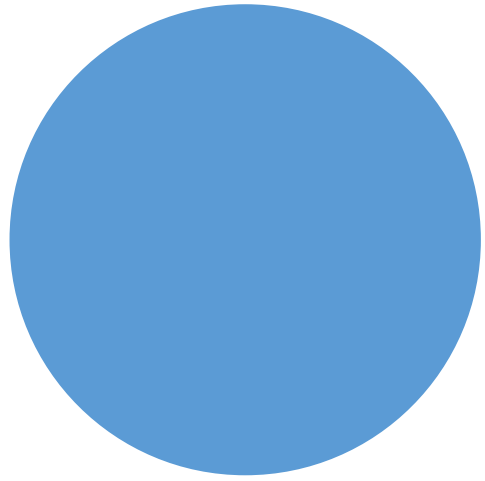
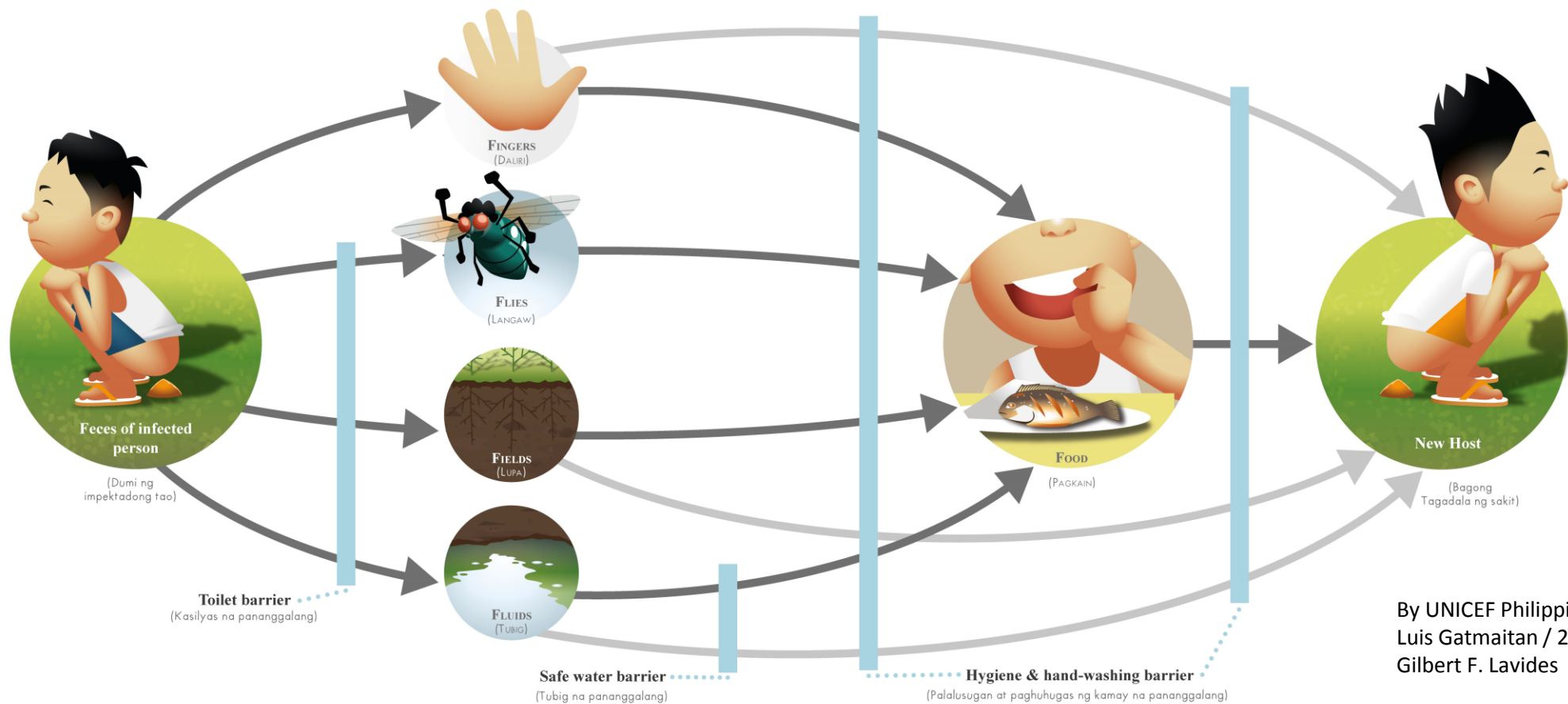


Hepatitis A in Europe: an overview IPFA May 2019

Dr Niamh O'Flaherty
MB MRCP FRCPath (micro)
Irish Blood Transfusion Service
and National Virus Reference
Laboratory Dublin

Disclosures



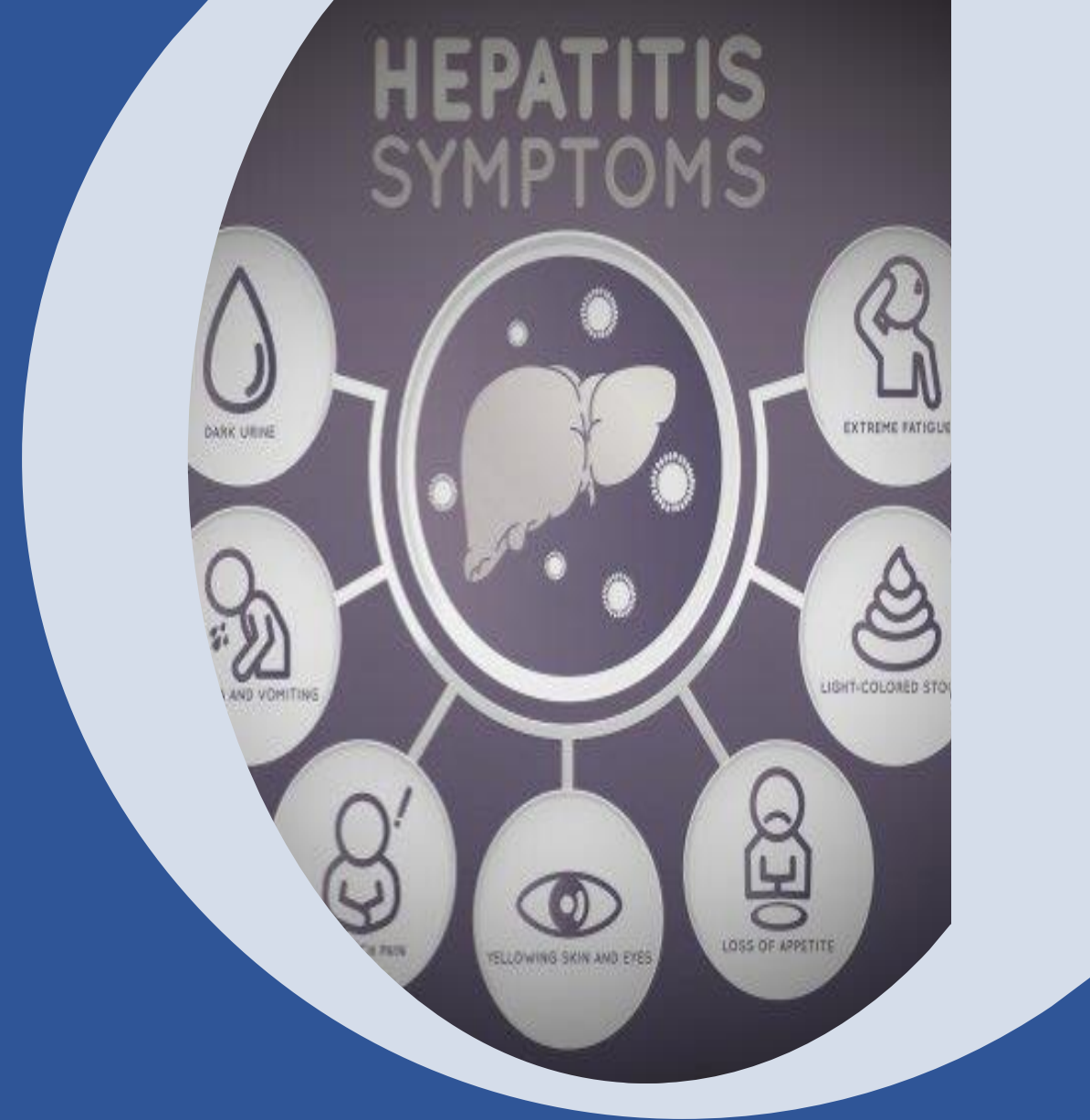


By UNICEF Philippines and
Luis Gatmaitan / 2014 /
Gilbert F. Lavides



Hepatitis A virus

- Incubation 30/7 (range 15-50)
- Maximal infectivity 2nd half incubation
 - Up to 30 days before symptoms
- Fulminant hepatitis in 0.015-0.5%
 - mortality 70-90% (without transplant)
- EU about 13 000 cases ~2.6/100 000 (range 0- 66)
- No chronic carrier state but relapses can occur for up to 6-9 months in 3-20%
- No specific treatment
- Vaccine since 1991



Hepatitis A in Europe- historical perspective

Hepatitis A: old and new.
Cuthbert J, CMR. Jan. 2001, p.
38–58

‘An ancient disease’- likely afflicted mankind since humans began to live in groups large enough to allow for sustained transmission

- Cockayne (1912) acknowledges first formal reference to [HAV] ‘*epidemic jaundice*’ in 1745
- The viral aetiology of was not widely accepted by physicians until 1930s
- Deliberate experimental transmission to human volunteers using duodenal juices
- Followed demonstration of transmission ‘short incubation hepatitis’ via parenteral route

*'...hepatitis A
virus is not an important cause of
posttransfusion
hepatitis''*
Knodel R G. *Gastroenterology*, 1975

*TT-HAV can occur if the right conditions
prevail*
Hollinger et al 1983

Vermeylen *Vox Sang* 1994
Seeburg *Lancet* 1981
Barbara JA *Lancet* 1982
Hettman A *VirusGenes* 2017

Lack of concern around transfusion transmission of HAVwhy?

