



Dutch Centre for Infectious Disease Control

## **HAV surveillance and epidemiology**

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

Thursday November 12, 15.35-15.55

# HEPATITIS A



GGD Amsterdam

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Dutch Centre for Infectious Disease Control (CIb)  
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# Hepatitis A surveillance

- Disease surveillance
  - Reportable since 1957 (?)
  - Starting 2008 December 1<sup>st</sup> 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

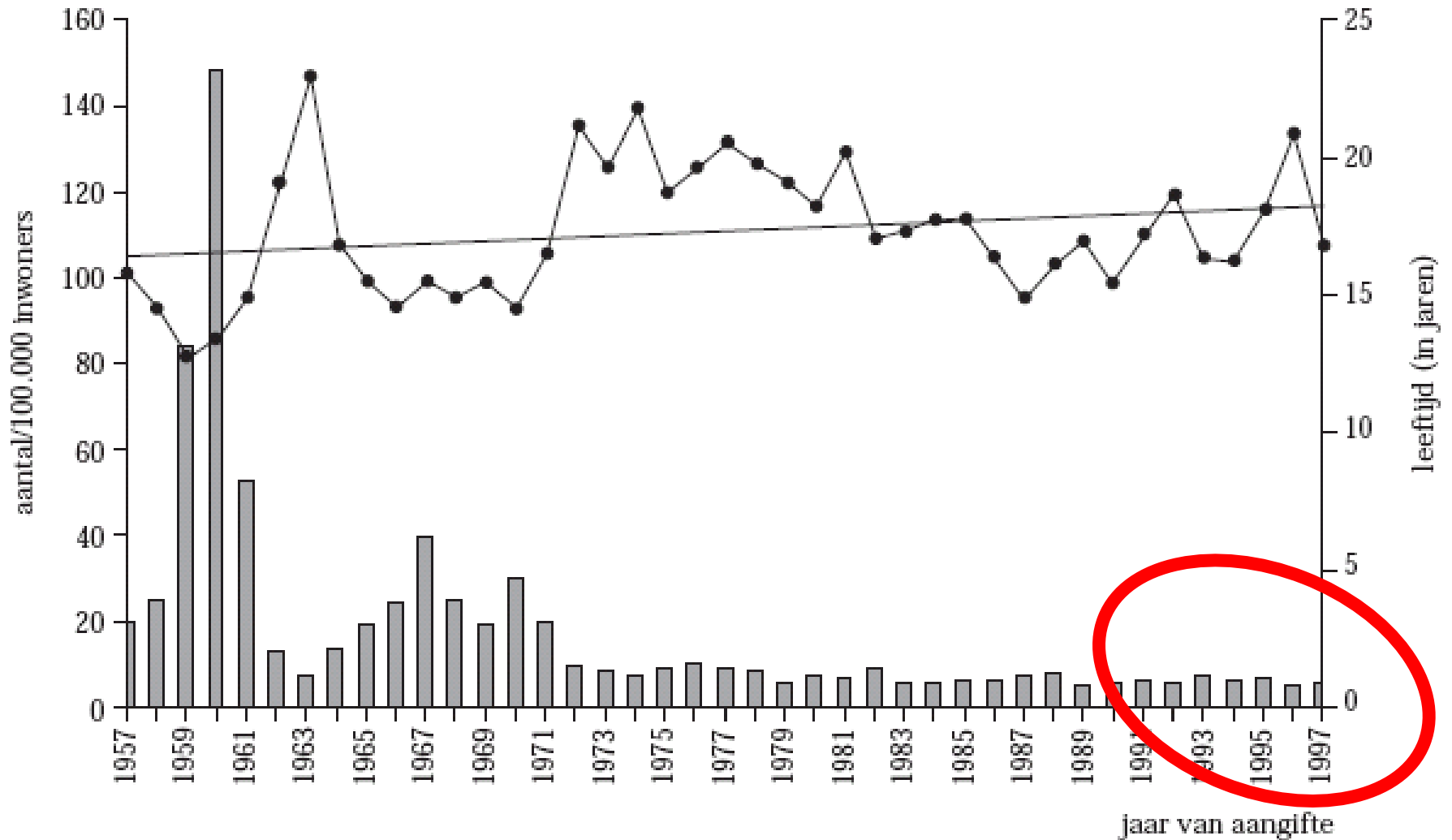
# Underreporting

- 1997 5 regions Netherlands: 50%  
©Talsma, Wijgergangs 1999 *InfBull*10(2)
- 1995 Amsterdam: 60%  
©CMR (Morbidity Registration GP's). Annual report 1996. NIVEL 1997
- 1979 Amsterdam: 70%  
© MHS. Annual report GP Sentinel Amsterdam 1979. Amsterdam: GG&GD, 1979: 5-6

