HAV surveillance and epidemiology

- Two distinct transmission patterns
- Enhanced surveillance for “unknown”

Thursday November 12, 15.35-15.55
HEPATITIS A

MHS Amsterdam
Sylvia Bruisten, Grace Tjon
Roel Coutinho, Anneke van den Hoek

CIb/LIS
Harry Fennema and Annelies Kroneman
Marion Koopmans

CIb/EPI
Yvonne Doorduyn

MHS Zuid-Holland West
Mariska Petrignani and Rianne van Hunnen

Dutch Centre for Infectious Disease Control (CIb)
Unit Preparedness and Response (LCI)
Hepatitis A surveillance

• Disease surveillance
  - Reportable since 1957 (?)
  - Starting 2008 December 1\textsuperscript{st} WPG (Public Health Law) (integrating Infectious disease, Quarantine and Prevention) reporting by medical doctor AND laboratory

• Sero-epidemiology PIENTER
  - 1996
  - 2008
  - MHS Rotterdam/ Amsterdam: specific risk populations

• Pathogen surveillance
  - Genotyping and sequencing
Underreporting

- 1997 5 regions Netherlands: 50%
  ©Talsma, Wijgergangs 1999InfBull10(2)

- 1995 Amsterdam: 60%
  © CMR (Morbidity Registration GP’s). Annual report 1996. NIVEL 1997

- 1979 Amsterdam: 70%
Reported HA 1957-97
Netherlands: Hepatitis A is NOT a serious public health problem <1 death/year

HAV notifications/month 1993-1998 Netherlands
Probable geographical source country.

...........Netherlands .......... unknown
---------Turkey Morocco ............ other

©Termorshuizen et al. NTvG 1998;142(43):2364-8
1992-95 registered cases HA
Origin and travel history

Largest cities (4) NL

129  MSM/DU
761  origin high endemic region
502+ origin low endemic region
1392

- a. Youth HE  travel +
- b. Youth LE  travel -
- c. Adults LE  travel +
- d. Youth HE  travel -
- e. Adults LE  travel -

© Gorkom et al. NTvG 1998
Seroprevalence total anti-HAV
Rotterdam 2001

<table>
<thead>
<tr>
<th>Age</th>
<th>Turkey</th>
<th></th>
<th>Morocco</th>
<th></th>
<th>Dutch</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%+</td>
<td>(n)</td>
<td>%+</td>
<td>(n)</td>
<td>%+</td>
<td>(n)</td>
</tr>
<tr>
<td>5-7 yrs</td>
<td>2.2</td>
<td>(137)</td>
<td>10.2</td>
<td>(137)</td>
<td>0.8</td>
<td>(120)</td>
</tr>
<tr>
<td>8-10 yrs</td>
<td>10.0</td>
<td>(110)</td>
<td>24.6</td>
<td>(122)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-13 yrs</td>
<td>17.8</td>
<td>(45)</td>
<td>31.8</td>
<td>(44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-16 yrs</td>
<td>22.2</td>
<td>(27)</td>
<td>57.7</td>
<td>(26)</td>
<td>3.1</td>
<td>(128)</td>
</tr>
</tbody>
</table>

Seroprevalence <10% born after 1960, 77% born before 1945

Termorshuizen, Epidemiol Infect 2000;124:459-66
Seroprevalence total antiHAV (infection/vaccination)

<table>
<thead>
<tr>
<th>Location</th>
<th>Group</th>
<th>%+ (n)</th>
<th>RRR (95%CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam</td>
<td>&gt;18 yrs</td>
<td>57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch A’dam</td>
<td></td>
<td>45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td></td>
<td>47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>1st g.</td>
<td>98.6 (306)</td>
<td>2.4 (1.8-3.3)</td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>1st g.</td>
<td>97.1 (265)</td>
<td>2.3 (1.6-3.2)</td>
<td></td>
</tr>
<tr>
<td>T&amp;M</td>
<td>2nd gen.</td>
<td>37.4 (57)</td>
<td>0.9 (0.5-1.7)</td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td></td>
<td>45.6 (509)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

(Termorshuizen 2000)

HEPATITIS A VIRUS

Genotyping

• 7 genotypes, 4 in humans (1, 2, 3 en 7)
  - 1 and 3 subgenotype
    • 1A, 1B
    • 3A, 3B

• Sequencing
  - VP3-VP1 (360 218 bp) more variable region
  - VP1-P2a (341 247 bp)
Feasibility study (pilot 1997/1998)
33 stool samples

- Collection stool samples feasible
- Positive samples (despite delay)
- Excretion HAV-RNA 33 days

Figure 2b

Genotype 1B, VP1-P2a 2000-2002 A’dam
103 isolates

JID 2004; 189: 471-82
1). Frequent import of HAV
- limited transmission to siblings/ school