'Short' viraemia , lack of a carrier state, adults tend to be symptomatic (deferred), prior immunity in donors and recipients and co-transfusion HAV antibody

First case reports:

- Seeburg et al Sweden 1980 & Barbara et al U.K 1981

1990s HAV epidemic in haemophilia patients

- Linked to clotting factor concentrates (SD plasma)
- Italy (50 cases), Germany(18 cases) and Belgium (6 cases) and Ireland (30)

2004 Swiss blood service: 1st case of (shortlived) HAV 're-infection' in an RBC recipient confirmed by molecular studies

2014 Hungary

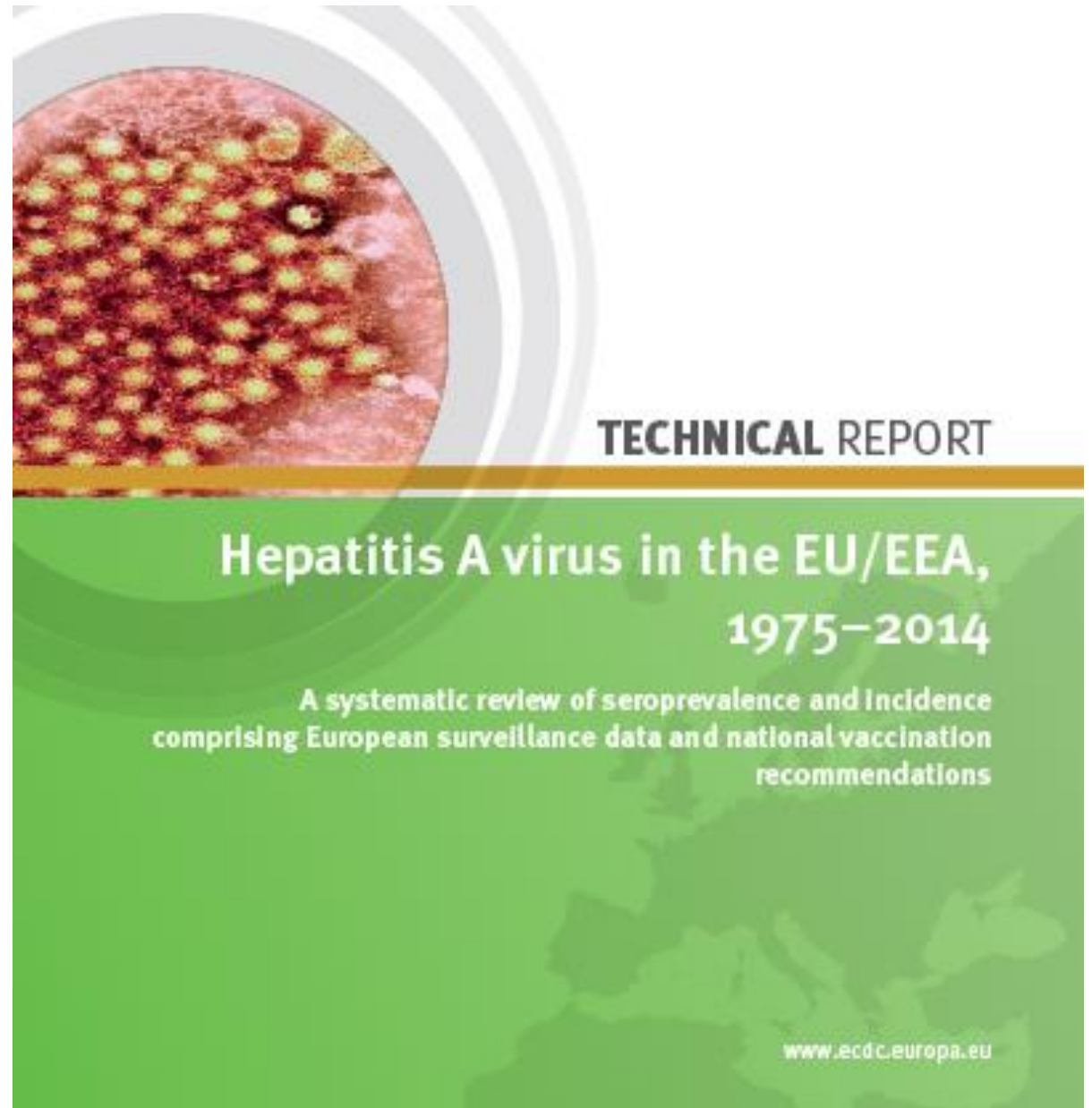
- 2 donations from an unvaccinated male apheresis platelet donor transmitted HAV to two recipients
- 2 secondary cases, identical sequences identified in all cases (GT 1A)

UK SHOT report outlined a TT-HAV case which occurred in 2017 from an apheresis platelet donation

- transient HAV RNA detected recipient (pre transfusion HAV IgG)