# Reported HA 1957-97

Netherlands: Hepatitis A is NOT a serious public health problem  
<1 death/year

Termorshuizen et al. Ned Tijdschr Geneeskd 1998

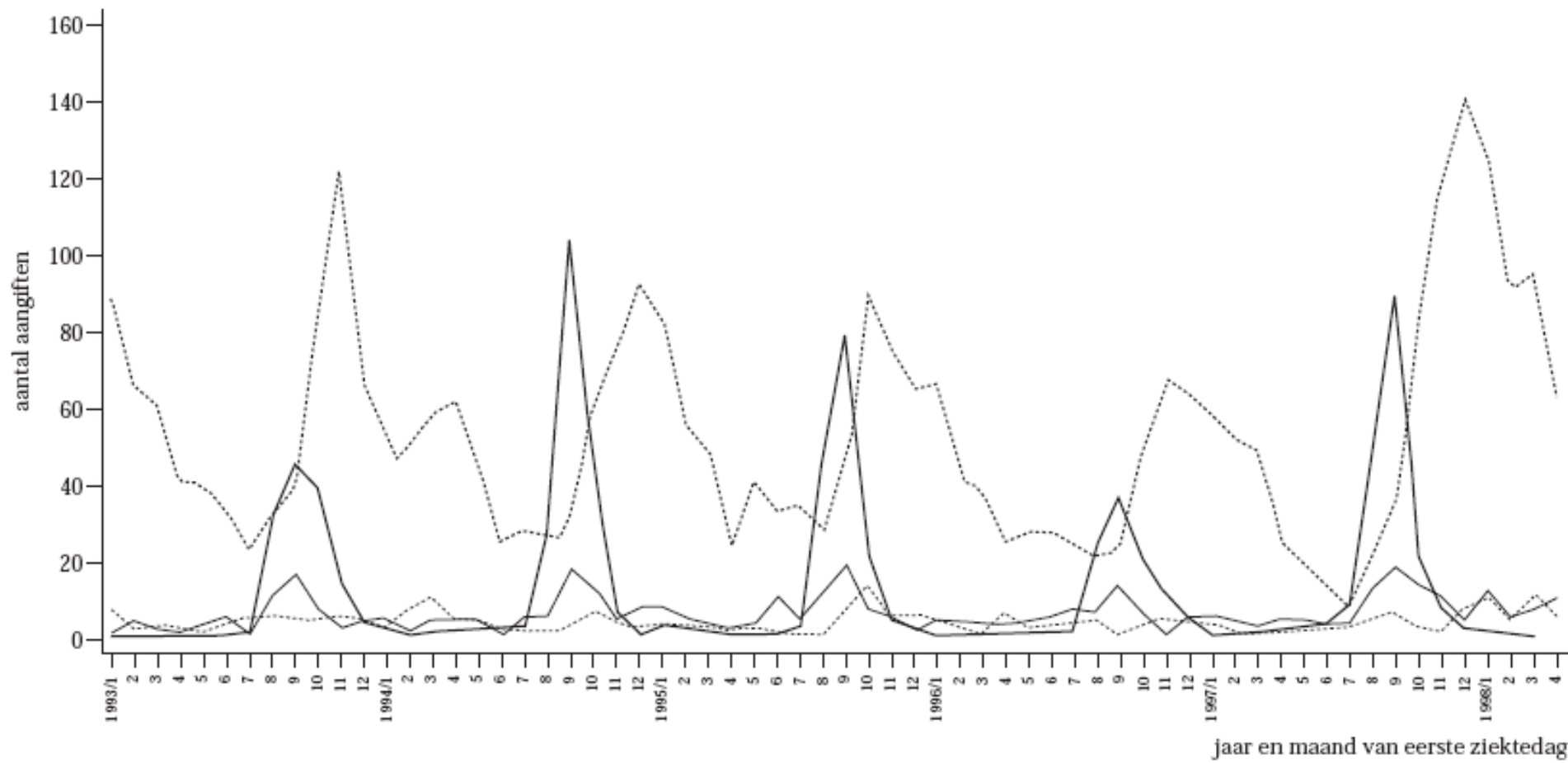


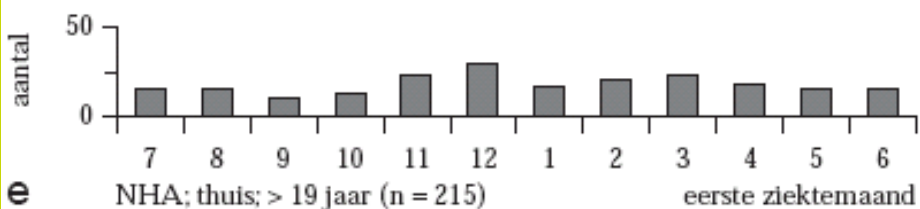
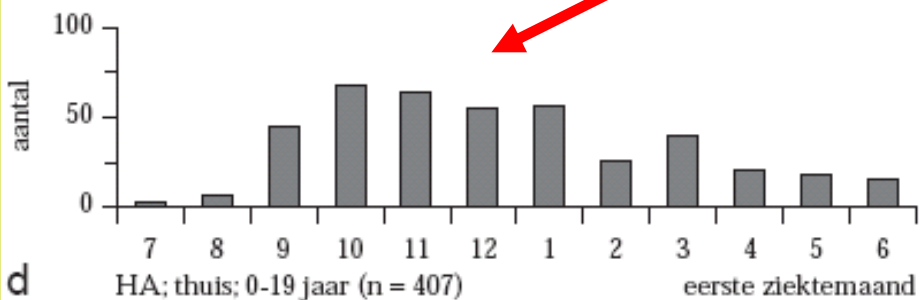
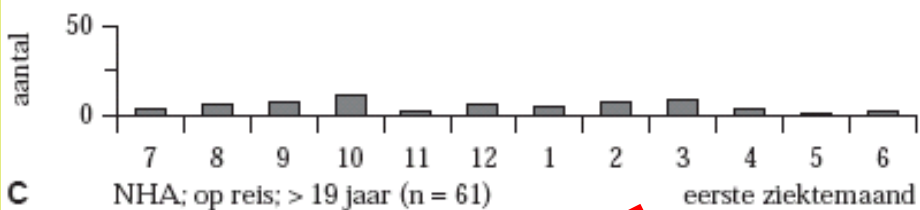
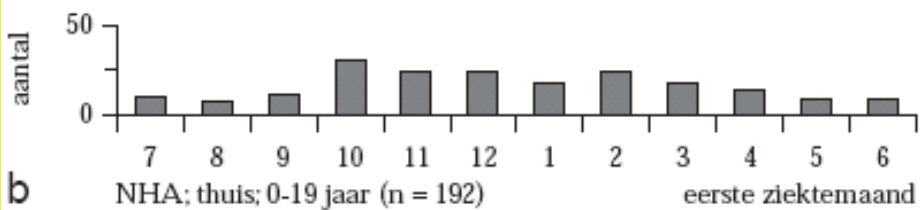
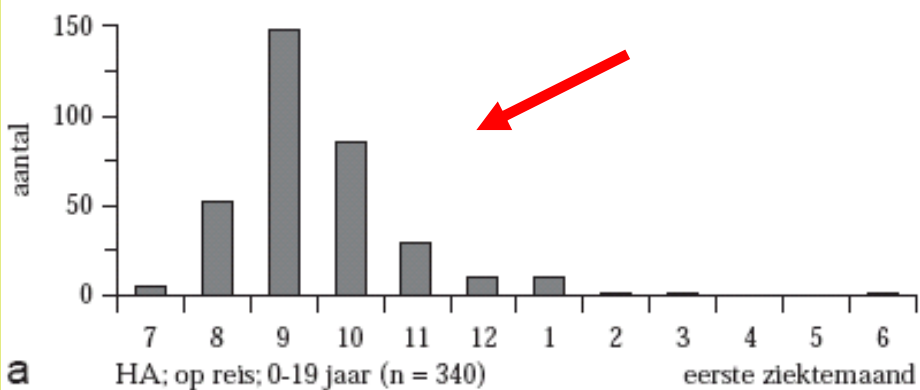
# HAV notifications/month 1993- 1998 Netherlands

Probable geographical source country.