• Case based source and contact tracing MHS
  no tertiary cases  
  (©Sonder et al. AJPH 2004; 94 (9): 1620-6)

• Targeted HB vaccination program
  all new born children with one or both parents originating from HBV
  endemic countries HBvaccine

• Combined HBV/ HAV vaccine
  Not cost saving, “may have favourable cost-effectiveness”
  (© Postma et al. Vaccine. 2004;22(15-16):1862-7)

• Vaccinate children in Morocco/ Turkey!
2). Man having sex with man

Seroprevalence total antiHAV (infection/vaccination)

over all 2004 Amsterdam 57%  NL 34%
Dutch >15 yrs A’dam 45%  NL 47%

<table>
<thead>
<tr>
<th></th>
<th>MSM</th>
<th>WSM</th>
<th>WSW</th>
<th>MSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>antiHAV+</td>
<td>48.1</td>
<td>58.4</td>
<td>79.5</td>
<td>55.0</td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>639</td>
<td>19</td>
<td>561</td>
</tr>
<tr>
<td>RRR (95%CI)</td>
<td>0.9 (0.6-1.3)</td>
<td>1.1 (0.9-1.2)</td>
<td>1.4 (1.1-2.0)</td>
<td>1</td>
</tr>
</tbody>
</table>

© Baaten et al. JMV 2007 Dec;79(12):1802-10
2). Continuous transmission HAV among MSM

- Source and contact tracing ineffective anonymous contacts
  
  - (©JvS ea, JID 2004;189:471-82)

- Separate clusters MSM – travellers
  
  - (©Tjon et al. JMV 2007;79(5):488-94)

- Free HBV vaccination programme MSM

- Additional HAV in HBV programme at 2x € 15,- no data uptake

- No cost-effectiveness study available
3). Food borne HA?

- European collaboration DIVINE/EVENT

- Netherlands notified cases: 20% “unknown source”
  
  (Eerden, NTvG 2004,148(28):1390-4)

- Molecular analysis Amsterdam: no unexpected clusters
  
  (JvS ea, JID 2004;189(3):471-82)

- 2008 (Petrignani GGD Delft/Zoetermeer)
  
  Nation wide collection of specimens, isolation, sequencing, phylogenetic analysis, clustering ⇒ extensive food history
Progress July 1st - October 22nd 2008

- 80 reported cases Osiris
  - 37 samples received
  - 28 samples en route
    - Ready for shipment in lab
    - En route LIS/Cl b
    - Received by LIS/Cl b, not yet sequenced
  - 15 samples not expected to be send

- Clusters identified
  - Family cluster, day care centre
  - Travelling companions (family)
  - At present: shellfish related cluster through FBVE (shellfish from the South America’s )
Summery hepatitis A in The Netherlands

1. Import
   - decreased import through travel (Turkey, Morocco)
   - limited transmission
   - effective source contact tracing
   - pre-travel vaccination acceptable level
   - transition in source countries
   - Vaccination programme HBV -> combined HBV/HAV?

2. MSM
   - ongoing transmission
   - no source and contact tracing possible
   - vaccination programme HBV -> combined HBV/HAV?

3. Food borne and other possible transmission routes
   - enhanced surveillance August 2008)
   - European collaboration
HEV surveillance and epidemiology
- underdiagnosis
- pig reservoir

Erwin Duizer, LIS/CiB
HEPATITIS E

Cib/LIS
Marion Koopmans
Erwin Duizer
Tineke Herremans
Harry Vennema
Ana Maria de Roda Husman
Saskia Rutjes
Katrina Borgen
Bas van der Veer
Jacintha Bakker

FBVE network
Hu: Gábor Reuter
Se: Helene Norder
Dk: Blenda Bottiger
Fr: Elisabeth Nicand
Fi: Tuija Kantala, Carl-Henrik von Bonsdorff, Leena Maunula, Maija Lappalainen
Es: Nereida Jiménez de Oya, Juan Carlos Saiz
It: Franco Ruggeri, Ilaria di Bartolo

Dutch Centre for Infectious Disease Control (Cib)
Unit Preparedness and Response (LCI)
Surveillance

• Disease surveillance
  - Not reportable

• Cluster investigation
  - © Widdowson et al 2003 CID; 36: 29-33

• Serological studies
  - Selected non ABCδ
  - Potential risk groups

• Agent surveillance
  - Genotyping
  - Sequencing

• Specific research projects
  - ©Bouwknegt 2007 JFoodProtect 70(12): 2889-95
  - ©Rutjes 2007 JVirolMethods 143: 112-6
Hepatitis E Virus

ssRNA virus
no envelope
~ 32 nm

Mammalian HEV
- genotype 1 “Burma”
- genotype 2 “Mexico”
- genotype 3 “US / Swine”
- genotype 4 “China”