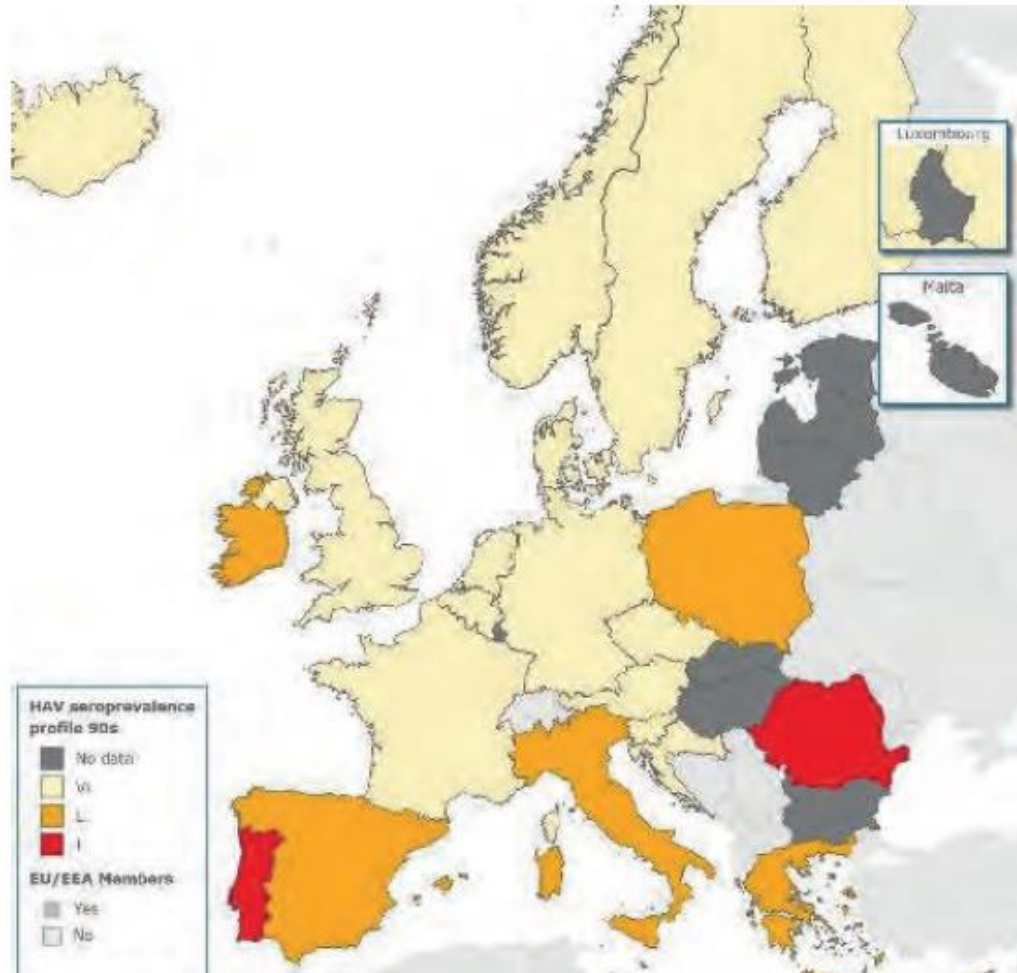
HAV Epidemiology in Europe

Age-specific seroprevalence
Incidence assessment
Susceptibility in adults > 30

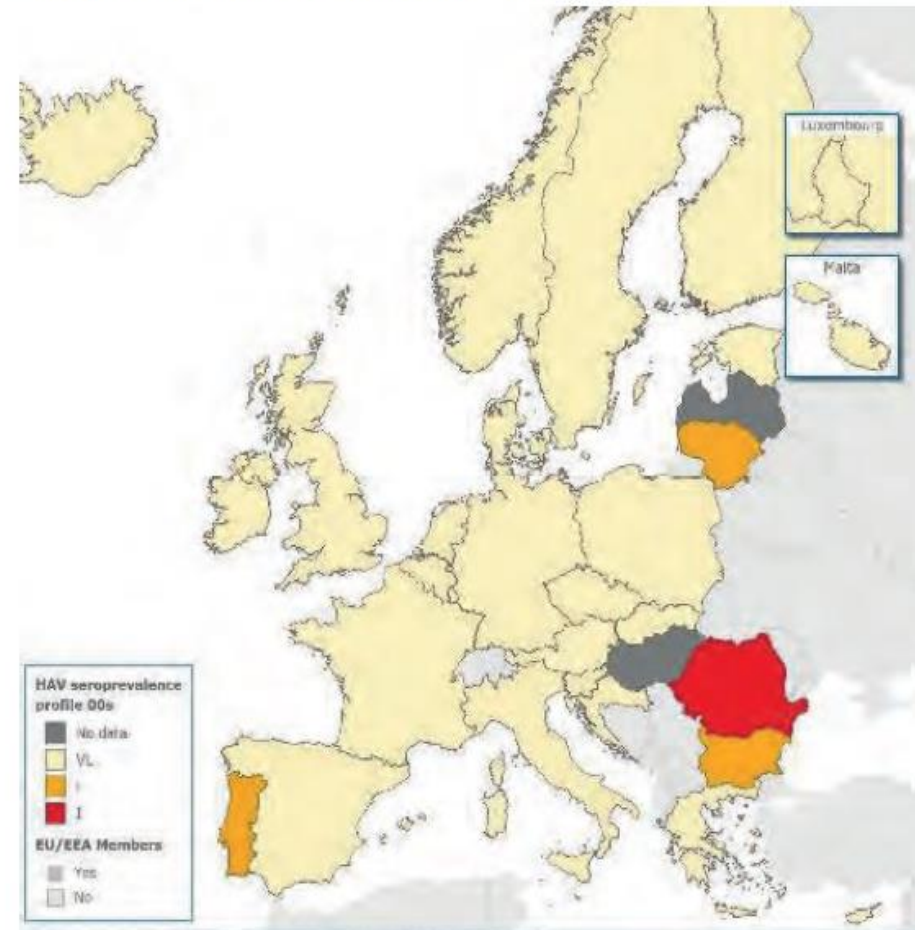


Changing HAV endemicity (seroprevalence) patterns in EU/ EEA over time

Studies with sampling year from 1990–1999



Studies with sampling year from 2000–2013

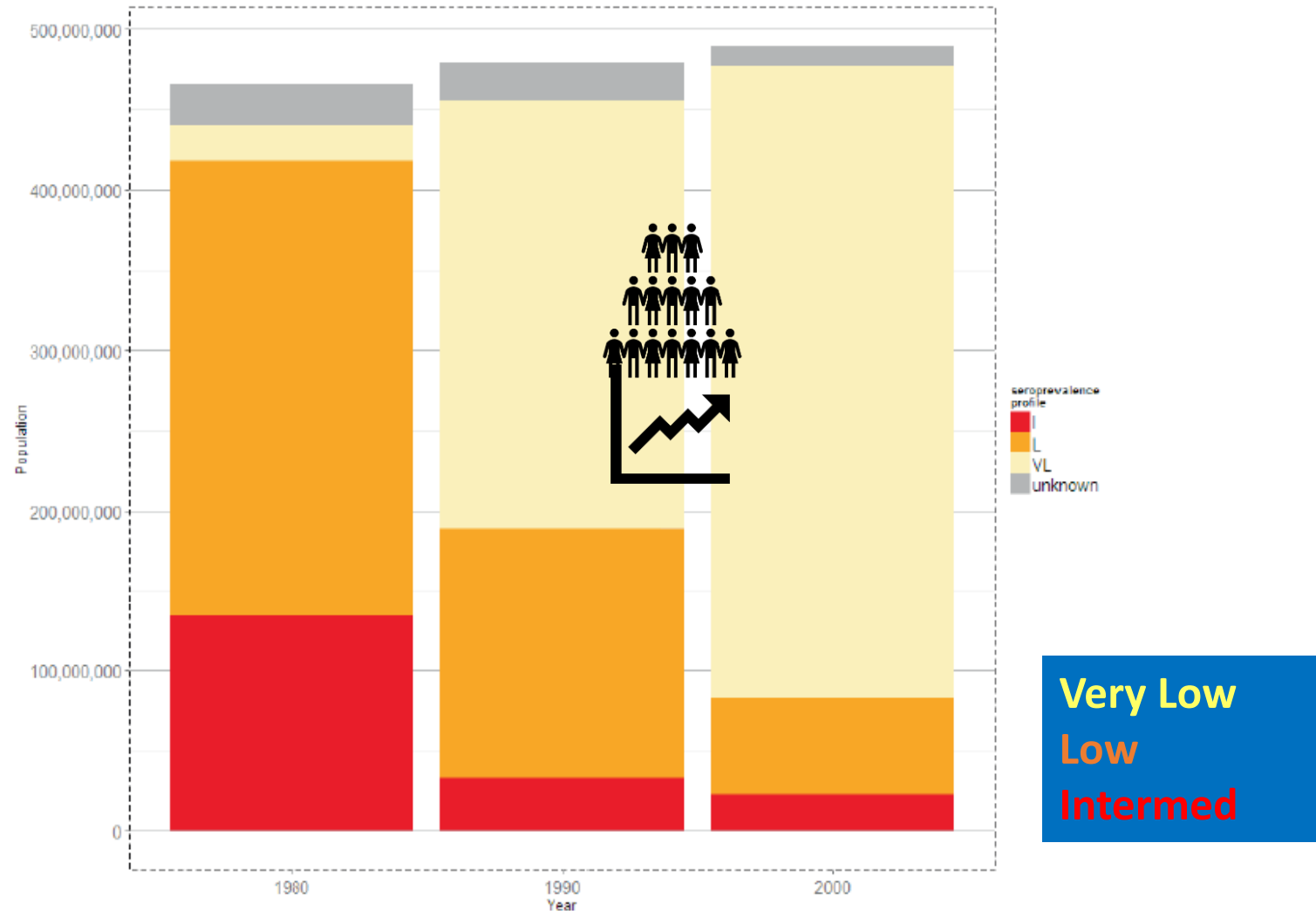


Intermed
Low
Very Low

Intermed
Low
Very Low

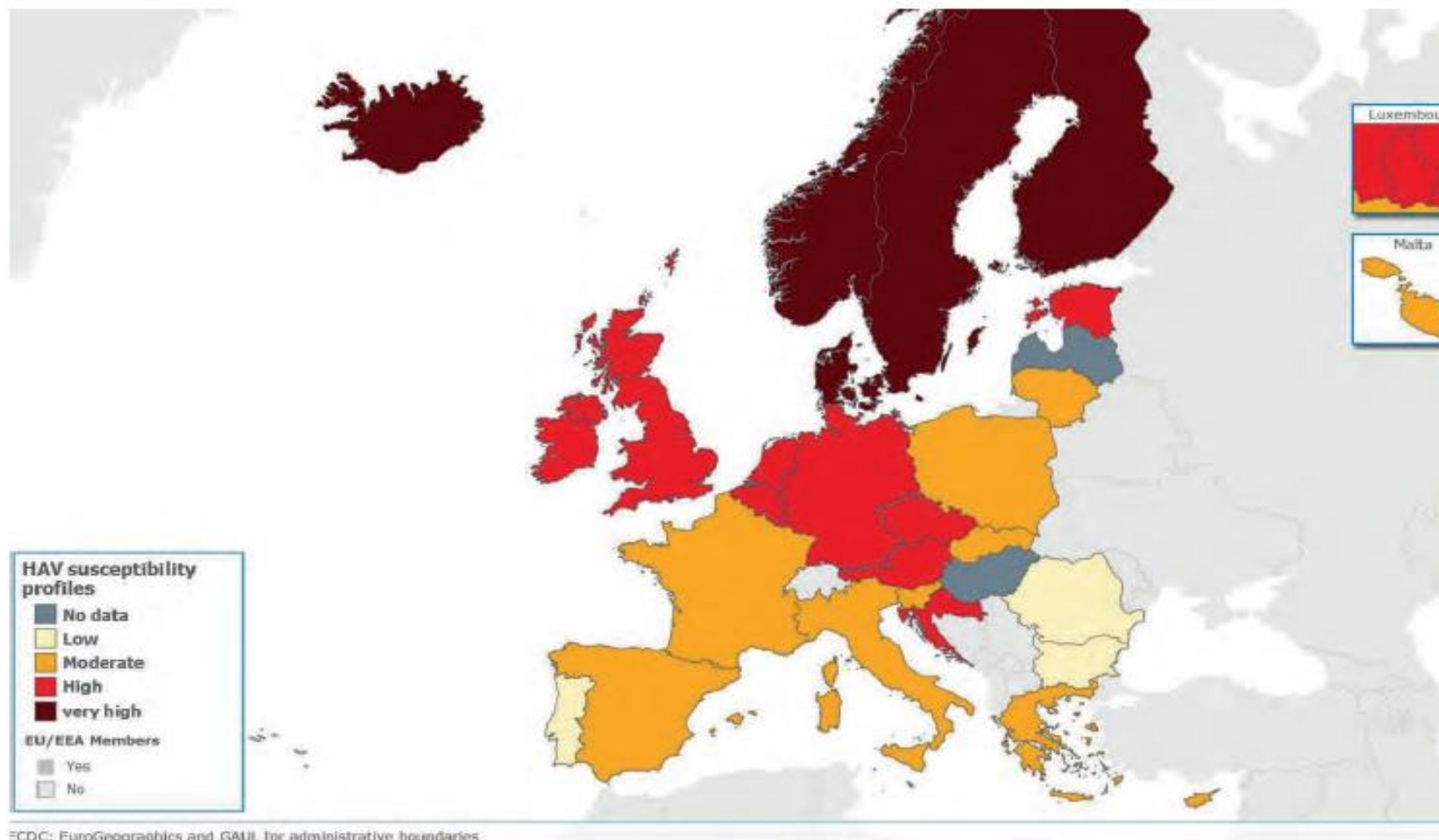
Growing HAV Susceptible Population

Figure 4.2. Size of the EU population for each seroepidemiological profile



Approximately 230 million EU / EEA citizens are in a high to very high HAV susceptibility region

Figure 4.4. Geographical distribution of the HAV susceptibility profiles, EU/EEA, 2000–2014.