.....Netherlands  
——Turkey Morocco  
..... unknown  
—— 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<sub>+</sub> origin low endemic region

1392

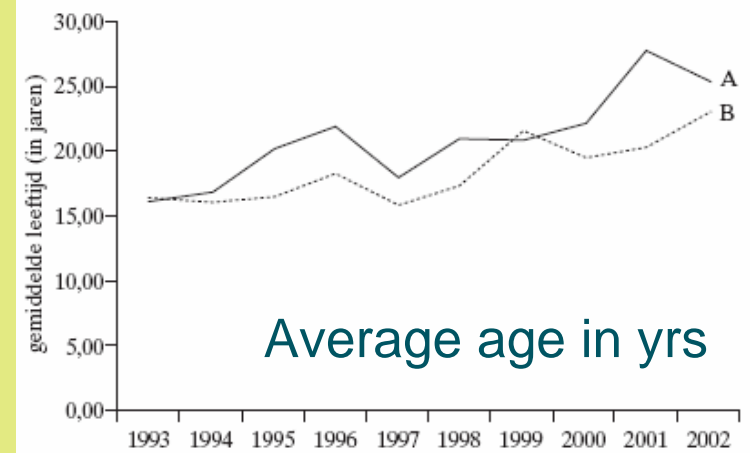
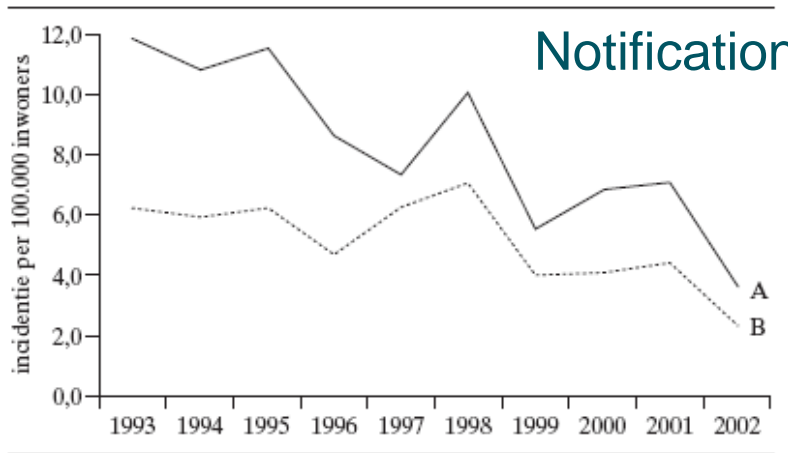
**a.** Youth HE travel +

b. Youth LE travel -

c. Adults LE travel +

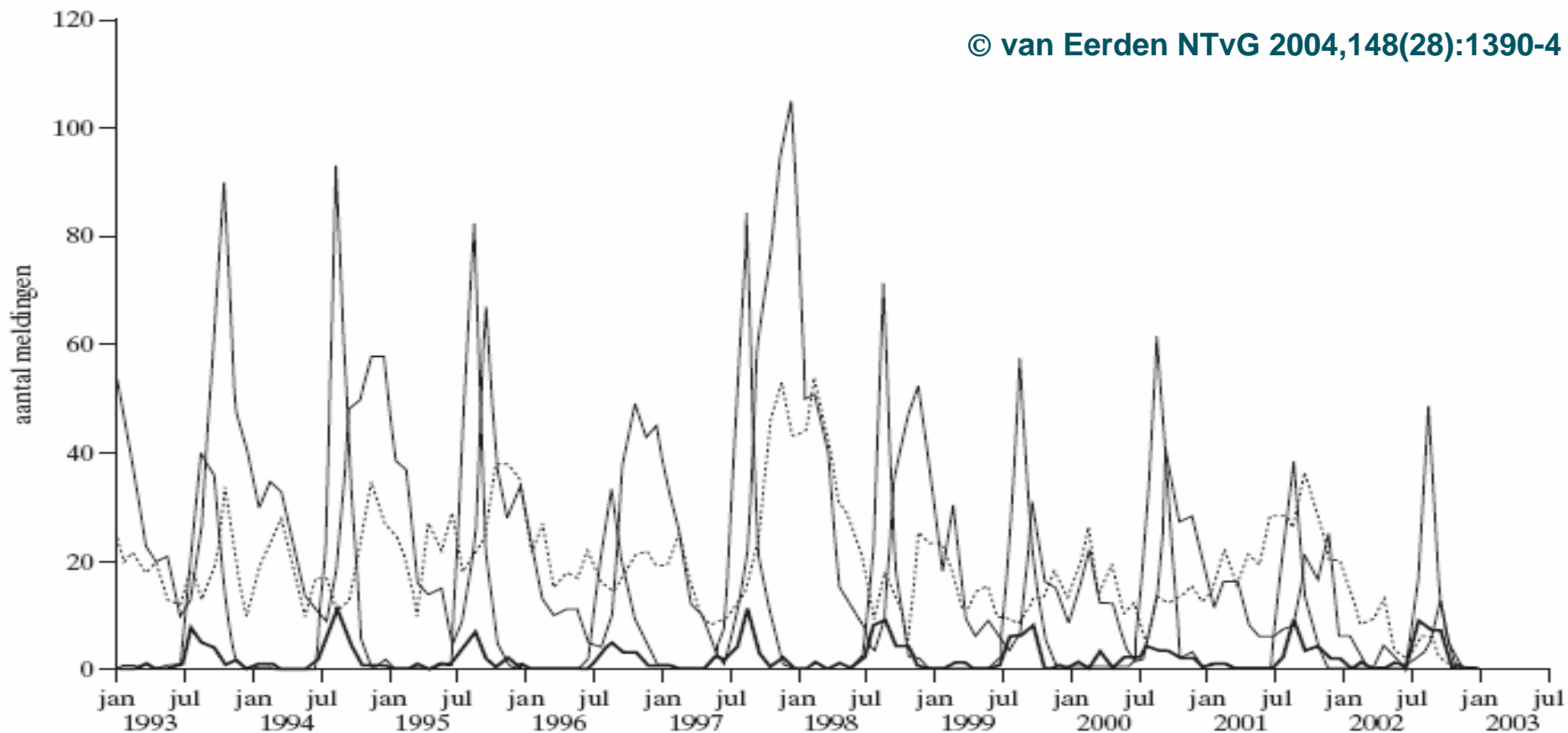
**d.** Youth HE travel -

e. Adults LE travel -



## Reported cases hepatitis A Netherlands 1993-2002

© van Eerden NTVG 2004,148(28):1390-4





# Seroprevalence total anti-HAV Rotterdam 2001

© Richardus et al. J Med Virol 2004;72(2):197-202

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

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

Termorshuizen, Epidemiol Infect 2000;124:459-66

# Seroprevalence total antiHAV (infection/vaccination)

Amsterdam >18 yrs

57%

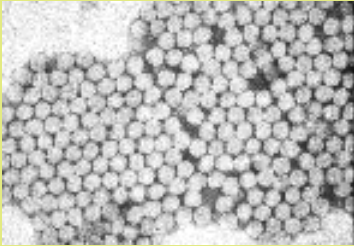
Dutch A'dam 45%

NL 47%

(Termorshuizen 2000)

