7%)
- sexual or household contact (7.8%)
- international travel (17.5%)
- MSM (5.9%)
- child/employee day care center (3.8%)
- suspected food or waterborne outbreak (6.5%)
- contact of daycare child/employee (4.6%)
- other contact with an HAV patient (9.0%)

“The development of a hepatitis A vaccine is one of WRAIR's greatest success stories.

Pioneered at WRAIR, the vaccine technology was transferred to SmithKline Beecham.
Havrix™:
GSK Biologicals’ hepatitis A vaccine

- HM 175 strain, live attenuated
- 1992: World’s first effective hepatitis A vaccine
- Available in 130 countries
- >360 million doses of HM 175 distributed
- ~162 Mio People protected against Hepatitis A

2. GSK Biologicals, Data on file, 2012
Vienna
27-29 January
1992
HAVRIX™
Launch symposium

International Symposium
on Active Immunization
against Hepatitis A

Butterworth-Heinemann
Havrix™ is indicated for active immunisation of persons ≥12 months of age against disease caused by hepatitis A virus

- **Havrix™ 1440 Adult:**
  - adults ≥16 years*

- **Havrix™ 720 Junior:**
  - children and adolescents from 12 months – 16 years

- In order to obtain more persistent immunity, a second dose is recommended between 6 and 12 months

*Age cut-off varies in different countries
**Havrix™: Immunogenicity**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>PI M1</th>
<th>PI I M7</th>
<th>N</th>
<th>SC%</th>
<th>GMT (mIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 6-month schedule</td>
<td></td>
<td></td>
<td>162–200</td>
<td>97–100</td>
<td>351–589</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>2320–4383</td>
</tr>
<tr>
<td>0, 12-month schedule</td>
<td></td>
<td></td>
<td>439</td>
<td>99</td>
<td>466</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150</td>
<td>100</td>
<td>4775</td>
</tr>
</tbody>
</table>

GMT, geometric mean titre  
SC, seroconversion

### Havrix™:
Rapid Seroconversion (after 1st dose)

<table>
<thead>
<tr>
<th>Time point</th>
<th>N</th>
<th>SC (%)</th>
<th>GMT (mIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 13</td>
<td>157</td>
<td>79</td>
<td>140</td>
</tr>
<tr>
<td>Day 14</td>
<td>150</td>
<td>85</td>
<td>228</td>
</tr>
<tr>
<td>Day 15</td>
<td>716</td>
<td>86</td>
<td>265</td>
</tr>
<tr>
<td>Day 16</td>
<td>407</td>
<td>93</td>
<td>326</td>
</tr>
<tr>
<td>Day 17</td>
<td>125</td>
<td>95</td>
<td>445</td>
</tr>
<tr>
<td>Day 18</td>
<td>67</td>
<td>99</td>
<td>595</td>
</tr>
<tr>
<td>Day 19</td>
<td>72</td>
<td>100</td>
<td>732</td>
</tr>
</tbody>
</table>

GMT, geometric mean titre
SC, seroconversion

**Havrix™: Protective Efficacy**

0, 1, 12-month schedule:

<table>
<thead>
<tr>
<th></th>
<th>Vaccine (N=19,037)</th>
<th>Control (N=19,120)</th>
<th>Vaccine efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 12-month dose (days 138–386)</td>
<td>2</td>
<td>32</td>
<td>94</td>
</tr>
<tr>
<td>Cumulative (days 138–532)</td>
<td>2</td>
<td>38</td>
<td>95</td>
</tr>
</tbody>
</table>

Havrix™:
Long-term persistence of antibodies

• **Children:**
  – Long-term data show anti-HAV GMTs >403 mIU/mL and 100% seropositivity after 60 months¹
  – Mathematical models predict persistence for 24.5 years²

• **Adults:**
  – Long-term data show anti-HAV GMTs = 242 mIU/mL after 12 years³
  – Mathematical models predict persistence beyond 25 years⁴,⁵