ECDC: EuroGeographics and GAUL for administrative boundaries

According to this classification, and considering country population size, we estimate that at the present time, 25 958 327 EU/EEA citizen live in countries with very high susceptibility profiles to HAV infection; 202 048 685 live in countries with a high susceptibility profile; 233 421 161 in countries with a moderate susceptibility profile; and 37 791 915 in countries at overall low susceptibility to HAV infection, based on the evidence collected from the

The paradox of HAV epidemiology and risk

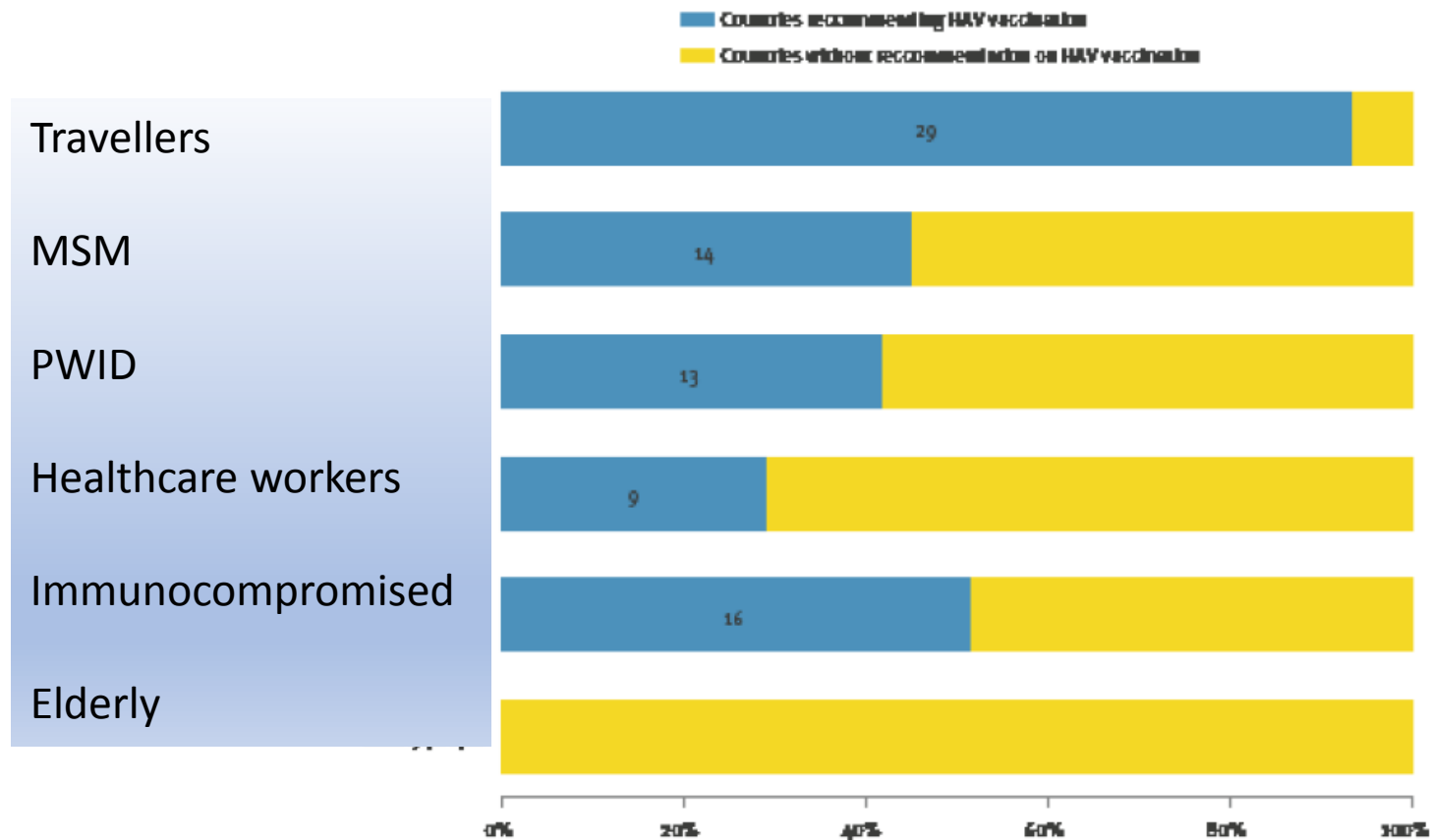
- High endemicity countries
 - low disease burden as the highest incidence is in children- mostly asymptomatic
 - Adults- protected by childhood infection and life long immunity
- Most Euro. countries have low and decreasing levels of immunity and endemicity
- More prone to outbreaks
 - Relative increase in susceptibility in adults
 - Higher burden of severe disease



Vaccination recommendations EU/EEA

FIGURE 2

EU/EEA countries recommending hepatitis A virus vaccination to groups defined by the WHO as at high risk for exposure or at risk of serious clinical outcome, 2013 (n = 30^a)



+ Countries recommending vaccination
- Countries without recommendation for vaccination

RAPID COMMUNICATIONS

Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 – linked to other German cities and European countries

Berlin's MSM scene is nationally and internationally well connected allowing for importation and exportation of HAV strains from or to various places in Europe'

RAPID COMMUNICATIONS

Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017

Characteristics of concern ..infection in a sex worker, co-infection with STI and use of sex-on-premises , apps (Grindr, Recon)....potential drivers of the outbreak

RAPID COMMUNICATIONS

Hepatitis A outbreak in HIV-infected MSM and in PrEP-using MSM despite a high level of immunity, Lyon, France, January to June 2017

SURVEILLANCE AND OUTBREAK REPORT

Hepatitis A outbreak disproportionately affecting men who have sex with men (MSM) in the European Union and European Economic Area, June 2016 to May 2017

RAPID COMMUNICATIONS

Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017

RAPID COMMUNICATIONS

Hepatitis A outbreak since November 2016 affecting men who have sex with men (MSM) in Chile connected to the current outbreak in MSM in Europe, situation up to October 2017

'High outbreak potential of hepatitis A in MSM community'
'high interconnectedness through global travel'



RESEARCH ARTICLE
A large ongoing outbreak of hepatitis A predominantly affecting young males in Lazio, Italy; August 2016 - March 2017
Simone Lanini¹*, Claudia Minosse¹*, Francesco Vairo¹, Annarosa Garbuglia¹, Virginia Di Bari¹, Alessandro Agresta¹, Giovanni Rezza², Vincenzo Puro¹, Alessio Penderenza³, Maria Rosaria Loffredo⁴, Paola Scognamiglio¹, Alimuddin Zumla⁵, Vincenzo Pandolfi⁶

SURVEILLANCE AND OUTBREAK REPORTS

Hepatitis A outbreak predominantly affecting men who have sex with men in Northern Ireland, October 2008 to July 2009

O Sfetcu (Otilia.Sfetcu@ecdc.europa.eu)^{1,2}, N Irvine³, S L Ngul³, C Emerson⁴, C McCaughey⁵, P Donaghy¹
1. Health Protection Service, Public Health Agency, Northern Ireland, United Kingdom



Confirmed hepatitis A cases by strain and geographical distribution in multi-strain outbreak affecting predominantly MSM, 1 June 2016–31 May 2017, participating European Union/European Economic Area countries (n = 1,400 cases)