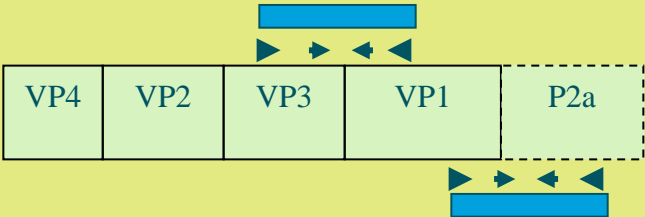
	Turkey 1 <sup>st</sup> g.		Morocco 1 <sup>st</sup> g		T&M 2 <sup>nd</sup> gen.		Dutch	
	%+	(n)	%+	(n)	%+	(n)	%+	(n)
antiHAV+	98.6	(306)	97.1	(265)	37.4	(57)	45.6	(509)
	RRR (95%CI)		RRR (95%CI)		RRR (95%CI)		Ref	
MuIVar	2.4	(1.8-3.3)	2.3	(1.6-3.2)	0.9	(0.5-1.7)	1	

# HEPATITIS A VIRUS

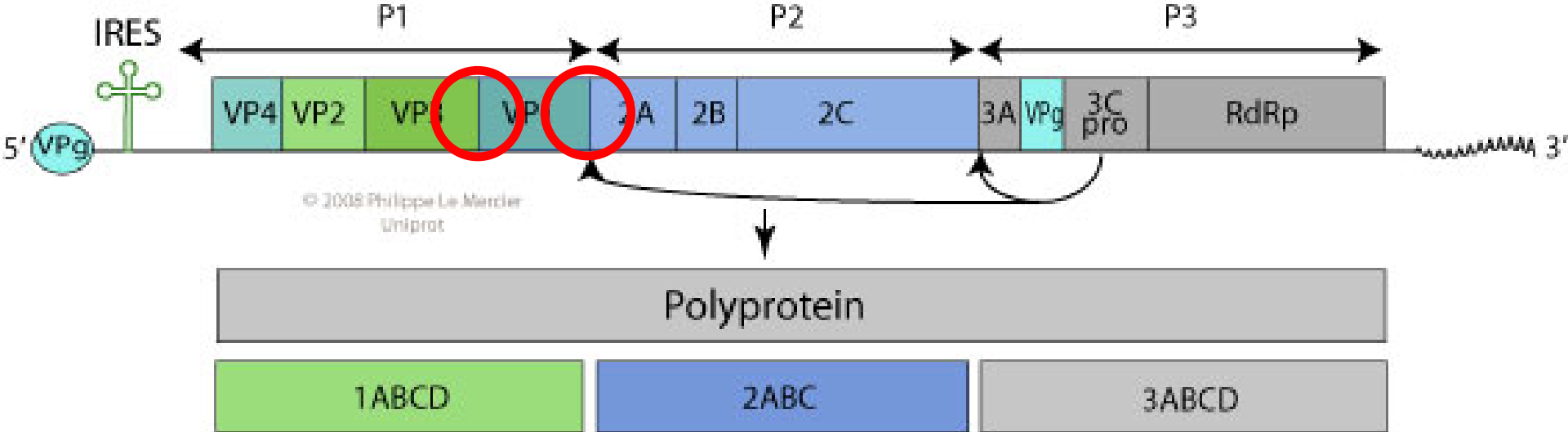


## Genotyping

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



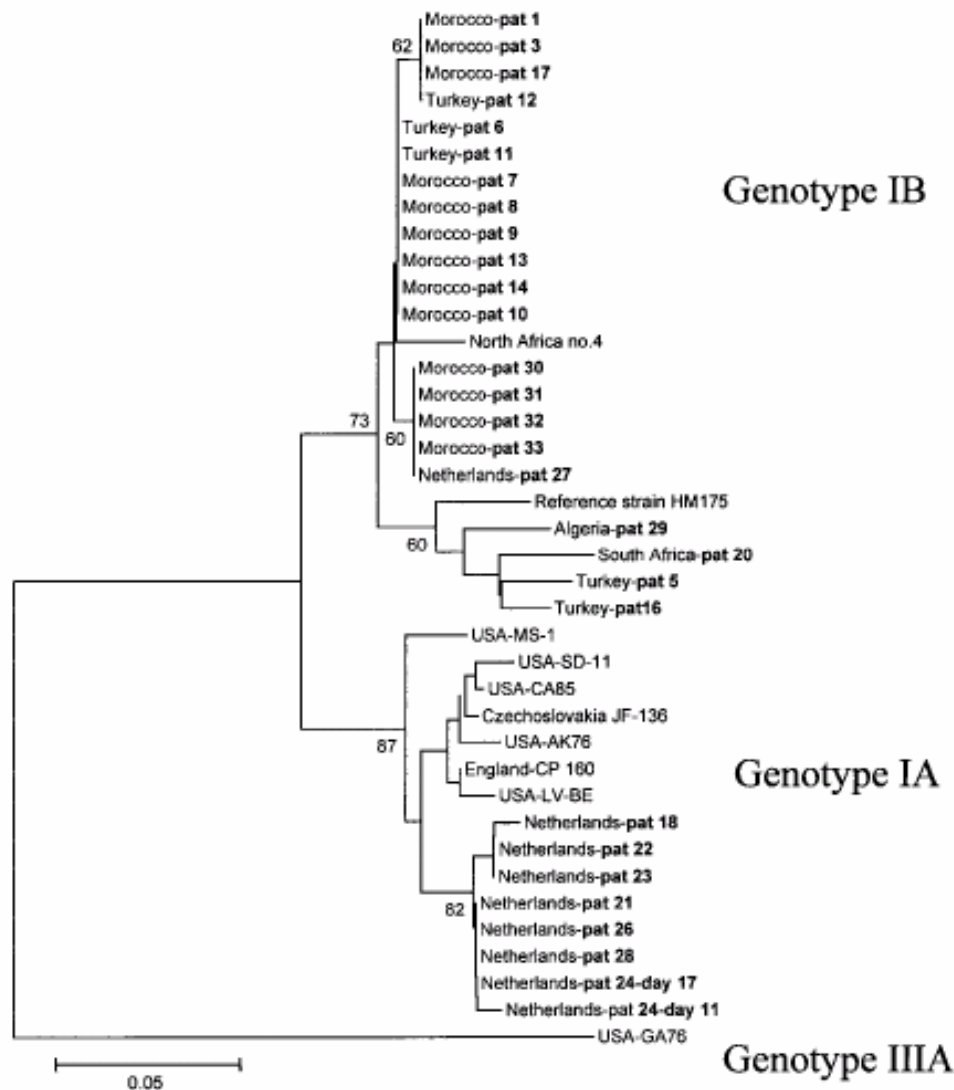
- Sequencing
  - VP3-VP1 (360 218 bp) more variable region
  - VP1-P2a (341 247 bp)



