



Hepatitis, travelers risk and how to address them

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Advice (LCR)

Director Travel Clinic Public Health Service Amsterdam



disclosure

No conflicts of interest



outline

Hepatitis A and B

- Worldwide perspective, epidemiology and recent changes
- Risks in travelers, recent changes and how they relate to the worldwide perspective
- Vaccine shortages; how to address them

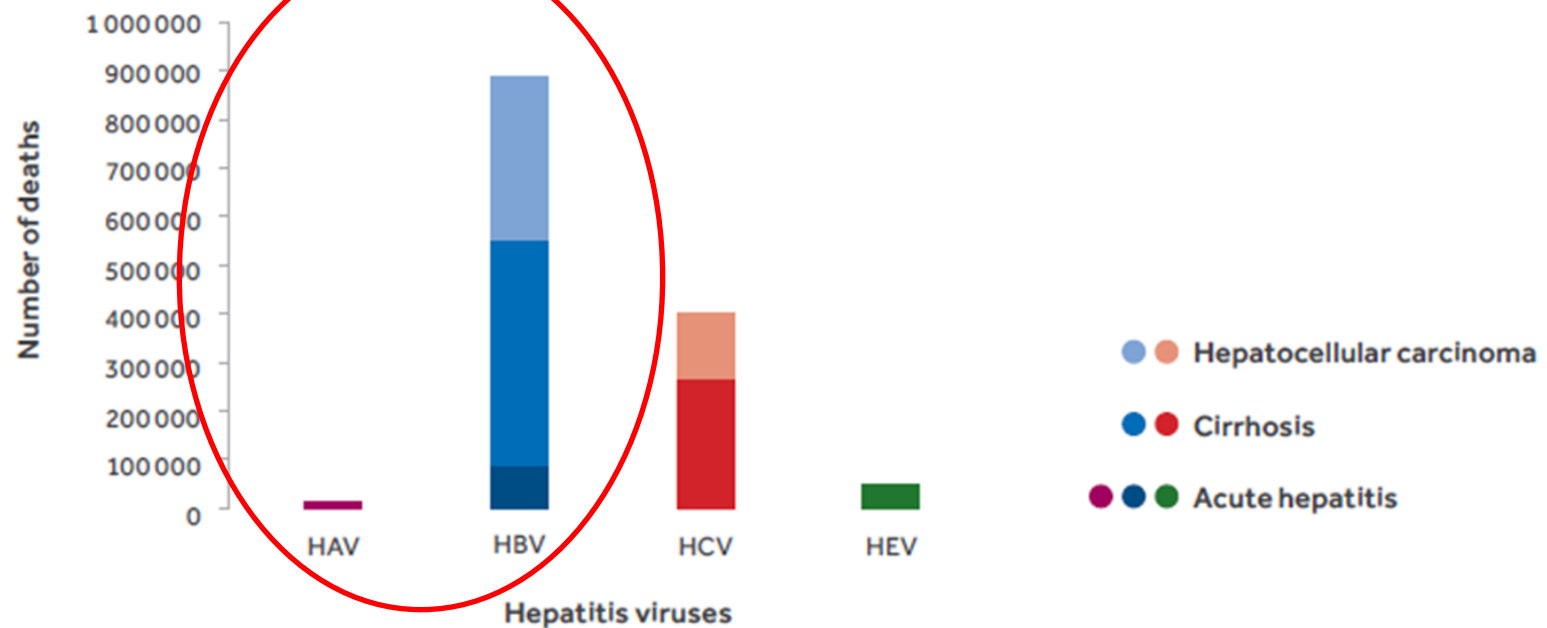


Hepatitis A and B

	Hepatitis A	Hepatitis B
transmission	Feco-orally, food/water	Birth, blood-blood, sexually
Incubation (average)	2-7 wks (4 wks)	4-26 wks (7 wks)
Chronic disease	no	90% infected at birth 5% infected adults
Immunity	after recovery	After recovery
Treatment	no	Suppress replication
Mortality	Acute hepatitis, low	Acute and chronic: higher
	RISK GROUPS	RISK GROUPS
RISK GROUPS	Contacts of patients, MSM, PWID	Immigrants (1st generation), MSM, HCW, SW, PWID
TRAVELLERS	Yes, obvious	Less obvious
15-05-18		4

Mortality viral hepatitis

Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015:
 most viral hepatitis deaths are due to the late complications of HBV and HCV infection



HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus

Source: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)



