Universal Hepatitis B vaccination in the Netherlands

Reasons for implementation

C. Richter, infectious diseases, Rijnstate hospital and member of advisory committee NHC, NL
Impact of hepatitis B

- Two billion people have been exposed
- 500,000-1 million die annually
- 450 million chronically infected
- In Europe 1 million are exposed to HBV each year, 90,000 become chronic carriers
- Accounts for at least 53% of all primary liver cancers, only second to tobacco as leading cause of human cancer
Major reasons for implementation universal hepatitis B-vaccination

- Follow WHO recommendation
- Universal vaccination has proven to be effective, can be easily integrated into Dutch immunisation programme
- Risk group- approach has failed, no evidence that it can protect the population
- Morbidity, mortality will decrease (including risk of livercancer)
- Cost-effective over time
WHO recommendations for Universal HBV vaccinations

• 1991: Global Advisory Group of EPI of WHO calls for all countries to add the hepatitis B vaccine to their NIP by 1997
• VHPB report 1995: 75 countries had already official policy to include it in their NIPs
• Spain, Italy, France, Portugal, Germany, Poland, USA, Canada…had included
• Netherlands, Belgium, Greece, Turkey, Switzerland seriously considered
• Great Britain, Ireland and Scandinavian countries not convinced
What is the situation now?
Number of countries introduced HepB vaccine* and global infant HepB3 coverage, 1989-2007

* Includes India and Sudan where introduction is part of the country excluding 3 countries where HepB administered for adolescence

Countries having introduced HepB vaccine and infant HepB3 coverage, 2007

171 countries introduced in national infant immunization schedule
- HepB3 ≥ 80% (139 countries or 72%)
- HepB3 < 80% (31 countries or 16%)
- HepB vaccine introduced but no coverage data reported (1 country or 0.5%)
- HepB* vaccine not introduced (22 countries or 11.5%)
- 3 countries introduced HepB in adolescent immunization schedule

Date of slide: 4 September 2008

* HepB* denotes the HepB vaccine given in infancy.

- “Currently, vaccination practices vary considerably across Europe, with countries such as UK, The Netherlands and Nordic countries having chosen not to include the hepatitis B vaccine in national childhood or adolescent vaccination schedules

- Given the high level of immigration within the EU, this lack of uniformity in vaccination policy threatens the potential for EU-wide strategies to contain the spread of HBV. Thus a uniform policy of vaccination is needed across the EU”
European Parliament, Hepatitis B expert meeting 2007

• “In line with WHO recommendations, Europe should encourage a cohesive policy of all newborns and adolescents as well as effective vaccination of populations at risk”
Situation in Europe

• All countries included hepatitis B vaccination into NIPs except the following low prevalence countries (< 2%):
  – Scandinavian countries
  – The Netherlands
  – United Kingdom
  – Ireland
  However: Changing policy in
  – United Kingdom and Ireland?
United Kingdom, Ireland

• The British Medical Association called upon the Department of Health at their June 2007 representative meeting to introduce the HBV-vaccine into the childhood schedule without further delay (Pollard, BMJ 2007)

• Cost-effective analysis in Ireland shows that universal infant immunisation would be a cost-effective intervention, universal adolescent vaccination would be more costly, the current program targeting high risk groups more difficult to implement and less effective (Tilson, European Journal of Public Health 2007)
What successes have been reached with NIPs?

• Example Taiwan – high endemic country

• Example Italy – intermed. endemic country
Taiwan- 20 years experience

• Start immunisation of children with HBsAg pos. mother in 1984, of all newborns in 1986
Taiwan, Age specific HBsAg rates