# Feasibility study (pilot 1997/1998)

## 33 stool samples

© Bruisten et al. J Med Virol 2001;63:88-95



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

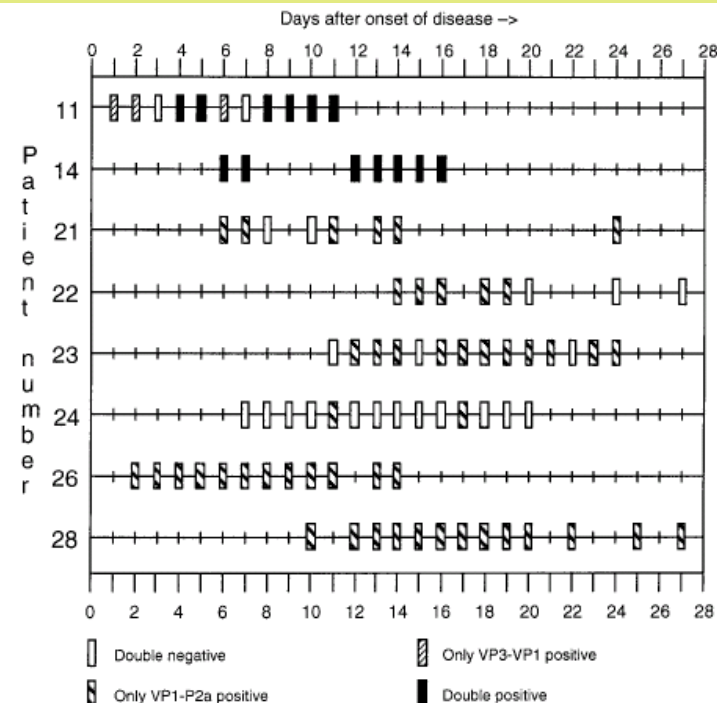
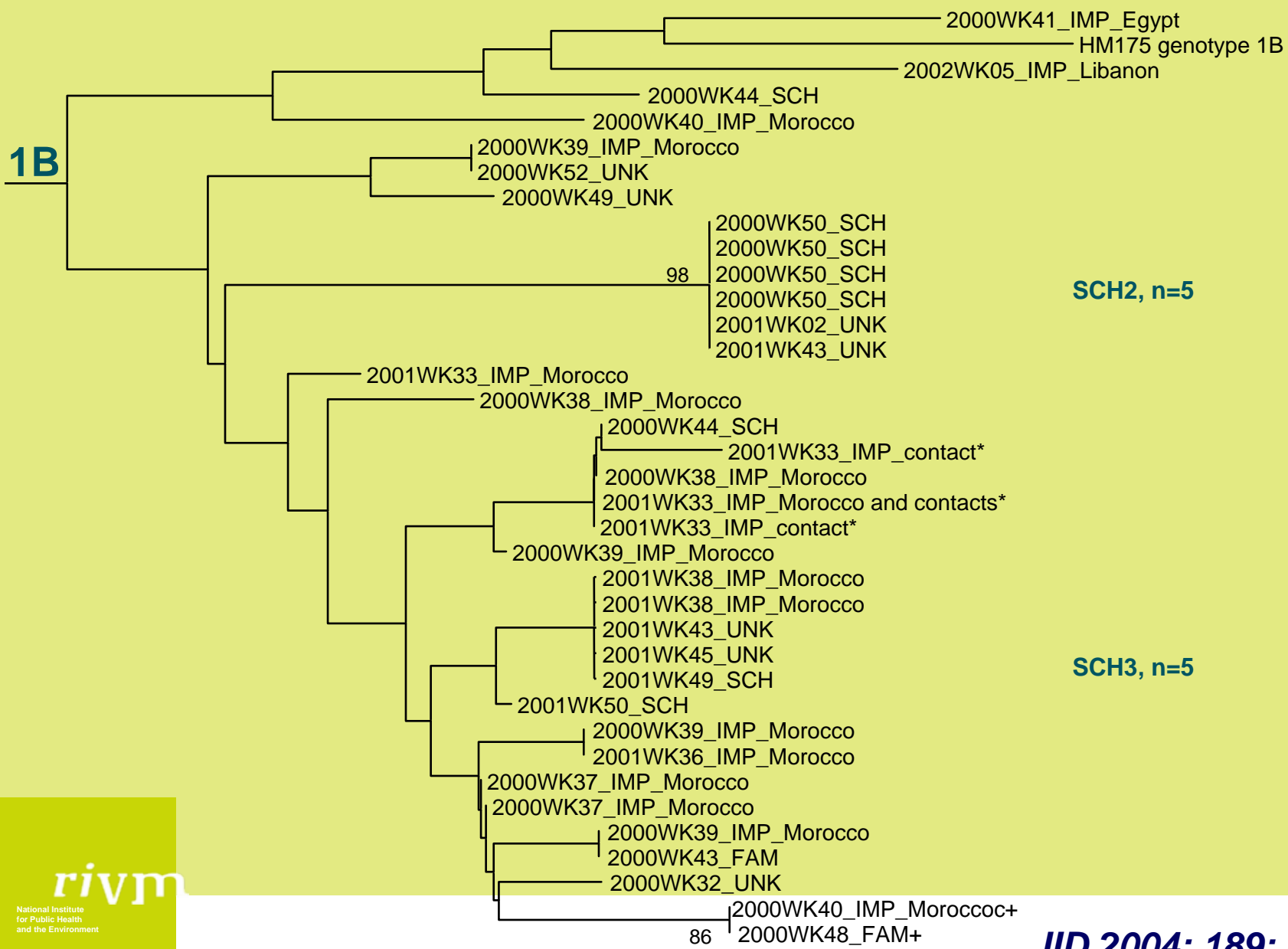