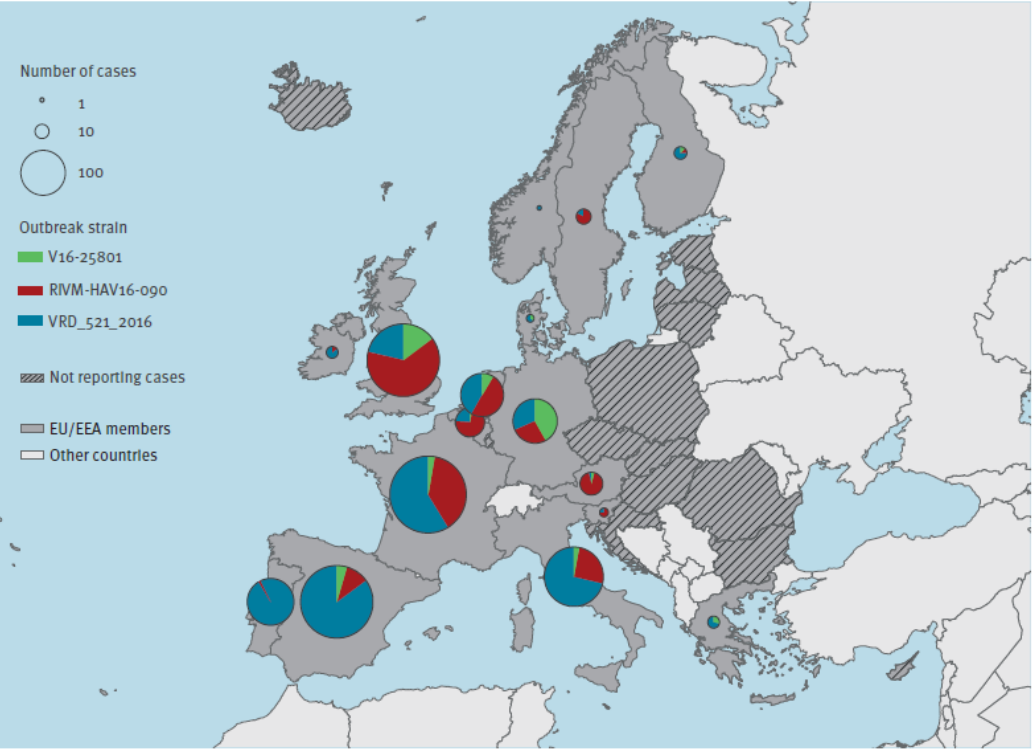
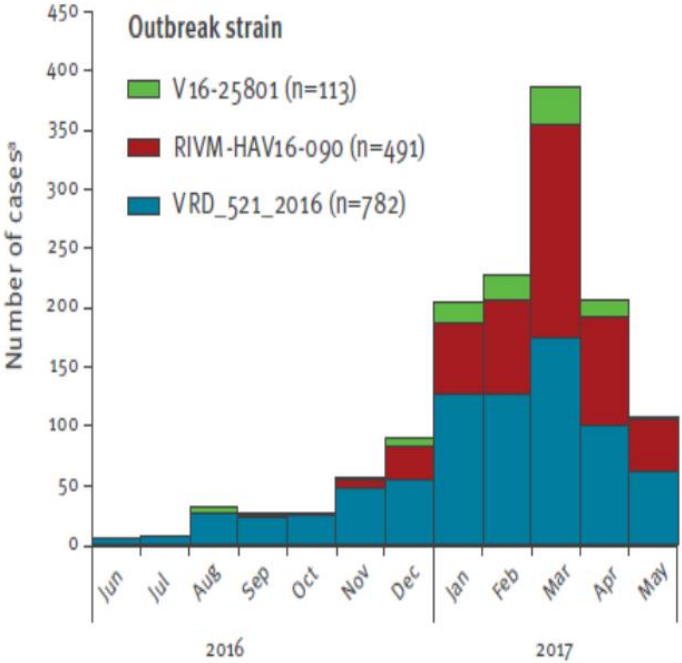


FIGURE 1

Confirmed hepatitis A cases by strain and date of reporting in multi-strain outbreak affecting predominantly MSM, 1 June 2016–31 May 2017, participating European Union/European Economic Area countries, (n = 1,386 cases)

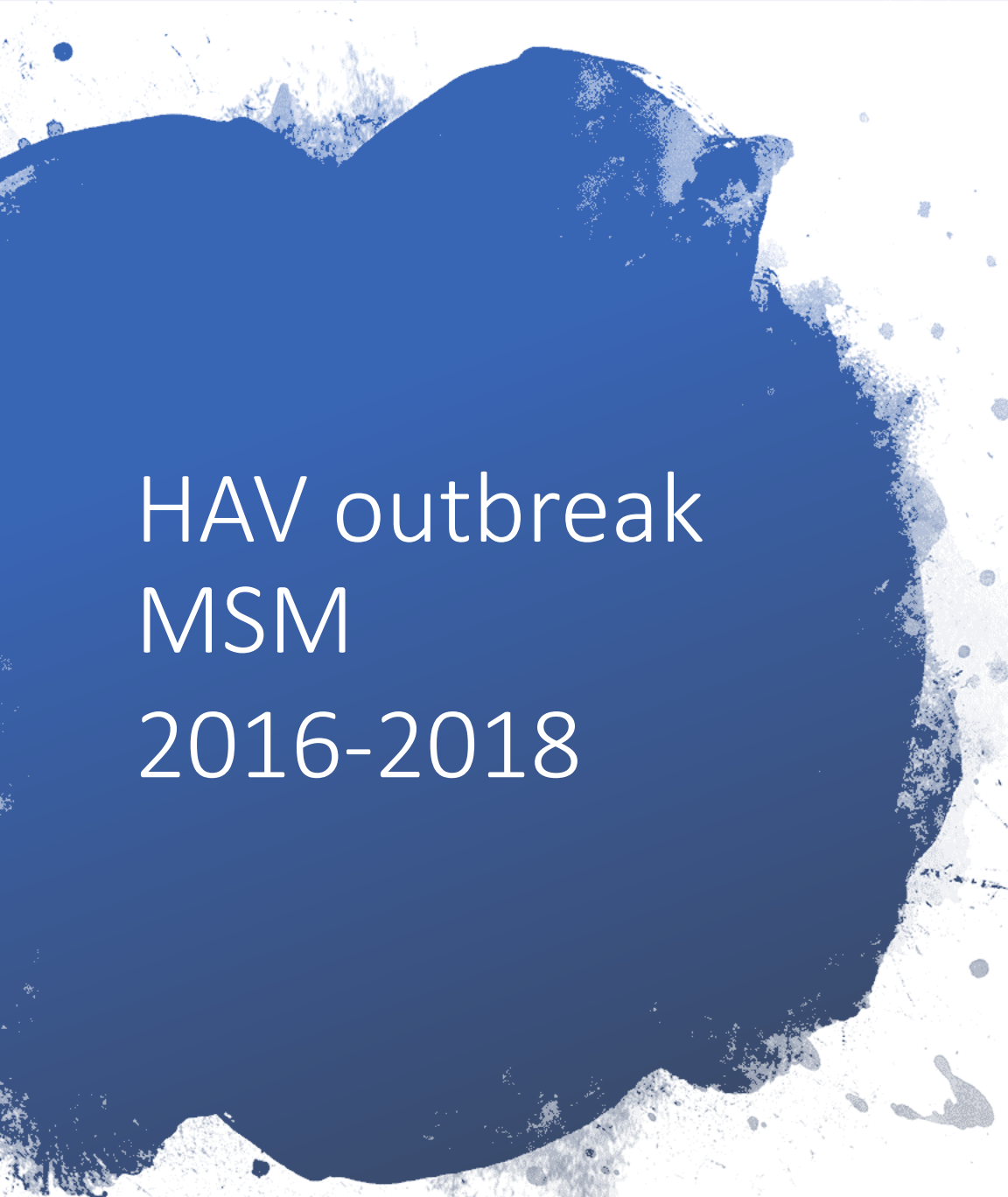


Over 4000 cases
20 countries
Male to female
ratio 3:1

High-risk behaviour

Characteristics	RIVM-HAV16-090		V16-25801		VRD 521_2016		Not-sequenced		Total	
	n	% ^a	n	% ^a	n	% ^a	n	% ^a	n	% ^a
Total	166	54	39	13	86	28	17	5	308	100
Regular sex partners ^c										
1-2	50	96	13	81	22	100	4	100	89	95
3-5	2	4	2	13	0	0	0	0	4	4
6-10	0	0	1	6	0	0	0	0	1	1
> 10	0	0	0	0	0	0	0	0	0	0
Subtotal	52	100	16	100	22	100	4	100	94	100
Casual sex partners ^c										
1-2	34	65	9	75	11	52	6	86	60	65
3-5	12	23	1	8	8	38	1	14	22	24
6-10	3	6	1	8	2	10	0	0	6	7
> 10	3	6	1	8	0	0	0	0	4	4
Subtotal	52	100	12	100	21	100	7	100	92	100
Anonymous sex partners ^c										
1-2	24	60	4	33	8	47	0	0	36	48
3-5	9	23	3	25	8	47	2	33	22	29
6-10	3	8	3	25	0	0	2	33	8	11
> 10	4	10	2	17	1	6	2	33	9	12
Subtotal	40	100	12	100	17	100	6	100	75	100
Condom use										
Always	28	36	8	36	13	54	2	20	51	38
Most time (> 50%)	12	16	0	0	1	4	6	60	19	14
Sometime (< 50%)	18	23	6	27	4	17	1	10	29	22
Never	19	25	8	36	6	25	1	10	34	26





HAV outbreak MSM 2016-2018

- Combination of travel and sexual networks- sustained outbreak
- 92% unvaccinated
- 66% hospitalised
- High proportion engaged in high-risk behaviour-especially when abroad
- Significant level of 'interconnectedness'

RAPID COMMUNICATIONS

Spillover of a hepatitis A outbreak among men who have sex with men (MSM) to the general population, the Netherlands, 2017