Figure 1. Age-specific hepatitis B surface antigen seropositive rates in the years of 1984, 1989, 1994, 1999, and 2004 in Taipei, Taiwan. In 1984, none of the subjects were under the universal vaccination coverage. In 1989, only children below 5 years of age were covered. Subsequently, children below 10, 15, and 20 years of age were covered by the universal vaccination in 1994, 1999, and 2004, respectively. Those who were born before the implementation of this program had a higher HBsAg carrier rate than those born after the implementation. The dotted line for 1984 represents the data before universal vaccination implementation, whereas the solid lines for 1989, 1994, 1999, and 2004 represent the data after the program.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>HBs Seroprevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>0.9</td>
</tr>
<tr>
<td>1-4</td>
<td>0.4</td>
</tr>
<tr>
<td>5-14</td>
<td>0.5-0.6</td>
</tr>
<tr>
<td>15-19</td>
<td>1.5-2.1</td>
</tr>
<tr>
<td>20-21</td>
<td>6.7</td>
</tr>
<tr>
<td>22-25</td>
<td>10.3</td>
</tr>
<tr>
<td>26-27</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Ni, gastroenterology, 2007
Decrease of HCC among children in Taiwan

<table>
<thead>
<tr>
<th>Born</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>81-84</td>
<td>0.67</td>
</tr>
<tr>
<td>84-90</td>
<td>0.61</td>
</tr>
<tr>
<td>90-96</td>
<td>0.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>66-77</td>
<td>1.0</td>
</tr>
<tr>
<td>78-83</td>
<td>0.83</td>
</tr>
<tr>
<td>84-89</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Chang, Jama 2000
Average mortality from fulminant hepatitis in Taiwan

1975-84: 5.36/100,000
1985-98: 1,71/100,000

Kao, J Pediatr. 2001
Italy, impact of the universal vaccination programme

- Universal programme started in 1991 for all infants as well as 12-year-old adolescents
- In 2004, the vaccination programme for adolescents ended
- Incidence of acute hepatitis B (AHB) was estimated since 1991
- 12 million children vaccinated in the first 10 years, 93.6% coverage among teenagers

Mele, clin infect dis 2008
### Table 1. Incidence of acute hepatitis B cases notified in Italy, by age group, National Surveillance System for Acute Viral Hepatitis (SEIEVA), 1991–2005.

<table>
<thead>
<tr>
<th>Year</th>
<th>0–14 years</th>
<th>15–24 years</th>
<th>≥25 years</th>
<th>Total</th>
<th>Population surveyed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>1</td>
<td>12</td>
<td>4</td>
<td>5.1</td>
<td>16,401,503</td>
</tr>
<tr>
<td>1992</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>22,622,762</td>
</tr>
<tr>
<td>1993</td>
<td>1</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>22,622,762</td>
</tr>
<tr>
<td>1994</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>22,804,610</td>
</tr>
<tr>
<td>1995</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>23,060,981</td>
</tr>
<tr>
<td>1996</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>25,900,950</td>
</tr>
<tr>
<td>1997</td>
<td>0.5</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>31,892,134</td>
</tr>
<tr>
<td>1998</td>
<td>0.4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>31,892,134</td>
</tr>
<tr>
<td>1999</td>
<td>0.3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>32,331,986</td>
</tr>
<tr>
<td>2000</td>
<td>0.1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>33,429,357</td>
</tr>
<tr>
<td>2001</td>
<td>0.5</td>
<td>1.5</td>
<td>2.5</td>
<td>2</td>
<td>33,429,357</td>
</tr>
<tr>
<td>2002</td>
<td>0.2</td>
<td>1.3</td>
<td>2</td>
<td>1.5</td>
<td>33,429,357</td>
</tr>
<tr>
<td>2003</td>
<td>0.1</td>
<td>0.9</td>
<td>2.3</td>
<td>2</td>
<td>33,429,357</td>
</tr>
<tr>
<td>2004</td>
<td>0.1</td>
<td>0.7</td>
<td>2.3</td>
<td>1.6</td>
<td>33,701,132</td>
</tr>
<tr>
<td>2005</td>
<td>0.02</td>
<td>0.6</td>
<td>1.8</td>
<td>1.3</td>
<td>35,194,296</td>
</tr>
</tbody>
</table>
Impact of hepatitis B vaccination in a highly endemic area of south Italy