1 serotype
Reported HEV infections in Humans per genotype

- Genotype 1 “Burma”
- Genotype 2 “Mexico”
- Genotype 3 “US / Swine”
- Genotype 4 “China”

Okamoto, 2007
Lu et al., 2005
FBVE, 2007
HEV in the Netherlands Gt3

Until recently
- Travel related; no diagnosis requested without travel history
- Zaaijer 1992
  - 8/269 acute hepatitis patients (3%)
  - 5/275 blood donors (2%)

Currently:
- Endemic HEV infections with genotype 3
- 5.6% HEV in acute hepatitis patients
- 2-6 % anti-HEV-IgG in blood donors
HEV in acute hepatitis patients: Average ~6% (IgM, PCR)

HEV prevalence in swine herds: Average ~50% (PCR)

Dalton et al., 2007
da Silva et al. 2008
Herremans et al., 2007
Haagsman et al., 2007
Reuter et al., submitted
Boutrouille et al., 2007
Buti et al., 2006
Olsen et al., 2006
Vulcano et al., 2007
Bernal et al., 1996
Nicand & Norder & Maunula, Kantala and Lappalainen, unpublished.
HEV Transmission routes: Genotype 3

- Fecal-oral
- Waterborne
- Zoonotic
- Food borne zoonotic
- Blood transfusion / organ transplantation
HEV transmission: fecal-oral, waterborne

Genotype 1 and 2:
- waterborne outbreaks, poor sanitation
- little person to person transmission (very different from HAV)

- Genotype 3:
- no (recognized) outbreaks
- little person to person transmission (very different from HAV)
- low infection rate:
  - oral gavage: swine to swine < 10% infection
  - swine to monkey < 10%?

HEV gt 3 in the environment: NL

River water (~20%)
Ditch water (leaky septic tank, patient related)
HEV serology in gt3 endemic regions

**Netherlands** (Bouwknegt et al., 2007)

<table>
<thead>
<tr>
<th>Group</th>
<th>Bayesian</th>
<th>Diagn. Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>swine veterinarians:</td>
<td>11</td>
<td>8.5%</td>
</tr>
<tr>
<td>non-swine veterinarians:</td>
<td>6</td>
<td>2.3%</td>
</tr>
<tr>
<td>general population:</td>
<td>2</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

**USA** (Meng et al., 2002)

- 5 states higher IgG in vets
- 2 states higher IgG in blood donors
- 1 state no difference

overall OR 1.6

**Italy** (Volcano et al., 2007)

- general population 2.9%
- pig breeders 3.3%

highest: 33% in male housekeepers and employees of abattoirs
HEV in food and pig herds in NL (all gt3)

ANIMALS

HEV prevalence in pig herds: 30 - 55%
HEV prevalence in Wild boar ~4%

HEV RNA in commercially available pig livers (butcher/supermarket)
- 4/62 (6.5%) positive for HEV RNA (65 pdu/g)

HEV RNA in muscle tissue (contact-infected pigs)
M. longissimus: karbonade 6/13
M. iliopsoas: varkenshaas 7/13
M. biceps femoris: hamlap 7/13

Bouwknegt et al, submitted
Transmission of HEV gt 3: Blood borne, transplantation

HEV RNA in donorblood and transfuion transmitted HEV is reported.

Risk factors

- Hemophilia: Japan (Anti-HEV IgG antibody 16.3% versus 3.7 in blood donors, patients undergoing hemodialysis (9.4%). Toyoda et al., 2008
- Hemodialysis: Greece (4.8 versus 0.26 in blood donors) Stefanidis et al., 2004
- Liver/kidney transplantation: France (13.5% versus in 3.2% blood donors) Kamar et al., 2008

Chronische HEV geïnfecteerden: levertransplantatie Haagsma et al., 2008

Case A: >8 jr PCR positief in bloed, ook eenmalig in feces:
man en kind GEEN seroconversie

Case B: 4 jr PCR positief in bloed

Source of infection unknown!
Non-travel hepatitis E in NL
Risk factors

2004-2006 > 19 cases

• M/F 17/19
• Age 50 years (median)
• Underlying disease 11/19
• Consumption pig meat ≥ 1/week 16/19
• Dog owners 6/19
• Blood transfusion in incubation 2/19

© Borgen 2008 BMC Inf Dis 8:61
Conclusions

HEV genotype 3 strains are endemic in NL

• HEV in the Netherlands is under diagnosed

• Exact mode of transmission is unknown

• Pigs are a huge reservoir… role in human infections is unclear