Ingrid HM Frieema¹, Gerard JB Sonder², Mariska WF Petrignani², Annemarie E Melberg³, Gini GC van Rijckevorsel², Wilhelmina LM Ruijs³, Harry Vennema⁴

1. Centre for Infectious Diseases, Epidemiology and Surveillance, Centre for Infectious Disease Control, National Institute for

FIGURE 1

Number of notified cases (n=432) stratified to MSM-strains (n=265), other strains (n=119) and no strain data (n=48) per month of disease onset, January 2017–April 2018

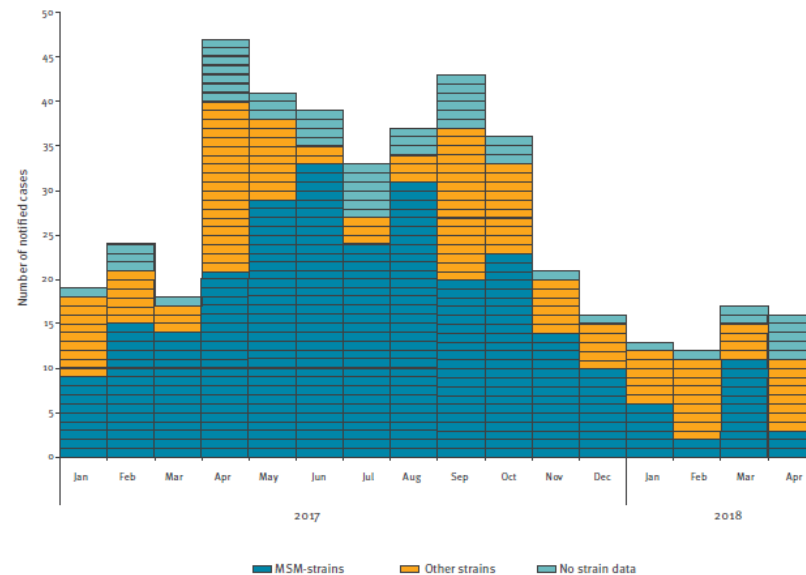
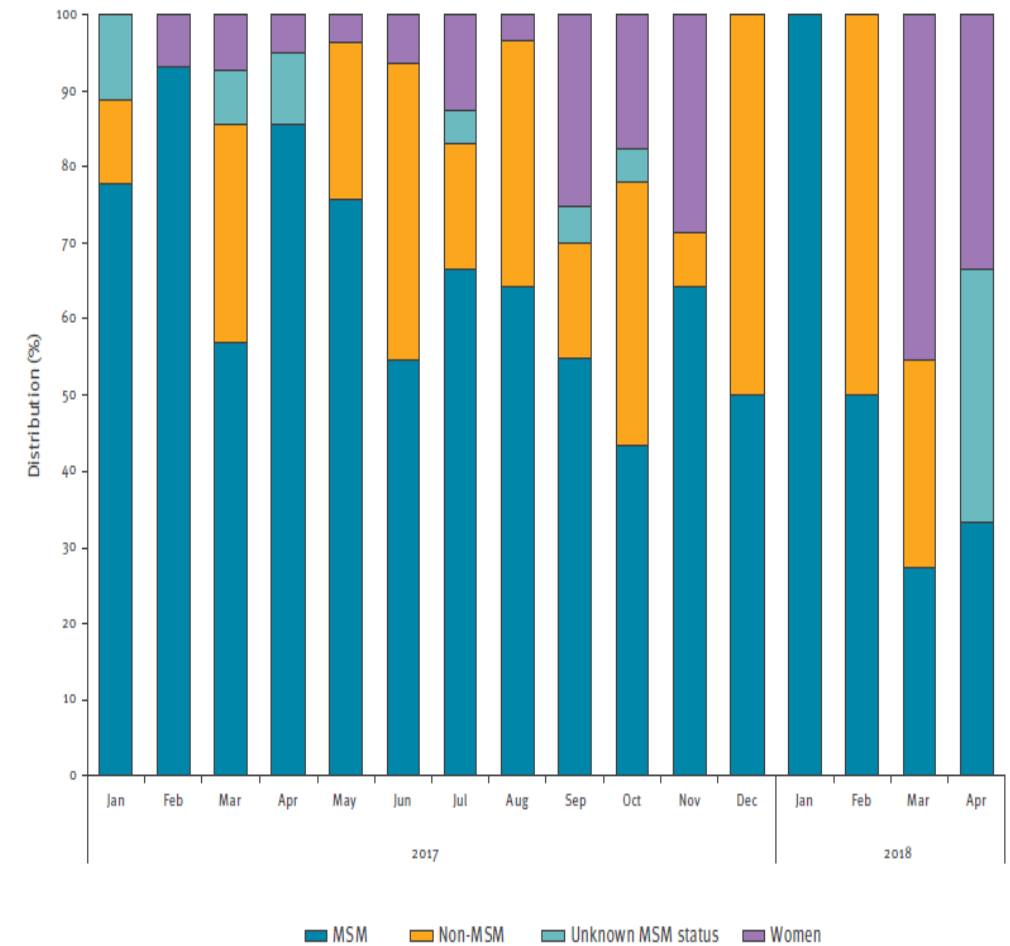


FIGURE 2

Distribution of the MSM-strains (n=265) in MSM (n=169), non-MSM (n=59), unknown MSM status (n=8) and women (n=29) per month, January 2017–April 2018



HAV and food in Europe

- HAV (and norov) are the most commonly implicated viral food contaminants
- Europe has the highest no. of reported HAV foodborne outbreaks (64% of HAV outbreaks).
- Long incubation makes identifying food sources challenging (sequencing / data sharing across states is important)
- Knowledge lacking on survival of HAV and efficiency of washing and decontamination in virus removal
- Berries are an ideal vehicle for HAV
- Consumption of berries has increased 4.5 fold 1998-2005



Mussel Farming





Faecal contamination of food

Pre-harvest:

Irrigation water, human handling, sewerage contamination

Post-harvest: human handling - berry harvesting is particularly 'hands-on') rinse water, ice, packaging, equipment, mixing batches





Contents lists available at ScienceDirect

International Journal of Food Microbiology

journal homepage: www.elsevier.com/locate/ijfoodmicro



Short communication

Occurrence of hepatitis A and E and norovirus GI and GII in ready-to-eat vegetables in Italy



V. Terio ^{a,*}, M. Bottaro ^a, E. Pavoni ^b, M.N. Losio ^b, A. Serraino ^c, F. Giacometti ^c, V. Martella ^a, A. Mottola ^a,

RESEARCH

Underdiagnosis of Foodborne Hepatitis A, the Netherlands, 2008–2010¹

Mariska Petrignani, Linda Verhoef, Harry Vennema, Rianne van Hunen, Dominique Baas, Jim E. van Steenbergen, and Marion P.G. Koopmans

RAPID COMMUNICATION

Hepatitis A outbreak linked to imported frozen strawberries by sequencing, Sweden and Austria, June to September 2018

Theresa Enkirsch^{a,*}, Ronnie Eriksson^a, Sofia Persson^a, Daniela Schmid^a, Stephan W. Aberle^a, Emma Löf^a, Bengt Wittesjö^b, Birgitta Holmgren^a, Charlotte Johnzon^a, Eva X. Gustafsson^a, Lena M. Svensson^a, Lisa Labbé Sandelin^a, Lukas Richter^a, Mats Lindblad^a, Mia Brytting^a, Sabine Maritschnik^a, Tatjana Tallo^a, Therese Malm^a, Lena Sundqvist^a, Josefine Lundberg Ederth^a

¹. Public Health Agency of Sweden, Solna, Sweden

SURVEILLANCE AND OUTBREAK REPORTS

Large and prolonged food-borne multistate hepatitis A outbreak in Europe associated with consumption of frozen berries, 2013 to 2014

E Severi (Ettore.severi@ecdc.europa.eu)^{1,2,*}, L Verhoef¹, L Thornton¹, B R Guzman-Herrador¹, M Faber¹, L Sundqvist¹, R Rimhanen-Finne¹, A M Roque-Afonso¹, S L Ngui¹, F Allerberger¹, A Baumann-Popczyk¹, L Müller¹, K Parmakova¹, V Alfonsi¹, L Tavoschi¹, H Vennema¹, M FitzGerald¹, M Myrmet¹, M Gertler¹, J Ederth¹, M Kontio¹, C Vanboeckstael¹, S Mandal¹, M Sadkowska-Todys¹, M E Tassinari¹, B Schlemmer¹, L O'Gorman¹, Katharina Stene-Johansen¹, I Wenzel¹, C Innes¹, K Ralston¹, A R Cicciaglione¹, L O'Connor¹

SURVEILLANCE AND OUTBREAK REPORT

International linkage of two food-borne hepatitis A clusters through traceback of mussels, the Netherlands, 2012

IL Boxman¹, L Verhoef², H Vennema¹, S Ngui¹, IH Friesema¹, C Whiteside¹, D Lees¹, M Koopmans^{1,2}
¹. Laboratory for Food and Food Safety, Food and Consumer Product Safety Authority (NVWA), Wageningen, the Netherlands
². Laboratory for Infectious Diseases and Screening, National Institute of Public Health and the Environment (RIVM), Bilthoven, the Netherlands
³. Virus Reference Department, Microbiology Services Division - Colindale, Public Health England, London, United Kingdom
⁴. Epidemiology and Surveillance Unit, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