Declining prevalence of HBsAg and HBV marker anti-HBc in healthy individuals

Da Villa, vaccine 2007
<table>
<thead>
<tr>
<th>Demographic characteristics of healthy individuals enrolled in 1978 and 2006 in Afragola, Naples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Total population</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>6–14 Years</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>15–20 Years</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>&gt;25–58 Years</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

Values in parenthesis are in percent.
Age specific prevalence of HBsAg in healthy individuals in 1978 and 2006, Afrigola, Naples

Da Villa, vaccine 2007
Age specific prevalence of anti-HBc in healthy individuals tested in 1978 and 2006 in Afragola, Naples
Present situation in Italy

- Most cases AHB occur in non-immunized people > 25 years who acquire infection through: IDU, household contact, unsafe sexual activity, treatments or procedures with percutaneous exposure and iatrogenic exposure
- Household contacts: 47% were aware of carrier’s condition, 88% of whom not vaccinated!
- More efforts needed for high risk-groups, and enhanced infection control measures during invasive procedures
Cost effectiveness of immunisation programme in Italy (started 1991)

Annual costs of vaccination:
   Direct: 41.000.000 USD
   Indirect: 16.000.000

Assistance/social costs of acute viral hepatitis
   1985-1990: 483.000.000 (35.500 cases)
   1991-1996: 239.000.000 (17.600 cases)

Savings during years of vaccination: 244.000.000

Da Villa, vaccine 1999
Is Hepatitis B vaccination safe?

• Billions of doses used
• Excellent record of safety
• Only minor adverse events
• No causal relationship found between hepatitis B vaccine administered to adults and incidence of MS or relapse of MS (Institute of Medicine, USA, WHO global advisory committee on vaccine safety)
Persistence of anti-HBs in children and adolescents eleven years after vaccination in Italy

A. 1212 children: 64.3% had anti-HBs >10 mIU/ml eleven years after vaccination, after 1 booster vaccination of children <10: 98.5% had anti-HBs > 10

B. 521 adolescents (12 years of age): 87.3% had anti-HBs >10, after 1 booster: 100%

All countries can be turned into low endemic areas

But what to do in low endemic countries like The Netherlands?

Is targeting high risk groups sufficient?
Fact-sheet NL

• Prevalence 0.4% (higher among immigrants)

• Incidence 2/100,000 – but: including all subclinical, undiagnosed and unreported cases probably 27/100,000 (Kretzschmar, Lancet Infect Dis 2008)

• Around 60,000 chronic infections
Notification rates of hepatitis B 2003-2007

Aangiftecijfers Hepatitis B 2003-2007

2003
2004
2005
2006
2007

Acuut  Chronisch  Onbekend
Reported incidence of acute hepatitis in the NL

• 2003: 3.1/100,000

• 2007: 2.1

• In women stable incidence of 0.7 (no decrease)
Acute hepatitis B, related to risk groups

2007: seksueel contact 65%, IDU 0,9%, prik/bijtaccident 1%, overig 10%, onbekend 23% 19% in buitenland geboren, 17% geïnfecteerd in buitenland
<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>104 (31.9%)</td>
<td>78 (35.5%)</td>
</tr>
<tr>
<td>Heteros</td>
<td>84 (25.8%)</td>
<td>69 (31.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>88 (27.0%)</td>
<td>51 (23.2%)</td>
</tr>
</tbody>
</table>
Incidence of acute hepatitis in NL according to country of birth

• Low endemic country (NL): 1.5/100,000

• Intermediate end. country: 4.3

• High endemic country: 4.2

Koedijk, Ned Tijdschr Geneeskd 2007
Transmission route of the reported 220 patients with acute hepatitis in 2007

- homoseosexual: 35.5%
- heterosexual: 31.4%
- Unknown: 23%
- Others: 10%
- IDU: 0.9%
- Sexual: 0.9%
54.6% cases of acute hepatitis in the NL caused by heterosexual or unknown transmission

Is the focus on homosexual men justified? if yes, are all homosexuals reached and vaccinated at time?
### Vaccinatie 2002 t/m 2007