GMT, geometric mean titre
HAV, hepatitis A virus

5. Van Damme & Van Herck, *Travel Med Infect Dis* 2007; 5: 79–84
Antibody Persistence and Immune Memory in Healthy Adults Following Vaccination With a Two-Dose Inactivated Hepatitis A Vaccine: Long-Term Follow-Up at 15 Years

Koen Van Herck,1,2 Jeanne-Marie Jacquet,3 and Pierre Van Damme1*

Journal of Medical Virology 83:1885–1891 (2011)
Hepatitis A vaccine:
No need for a booster

International Consensus Group on Hepatitis A Virus Immunity:\(^1\)

“There is no evidence to lend support to HAV [hepatitis A virus] booster vaccination after a full primary vaccination course in a healthy individual”

“Hepatitis A booster vaccination is presently considered as unnecessary in fully vaccinated individuals” \(^2\)

2. Van Damme & Van Herck, Travel Med Infect Dis 2007; 5: 79–84
**Havrix™: Safety**

- Positive safety profile¹
- In clinical studies, most adverse events were mild²
- Local adverse events:²
  - injection site soreness most common
  - <0.5% severe
- Systemic adverse events:²
  - headache: 14% of adults and <9% of children
  - fatigue, fever, malaise, loss of appetite, nausea: 1–10%
  - abdominal pain, myalgia, etc: <1%
- Rare adverse events have been observed in post-marketing surveillance studies²

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Hepatitis A: Vaccination Strategies

- At risk\(^1,2\)
- Outbreak control\(^1\)
- Universal mass vaccination (UMV)\(^1,2\)

Military: Operational Needs

• Long history of infectious diseases taking their toll on soldiers

• From 53% to 69% of medical losses of Soviet troops (evacuations) in Afghanistan from 1980 to 1983 due to
  – Hepatitis A
  – Typhoid
  – Amoebic Dysentery
  – Other enteric and infectious diseases

• Such figures have been observed in other military campaigns

Voen Med Zh (2000);321(9):4-11,96
HBsAg positive children

- Hepatitis A may follow a more severe course and have a higher fatality rate in patients with chronic hepatitis B. Children who are HBsAg positive should therefore be vaccinated against hepatitis A.

- In these subjects, Havrix™ has been found to be well tolerated and immunogenic.

- Side effects of vaccination were usually mild, short-lived and similar to those observed in other subjects.

J Pediatr 1999; 134, 784
Havrix™ in outbreak control: Alaska

The hepatitis A paradox

- Improving socio-economic conditions
- Childhood exposure to virus

- Proportion of susceptibles among older children and adults
- Proportion of symptomatic disease increases with age

- Risk for clinically significant outbreaks
Vaccination coverage and HAV incidence
Puglia region and Italy, 1998-2006*

Vaccine offered to children 15-18 months, and to 12 years old

Hepatitis A Incidence, by Age and Population Group
Israel, 1993-2004

Hepatitis A outbreaks: Migration in The Netherlands

Adapted from Termorshuizen & van de Laar, *Ned Tijdschr Geneeskd* 1998; 142: 2364–8
Epidemiological risk groups for acute hepatitis A virus infection in the western hemisphere (reported cases in the USA; 2007)*

unknown (67.7%)
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Hepatitis A UMV success: USA

Hepatitis A Incidence

1987-1997 average incidence

2002 incidence

Rate per 100,000

- Red: >=20
- Yellow: 5 - 9
- Orange: 10-19
- White: 0 - 4

Adapted from Fiore, et al. MMWR Recomm Rep 2006; 55 (RR07): 1–23
Havrix™: Key Features

- Highly immunogenic
- Positive safety profile
- Flexible dosing schedule
- Rapid seroconversion
- Long-term protection
- No need for a booster dose of hepatitis A vaccine

Use in:
- at risk (e.g. travellers)
- outbreaks
- universal mass vaccination

“The best weapon against viral diseases, in spite of several efficacious antivirals, is still vaccination.” (S. Plotkin, 2008)

SO,
will the next decades see the eradication of Hepatitis A?
спасибо !
Thank you…