RAPID COMMUNICATIONS

Ongoing multi-strain food-borne hepatitis A outbreak with frozen berries as suspected vehicle: four Nordic countries affected, October 2012 to April 2013

S Gillesberg Lassen (sogl@ssi.dk)¹, B Soborg^{1,2}, S E Midgley³, A Steens^{2,4}, L Vold⁴, K Stene-Johansen⁵, R Rimhanen-Finne⁶, M Kontio⁶, M I Löfdahl⁷, L Sundqvist⁷, M Edelstein^{2,8}, T Jensen⁹, H T Vestergaard³, T K Fischer³, K Mølhak¹, S Frøholm^{1,10}

Journal of Applied Microbiology



Journal of Applied Microbiology ISSN 1364-5072

REVIEW ARTICLE

Key characteristics of foods with an elevated risk for viral enteropathogen contamination

T. Yeargin and K.E. Gibson

Division of Agriculture, Department of Food Science, University of Arkansas, Fayetteville, AR, USA

JOURNAL OF MEDICAL MICROBIOLOGY

RESEARCH ARTICLE
 Scavia et al., Journal of Medical Microbiology 2017;66:342–349
 DOI 10.1099/jmm.0.000433



A large prolonged outbreak of hepatitis A associated with consumption of frozen berries, Italy, 2013–14

Gaia Scavia^{1,†}, Valeria Alfonsi¹, Stefania Taffon¹, Martina Escher¹, Roberto Bruni¹, Dario De Medici¹, Simona Di Pasquale¹, Sarah Guizzardi², Benedetta Cappellietti², Stefania Iannazzo², Nadia Marina Losio³, Enrico Pavoni³, Lucia Decastelli⁴, Anna Rita Ciccaglione¹, Michele Equestre¹, Maria Elena Tosti¹, Caterina Rizzo^{1,*} and National Italian Task Force on Hepatitis A^{1,2,†}

RESEARCH ARTICLES

Food-borne diseases associated with frozen berries consumption: a historical perspective, European Union, 1983 to 2013

L Tavoschi (Lara.Tavoschi@ecdc.europa.eu)¹, E Severi¹, T Niskanen¹, F Boelaert², V Rizzi², E Liebana², J Gomes Dias¹, G Nichols^{1,2}, J Takkinen¹, D Coulombier¹

¹. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
². European Food Safety Authority (EFSA), Parma, Italy

Surveillance and Notification of food- borne HAV

- EPIS-FWD EU and non-EU (Epidemic Intelligence System for Food & Waterborne diseases) (ECDC 2010)
- Rapid Alert System for Food and Feed (RASFF) (EC, 1979)
- ECDC Threat-Tracking Tool (TTT, 2005)
- EFSA database on human food-borne outbreaks (EU, EAA member states, mandatory reporting ,2005)
- EWRS (early warning response system)
- HAV NET (RIVM, Netherlands)

The EU has one of the highest food safety standards in the world



Notifications related to berries contaminated with food-borne viruses and their associated outbreaks have increased in recent years

<https://ecdc.europa.eu/sites/portal/files/documents/21-05-2018-RRA-Hepatitis-A-multicountry-outbreak-EU.pdf>

Gassowski M Euro Surveill. 2018;23(27):pii=1800329
Enkirch T Euro Surveill. 2018;23(41):pii=1800528
Tavoschi Euro Surveill 2015;20(29):pii=21193
Gossner CM Euro Surveill. 2014;19(43):pii=20941
SG Lassen Euro Surveill. 2013;18(17):pii=20467
Carvahlo C November 2011.Euro Surveill. 2012;17(6):pii=20083

2018: Sweden, Austria

- Reported GT1B outbreak related to strawberries & single producer

2018

- Denmark & 6 other EU countries reported a GT1A and GT1B strains epidemiologically linked to Moroccan dates

2013-2014

- 12 EU/EEA countries associated with frozen mixed berries (GT1A)

2012-2013

- Nordic countries- approx. 100 cases (GT1B) linked smoothies made with frozen [straw]berries from Egypt & Morocco

2009-2011

- Semi-dried tomatoes from Turkey implicated in 3 HAV clusters in France (59, 2010) & Netherlands (14) & United Kingdom

11 frozen berry packing companies implicated

Investigation involved 6227 'transactions' and 1974 food operators

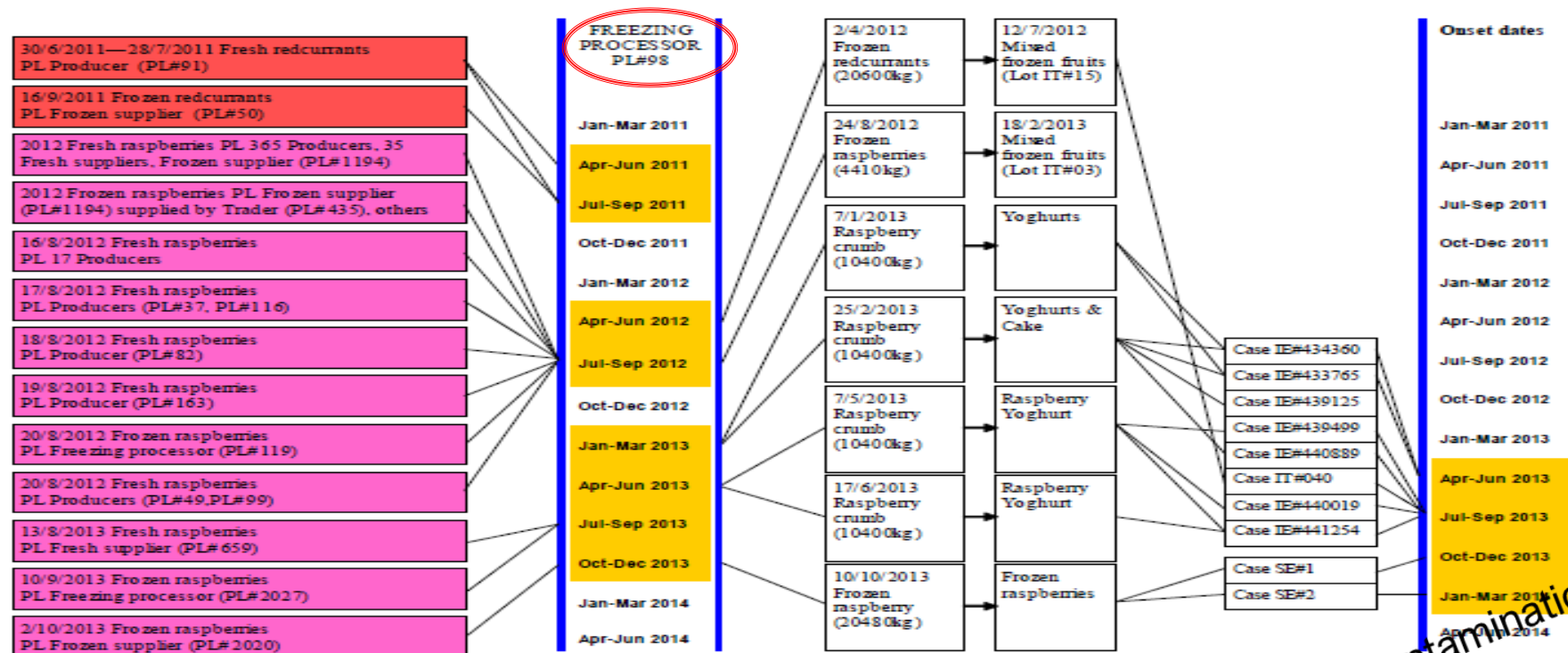
SCIENTIFIC REPORT OF EFSA

Tracing of food items in connection to the multinational hepatitis A virus outbreak in Europe¹

European Food Safety Authority^{2,3}

European Food Safety Authority

Tracing food items in connection to hepatitis A



No single point of contamination could be identified

Travel

an important risk factor for HAV infection in populations with a growing proportion of susceptible individuals

... consumption of contaminated food items or drinks during travel

A download of the HAVNET database in 2017 indicated that the source of infection for 52% of cases was travel to an endemic country

- The WHO and most EU/EEA countries recommend HAV vaccination to European travellers visiting countries with intermediate or high endemicity
- However, a recent survey among overseas travellers from France, Germany, Italy, Spain, and the United Kingdom (UK) suggested a moderate vaccine coverage against HAV
- with only half of the occasional travellers visiting endemic countries vaccinated

RAPID COMMUNICATIONS

Increase in hepatitis A in tourists from Denmark, England, Germany, the Netherlands, Norway and Sweden returning from Egypt, November 2012 to March 2013

E Macdonald^{1,2}, J Sane³, E Macdonald^{1,2}, L Vold⁴, C Gossner^{4,5}, E Severi⁶, on behalf of the International Outbreak

RAPID COMMUNICATION

Two concurrent outbreaks of hepatitis A highlight the risk of infection for non-immune travellers to Morocco, January to June 2018

SURVEILLANCE AND OUTBREAK REPORTS

Multistate foodborne hepatitis A outbreak among European tourists returning from Egypt– need for reinforced vaccination recommendations, November 2012 to April 2013

J Sane (jusa83@gmail.com)^{1,2}, E Macdonald^{2,3}, L Vold⁴, C Gossner^{4,5}, E Severi⁶, on behalf of the International Outbreak