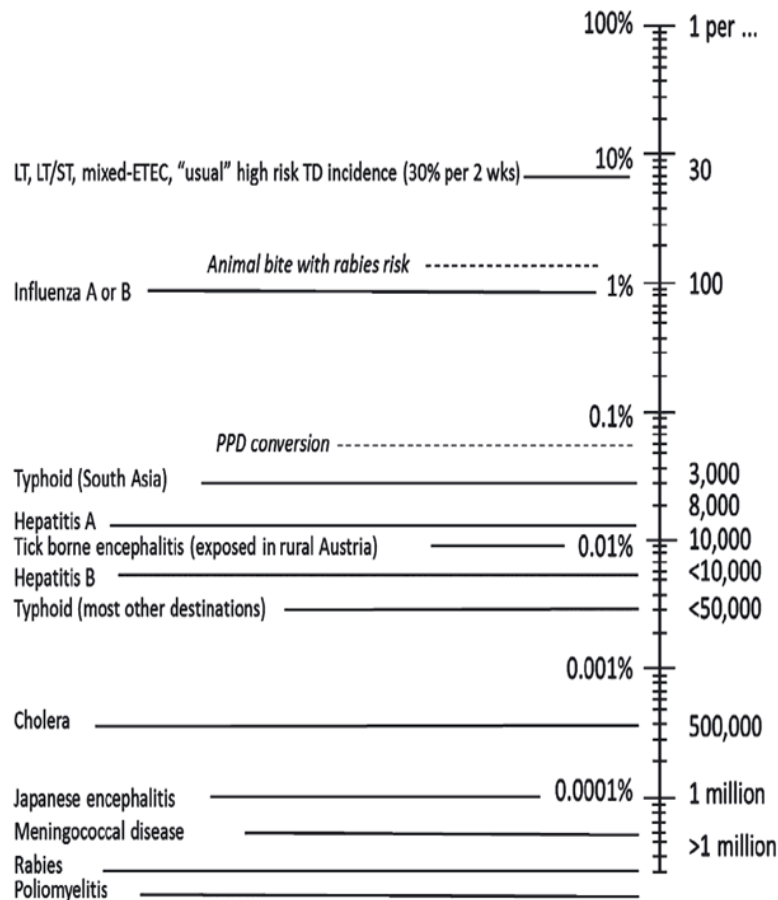
Hepatitis control

1) Treatment of infected people (HBV) to prevent morbidity, mortality and transmission (TaP)

2) Prevention of new infections

- Hepatitis A: hygiene, vaccination
- Hepatitis B: **TRAVEL MEDICINE** prevent blood-blood contact (medical care, tattoos) condoms, vaccination

Risks for travelers



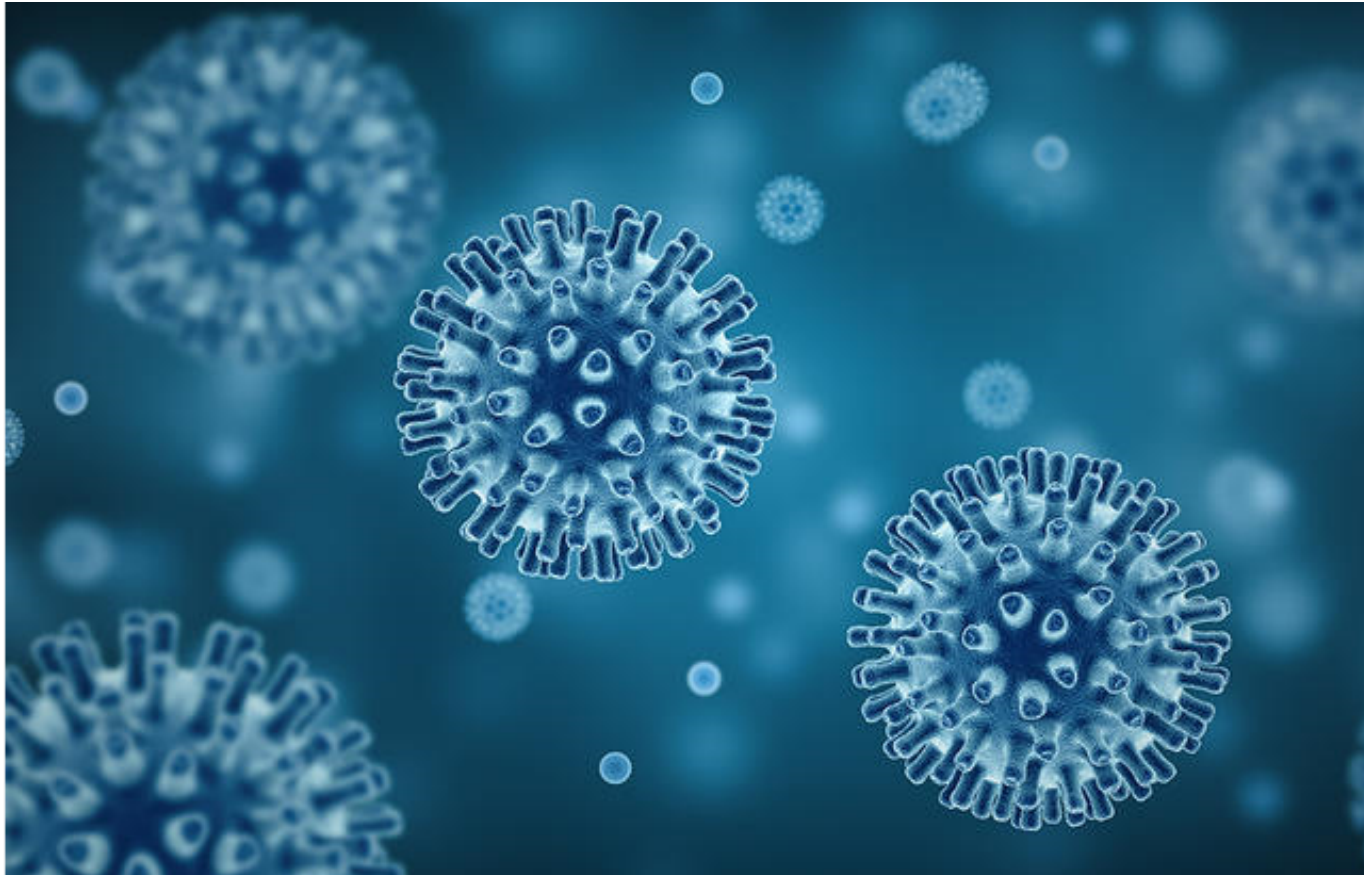
Hepatitis A (2005)