Figure 2b

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



1B

98

86

0.01

JID 2004; 189: 471-82



# 1). Frequent import of HAV

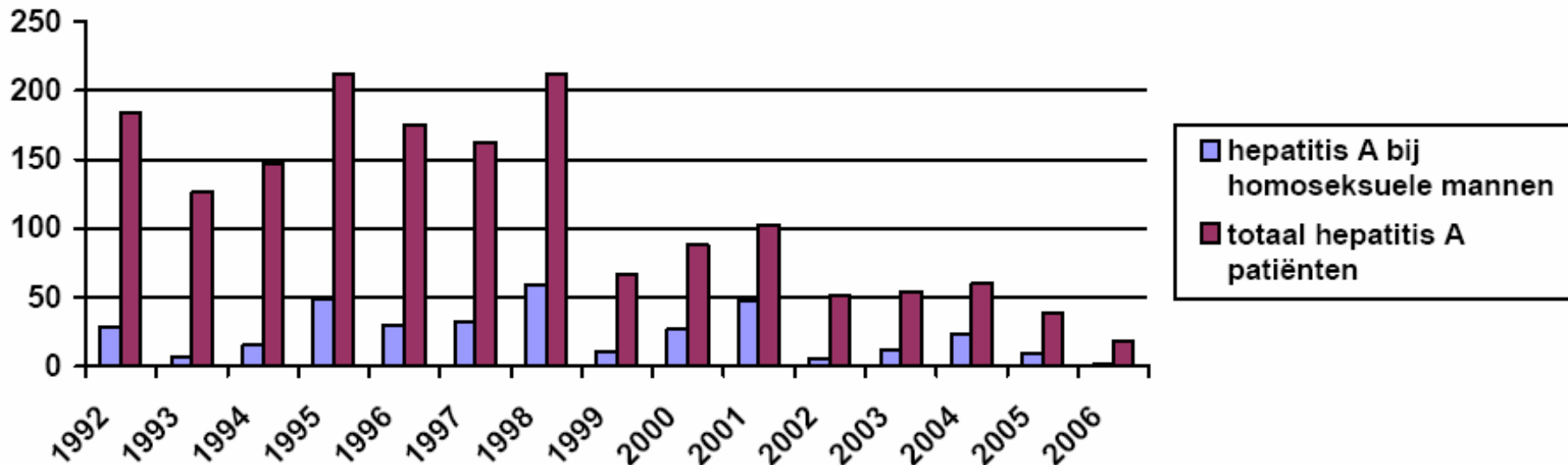
## - limited transmission to siblings/ school

- Case based source and contact tracing MHS  
no tertiary cases (©Sonder et al. AJPB 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

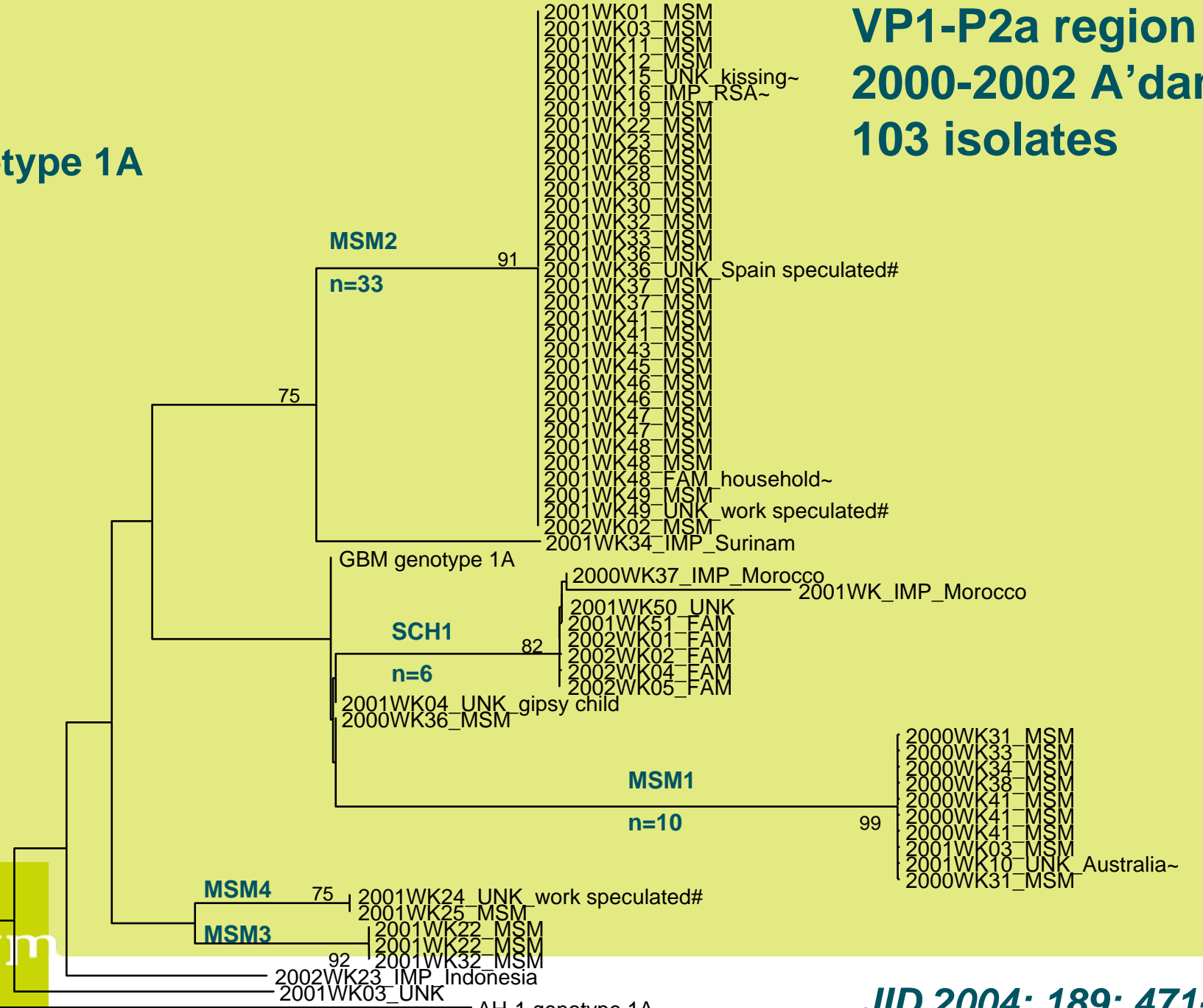
- Coutinho et al. 1980. Epidemiology of Hepatitis A in Amsterdam, October 1978 December 1979. *J Virol Methods*; 2(1-2):47-55
- Coutinho et al. 1983 Prevalence and Incidence of Hepatitis A among Male Homosexuals. *BMJ*; 287(6407):1743-1745
- Leentvaar et al. 1995. An Outbreak of Hepatitis-a among Homosexual Men in Amsterdam, 1991-1993. *Int J Epidemiol*; 24(1):218-222

Totaal aantal patiënten met hepatitis A, 1992-2006  
Infectieziekten, GGD Amsterdam



# Genotype 1A

# VP1-P2a region 2000-2002 A'dam 103 isolates





# Seroprevalence total antiHAV (infection/vaccination)

over all 2004 Amsterdam 57%

NL 34%

Dutch >15 yrs A'dam 45%

NL 47%

	MSM		WSM		WSW		MSW	
	%+	(n)	%+	(n)	%+	(n)	%+	(n)
antiHAV+	48.1	(47)	58.4	(639)	79.5	(19)	55.0	(561)
	RRR (95%CI)		RRR (95%CI)		RRR (95%CI)		Ref	
MulVar	0.9	(0.6-1.3)	1.1	(0.9-1.2)	1.4	(1.1-2.0)	1	

## 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 (Petrigani GGD Delft/Zoetermeer)  
Nation wide collection of specimens, isolation, sequencing,  
phylogenetic analysis, clustering ⇒ extensive food history