<table>
<thead>
<tr>
<th></th>
<th>Participants first vaccination</th>
<th>Anti-HBc positive (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Participants second vaccination</th>
<th>Participants fully vaccinated</th>
<th>Compliance&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Median age at moment of first vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>20,551</td>
<td>2622 (12.8)</td>
<td>15,329</td>
<td>13,106</td>
<td>73.1%</td>
<td>34</td>
</tr>
<tr>
<td>DU</td>
<td>13,316</td>
<td>1939 (14.6)</td>
<td>9,386</td>
<td>6,610</td>
<td>58.1%</td>
<td>37</td>
</tr>
<tr>
<td>CSW</td>
<td>10,083</td>
<td>1428 (14.2)</td>
<td>6,370</td>
<td>4,302</td>
<td>49.7%</td>
<td>29</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>38,065</td>
<td>1928 (5.1)</td>
<td>27,753</td>
<td>2,0779</td>
<td>57.5%</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>82,015</td>
<td>7917 (9.7)</td>
<td>58,838</td>
<td>44,797</td>
<td>60.5%</td>
<td>30</td>
</tr>
</tbody>
</table>
# Vaccinatie coverage

<table>
<thead>
<tr>
<th></th>
<th>Estimated total population</th>
<th>Fully vaccinated</th>
<th>Estimated anti-HBc positive</th>
<th>Vaccination coverage (range)</th>
<th>Susceptibles (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>278,000-392,000</td>
<td>15,582</td>
<td>13-36%</td>
<td>7% (5-9%)</td>
<td>162,000-325,000 (58-83%)</td>
</tr>
<tr>
<td>DU</td>
<td>24,000-46,000</td>
<td>7,064</td>
<td>15-53%</td>
<td>41% (18-63%)</td>
<td>4,200-32,000 (18-69%)</td>
</tr>
<tr>
<td>CSW</td>
<td>20,000-25,000</td>
<td>4,568</td>
<td>14-33%</td>
<td>28% (21-34%)</td>
<td>8,800-17,000 (44-68%)</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td>195,000</td>
<td>24,687</td>
<td>5-42%</td>
<td>18% (13-22)</td>
<td>88,000-160,000 (45-82%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>517,000-658,000</td>
<td>51,901</td>
<td>11-40%</td>
<td>17% (9-25%)</td>
<td>155,000-534,000 (30-81%)</td>
</tr>
</tbody>
</table>
Median age of vaccination and acute hepatitis B in MSM

• Age of vaccination: 36 years

• Age of hepatitis B: 39 years

Heijnen, infectieziekten Bulletin 11, 2007
Conclusion: Vaccination focus on homosexual men not very effective

- Low coverage of 7% (lowest coverage rate of all risk-groups)
- Of these 7% only 73% are fully compliant
- Age of vaccination by far too high

- Very questionable whether intensification of this program will be able at a cost-effective manner to reach at least 70% of MSM group at younger age
Vaccination of heterosexuals stopped in 2007 in the NL

- Difficult to explain to heterosexuals with high risk behaviour
Does pre-travel advice cover risk of hepatitis B?

• No!, hepatitis B vaccination is officially only advised for persons, particular children who stay for at least 6 weeks in countries with HBV-prevalence of >2% under primitive conditions

• Countries like Spain and Turkey are not on the list!

• Young people travelling frequently to HBV-endemic countries are generally not vaccinated in the NL!
People from the Netherlands- 
holidays abroad

- 17 million holidays abroad
- 1.7 million outside Europe
- 645,000 to Turkey
- Inside Europe: Italy, Spain very popular
Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- >8% - High
- 2–7% - Intermediate
- <2% - Low
Acute hepatitis B infection during vacation abroad

- 17% of all cases of acute hepatitis B in 2007, the infection was acquired abroad!
- 2 cases in young women being on holiday in intermediate endemic countries infected by sexual contact developed fulminant hepatitis and had to undergo livertransplantation
- 1 woman of 20 years died of acute hepatitis
Study of sexual risk behaviour among travellers (Dutch GGD/Antwerpen)