Travel-associated hepatitis A in Europe, 2009 to 2015

9.6 billion nights spent abroad by residents from 13 Euro countries

- > 5,000 travel-associated hepatitis A cases reported by 13 countries
- 27.8% of all reported hepatitis A cases were travel-associated
- More than 60% travelled to Africa (2.11 cases per million nights) and Asia
 - although these destinations accounted for less than 15% of all nights spent overseas
- 38.6% of cases with a known month of travel were reported between August and October
- HAV TTI cases have been linked to donors who had travelled to endemic countries prior to donating

TABLE 5Top destinations for travel-associated hepatitis A cases, 12 EU/EEA countries^a, 2009–2015 (n = 2,581)

Rank	Destination country	Region	Travel-associated cases		
			n	%	% <15 years
1	Turkey	Other European countries	318	12.3	61.3
2	Egypt	Africa	279	10.8	14.7
3	Morocco	Africa	200	7.7	52.0
4	Pakistan	Asia	140	5.4	73.6
5	Afghanistan	Asia	130	5.0	80.0
6	India	Asia	106	4.1	17.9
7	Syria	Asia	92	3.6	52.2
8	Spain	EU 28	86	3.3	3.5
9	Italy	EU 28	69	2.7	20.3
10	Lebanon	Asia	60	2.3	45.0
11	Namibia	Africa	59	2.3	15.3
12	Romania	EU 28	51	2.0	29.4
13	Iraq	Asia	42	1.6	73.8
14	Bulgaria	EU 28	31	1.2	22.6
14	France	EU 28	31	1.2	6.5
16	Ethiopia	Africa	29	1.1	79.3
17	Peru	Central and South America	28	1.1	25.0
18	Croatia	Africa	26	1.0	26.9
19	Philippines	Asia	25	1.0	24.0
20	Greece	EU 28	24	0.9	8.3
20	Thailand	Asia	24	0.9	8.3
Other destinations			731	28.3	25.2
Total			2,581	100	36.9

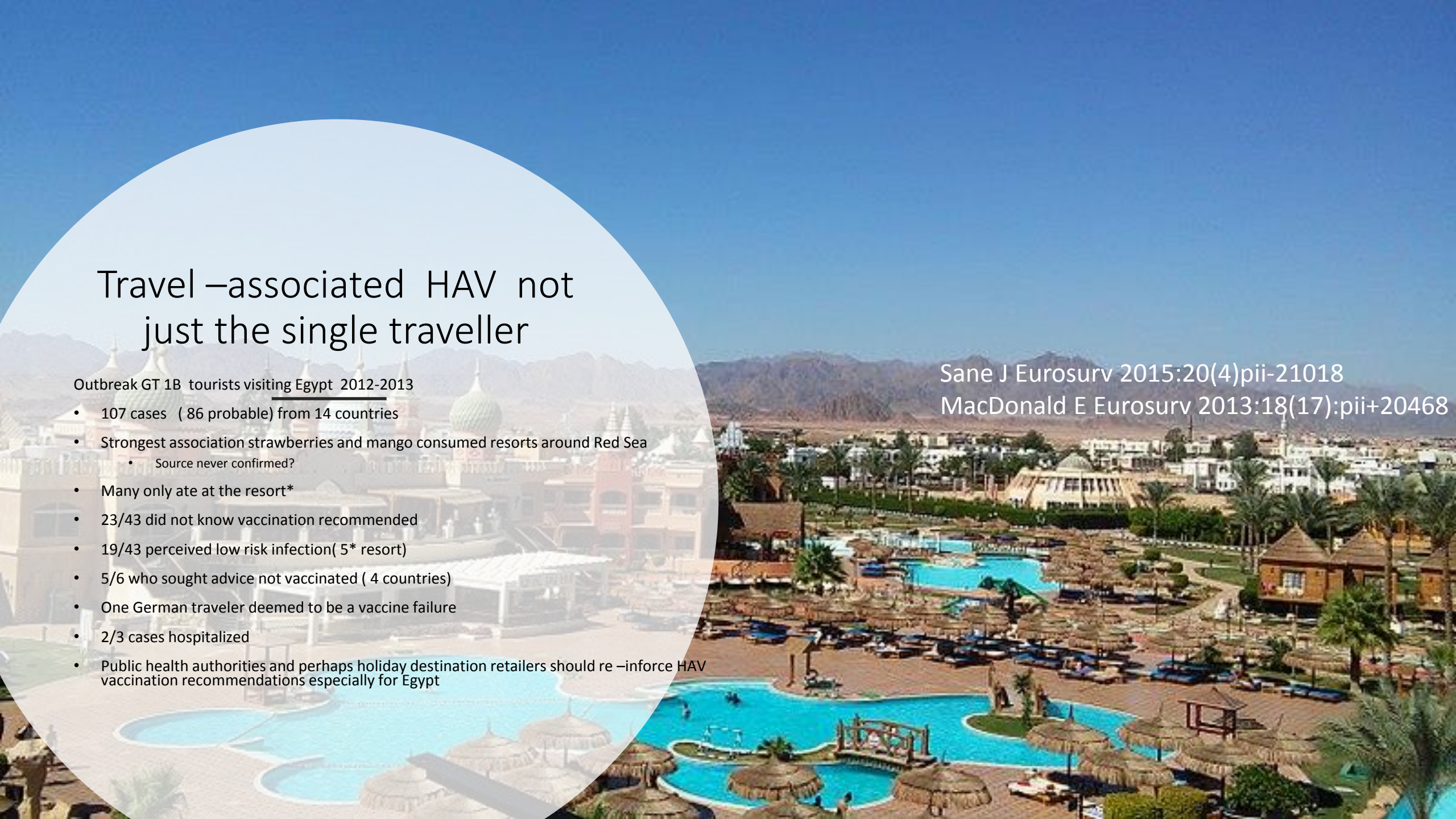
Travel –associated HAV not just the single traveller

Outbreak GT 1B tourists visiting Egypt 2012-2013

- 107 cases (86 probable) from 14 countries
- Strongest association strawberries and mango consumed resorts around Red Sea
 - Source never confirmed?
- Many only ate at the resort*
- 23/43 did not know vaccination recommended
- 19/43 perceived low risk infection(5* resort)
- 5/6 who sought advice not vaccinated (4 countries)
- One German traveler deemed to be a vaccine failure
- 2/3 cases hospitalized
- Public health authorities and perhaps holiday destination retailers should re –inforce HAV vaccination recommendations especially for Egypt

Sane J Eurosurv 2015;20(4):pii=21018

MacDonald E Eurosurv 2013;18(17):pii=20468



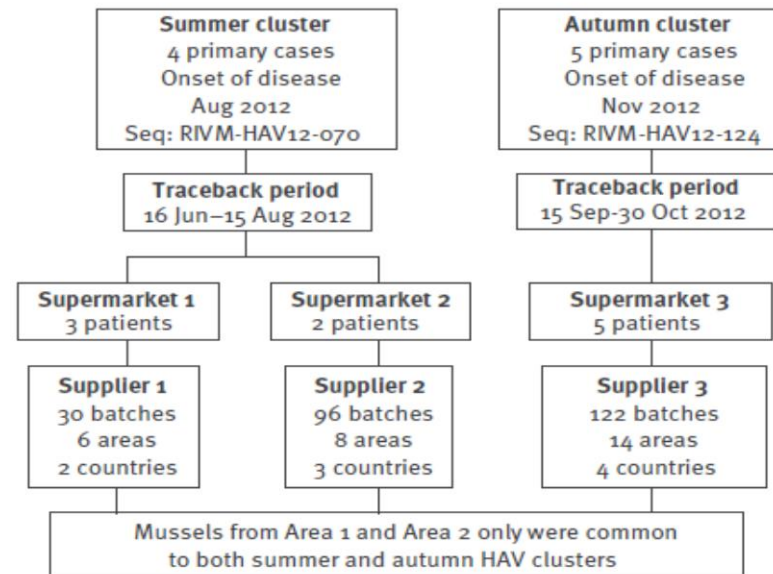
International linkage of two food-borne hepatitis A clusters through traceback of mussels, the Netherlands, 2012

Netherlands 2012

- 9 HAV infections involving 2 unique HAV Gt 1A strains linked to mussel consumption
- Traceback investigation helped identify 5 further identical cases in U.K. – one of whom travelled Chile, ill afterwards
- Mussels beds likely contaminated after heavy rainfall from sewage treated near U.K cases
- Collaboration and sequencing analysis led to successful identification of the source

FIGURE 2

Outcomes of traceback activities for potentially implicated mussels, food-borne hepatitis A clusters, the Netherlands, 2012



Conclusions

Threat

- HAV continues to challenge European public health

HAV is a significant pathogen

- Increasing susceptibility, significant morbidity, mortality and cost

Learn from other viruses

- Food safety regulations adequate^{1,2}
 - Should we give food safety advice to recipients
 - Should we encourage vaccination donors?!
 - Let's ensure vaccination of multi-transfused recipients

Implications for Blood Safety?

- TTIs are not common but continued travel-to and importation of foods from endemic countries..
- HAV outbreaks and clusters HAV are likely continue... thus there is potential for increasing HAV TTI in Europe

1. REGULATION (EC) No 882/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 29 April 2004
2. https://ec.europa.eu/food/safety/rasff_en