# Progress July 1<sup>st</sup> - October 22<sup>nd</sup> 2008

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- 80 reported cases Osiris
  - 37 samples received
  - 28 samples en route
    - Ready for shipment in lab
    - En route LIS/CIb
    - Received by LIS/CIb, 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



*rivm*

National Institute  
for Public Health  
and the Environment

Dutch Centre for Infectious Disease Control

## **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



**rivm**

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
  - © Zaaijer et al. 1992 *NedTijdschrGeneesk* 136 (44):2173-5
  - Selected non ABCδ
    - © Waar et al 2005 *JClinVirol*; 33: 145-9
  - Potential risk groups
- Agent surveillance
  - Genotyping
  - Sequencing
- Specific research projects
  - ©Bouwknegt 2007 *JFoodProtect* 70(12): 2889-95
  - ©Rutjes 2007 *JVirolMethods* 143: 112-6

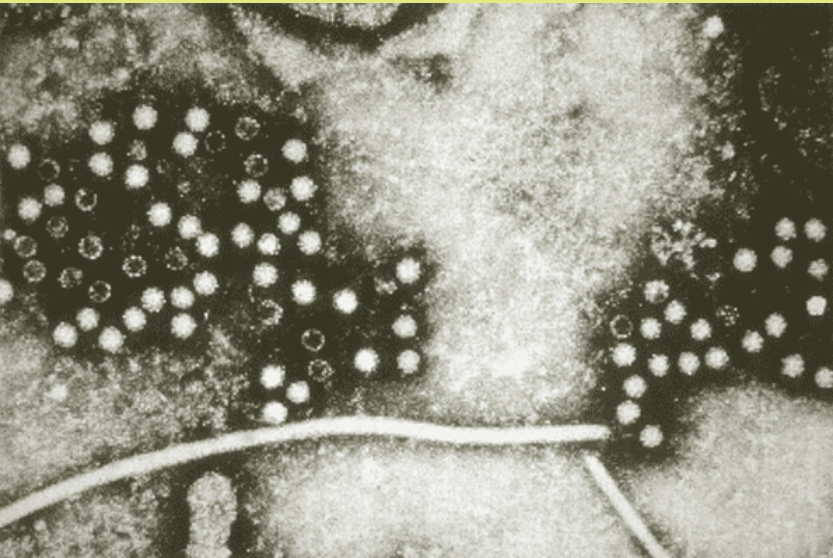
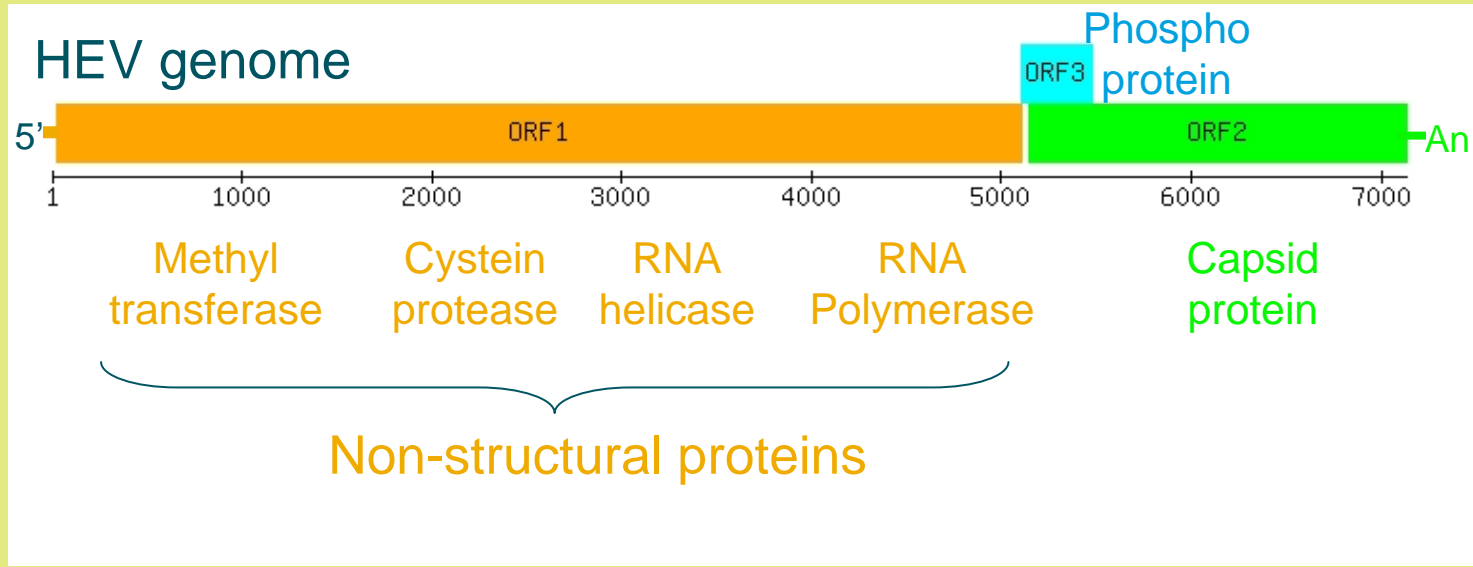


# Hepatitis E Virus

ssRNA virus

no envelope

~ 32 nm



## Mammalian HEV

genotype 1 “Burma”