- 1900 travellers
- 5% had sexual contacts with new partner
- In 53% unexpected (in women 75%)
- 30% no condom used
- 40% not vaccinated against hepatitis B
Are immigrants protected by the Dutch vaccination strategy?
Dutch vaccination policy for immigrant-children

• Since 2003 all children with one parent from country with >2% HBV prevalence are vaccinated in their first year of age

• But: older children who frequently travel to their home country are not vaccinated and children from abroad who want to live with their parents are not vaccinated as well
Arguments against exclusive vaccination of risk-groups (1)

- Difficult to address, no examples of high coverage rates- including The Netherlands
- Risk groups like MSM are vaccinated too late (NL: 36 years), already involved in risk behaviour
- Intensification of risk group approach only is cumbersome, increasingly expensive, effect??
- Majority of persons who are at risk for acute hepatitis B in the Netherlands do not belong to any risk group and are not protected
- Early childhood transmission with high chance of developing chronic hepatitis B is not interrupted
Arguments against exclusive vaccination of risk-groups (2)

- Even addition of antinatal screening and vaccination of children (<1 year of age) with one parent from endemic country—although important—is not sufficient:
  - Older children are missed
  - Parents of these children are missed (incidence of acute hepatitis nearly 3 times higher than in persons born in the Netherlands)
Arguments against exclusive vaccination of risk-groups (3)

• Stigmatization of risk-groups
• Focus on immigrant children/adults may increase fear in the Dutch population and hinder the integration process
• Wrong suggestion that hepatitis B is not a concern for the rest of the population
• Whether immigrants transmit the virus to the Dutch population is an irrelevant question!
  - Any young active Dutch person can start sexual relationship at any time with person from HBV-endemic country at home or abroad!
  - Immigrants have same right of protection
Arguments for universal hepatitis B vaccination (1)

- Proven efficacy (decreases acute infections and morbidity/mortality) and safety
- Proven longstanding immunity
- Simple integration into childhood vaccination program possible
- Comply with appeal of WHO and European Community
- Cost-effective in the long run
Arguments for universal hepatitis B vaccination (2)

- The whole population gets protection without difference of country of birth and sexual behaviour
- Protection starts before risk behaviour starts- in the future targeting of risk groups will be unnecessary
- It should be an ethical duty of each country to protect all people against oncogenic virus
Arguments for universal hepatitis B vaccination (3)

• Impact on HBV-epidemiology:
  – Incidence of acute infections will decrease
  – Prevention of early childhood infection decreases number of persons entering unnoticed the large pool of chronic infections
  – Decrease of chronic infections will not only depend on successful vaccination programs worldwide (less and less immigrants will be infected), but in the next 20 years mainly on early detection and treatment
Universal vaccination for children, adolescents or both?

A. Children

- Easy to integrate into childhood vaccination program
- High coverage rate guaranteed
- Prevents early childhood transmission
- Relative low costs – incremental costs of hexavalent vaccine over 5 component vaccine
- But: less immunogenic compared to adolescent vaccination?
Universal vaccination for children, adolescents or both?

B. Adolescents

- Effect of vaccination 12 years earlier than with child-vaccination

But:

- higher costs for vaccine and campaign
- very doubtful high coverage rate
- Does not prevent early childhood transmission
Universal vaccination for children, adolescents or both?

C. Both (like in Italy)?

• Immediate protection for all vaccinated children and adolescents
• After 12 years vaccination for adolescents can stop
• But: higher costs for the first 12 years
The effect of various vaccination strategies in the NL

Figure: The effect of various vaccination strategies on incidence of hepatitis B infection as predicted by a mathematical model. Vaccination of children whose parents originate from high-endemicity countries starts in year 1, universal vaccination of neonates or adolescents starts in year 5.

Kretzschmar, Lancet infect dis 2008
Conclusion

• Universal Hepatitis-B vaccination needs to be implemented in the Netherlands without further delay

• Additional vaccination of high risk groups remains necessary for a limited period of time