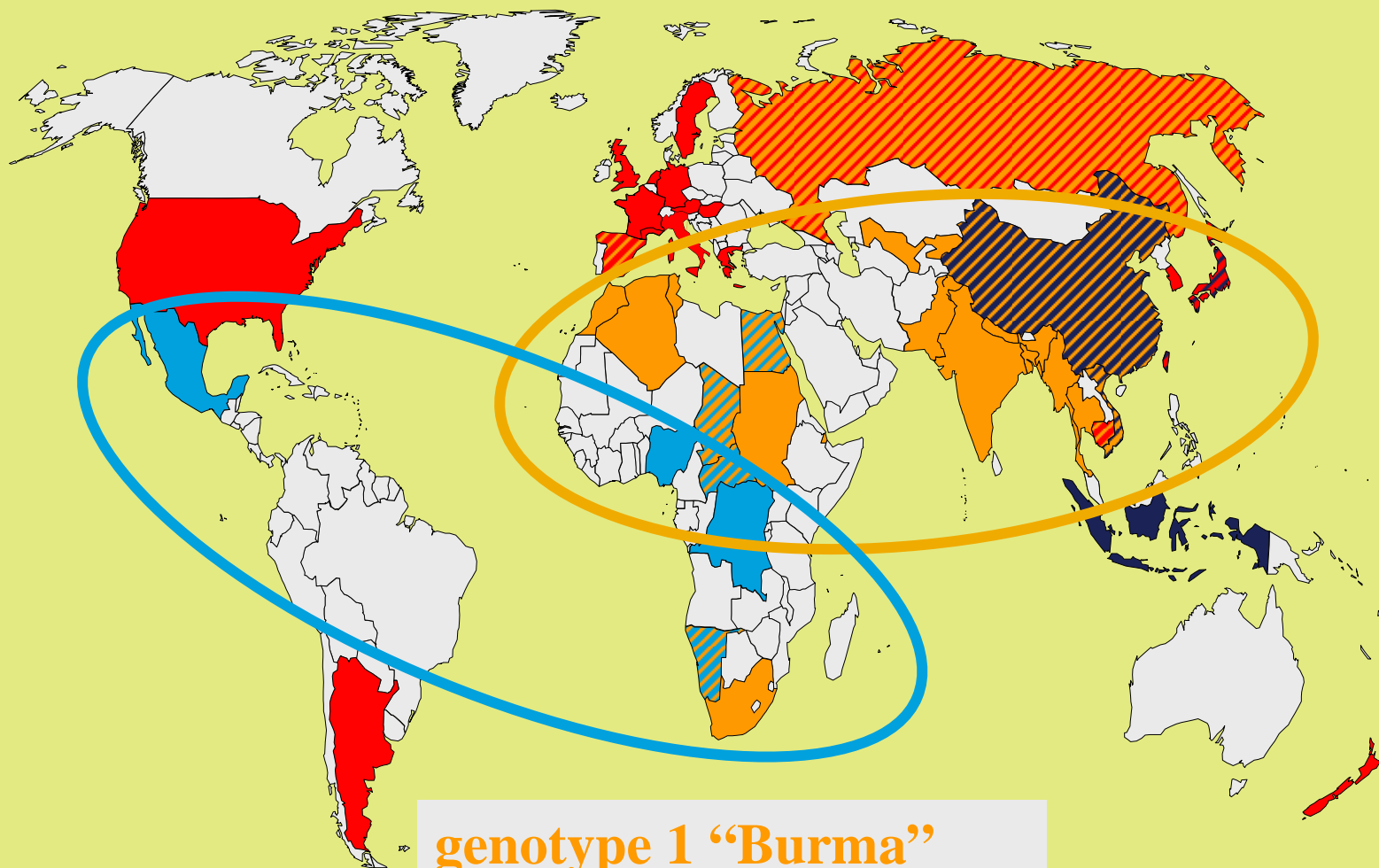
genotype 2 “Mexico”

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

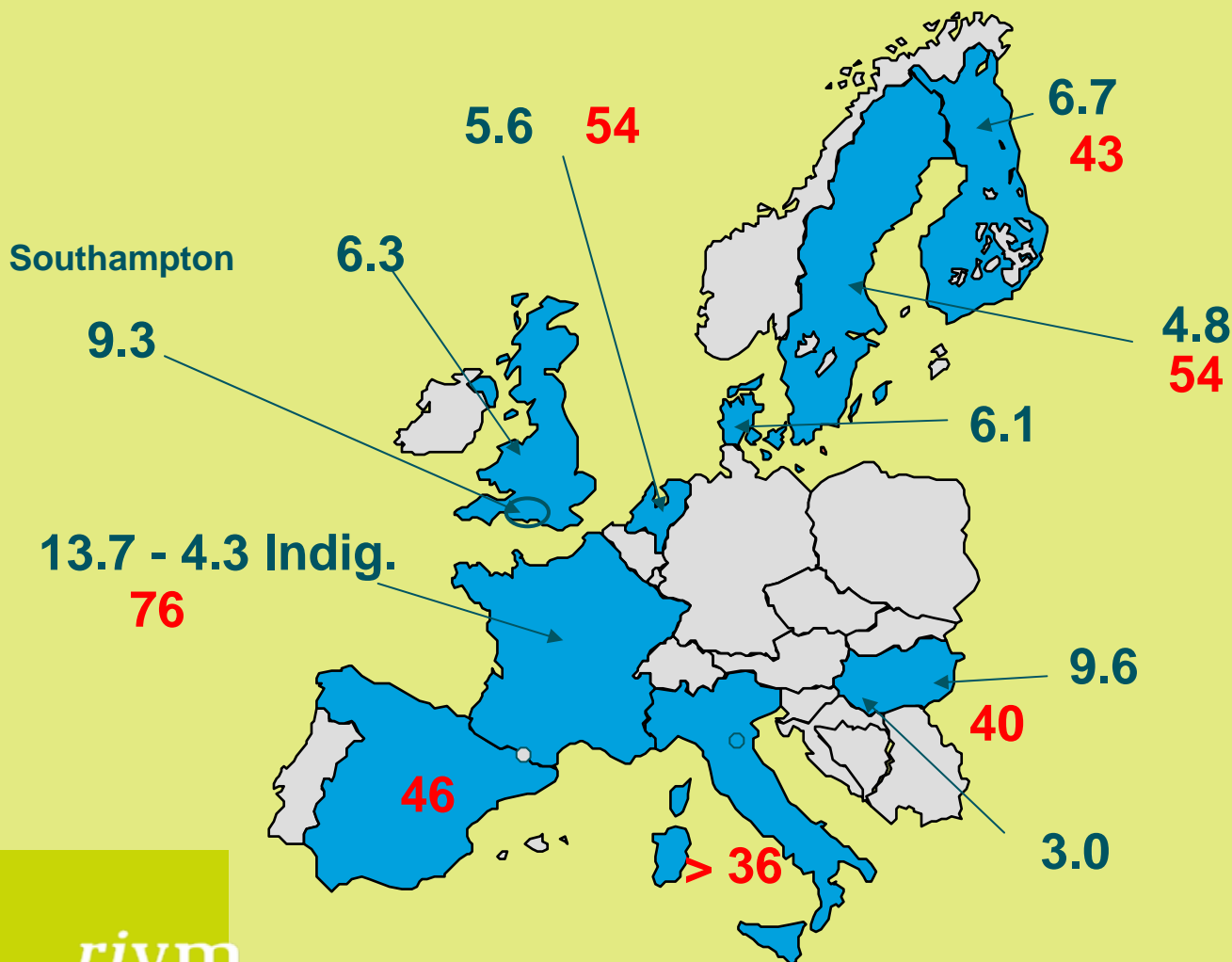
- Travel related; no diagnosis requested without travel history
- Zaaijer 1992
  - 8/269 acute hepatitis patients (3%)
  - 5/275 blood donors (2%)

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)

	Bayesian	Diagn. Algorithm
swine veterinarians:	11	8.5%
non-swine veterinarians:	6	2.3%
general population:	2	6.4%

## 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



## Transmission of HEV gt 3: Blood borne, transplantation

HEV RNA in donorblood and transfusion 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  $\geq$  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

# HEPATITIS E

CIb/LIS

Marion Koopmans

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