risk: 1:2,500 – 1: 9,000

Hepatitis B

risk: < 10.000

Hepatitis A



Hepatitis A and travel

1810

J. Whelan et al. / Vaccine 31 (2013) 1806–1811

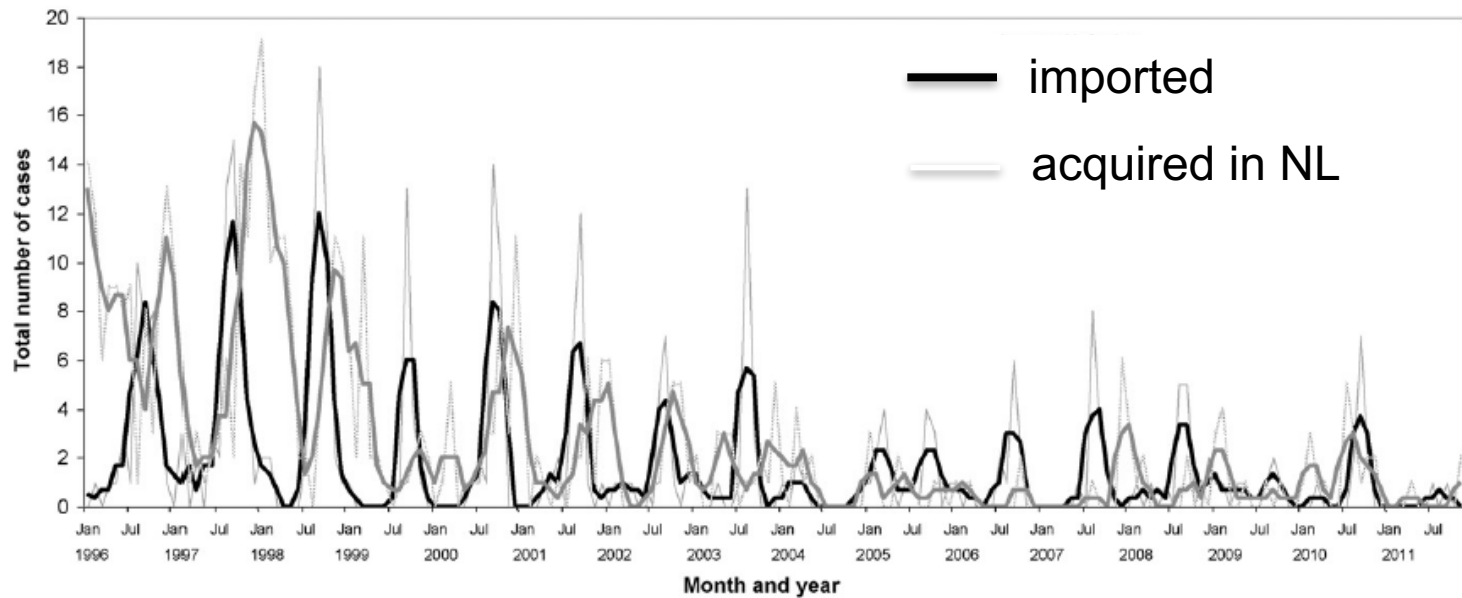
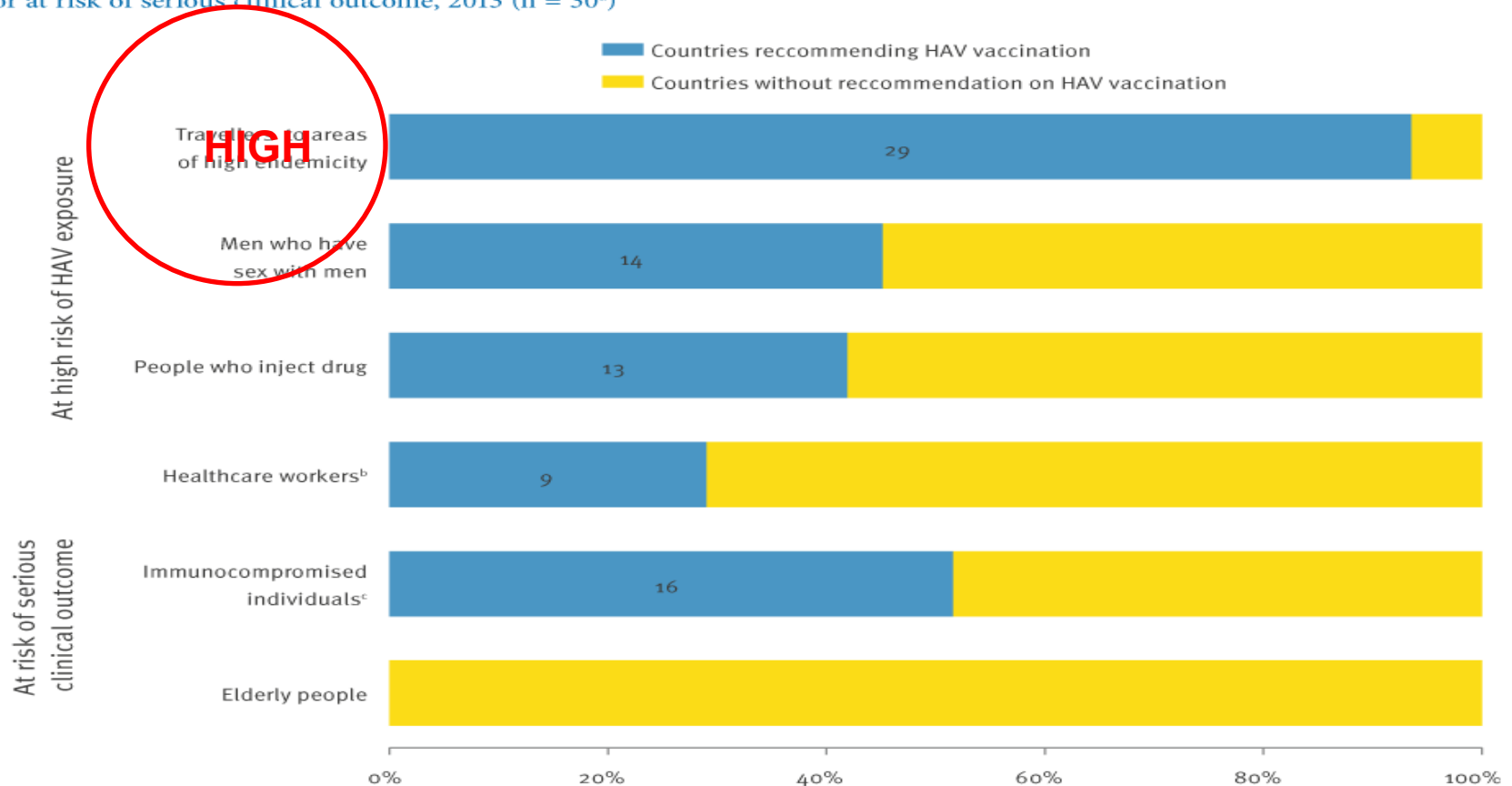


Fig. 4. Time series analysis of date of onset of hepatitis A cases ($n = 819$) for imported and domestic infections respectively, January 1996–December 2011. Imported infections (—) increased annually from August to October, peaking in September. This was followed by an increase from October to January (peaking in December) in those who were infected in the Netherlands (–).

Hepatitis A vaccine recommendations Europe

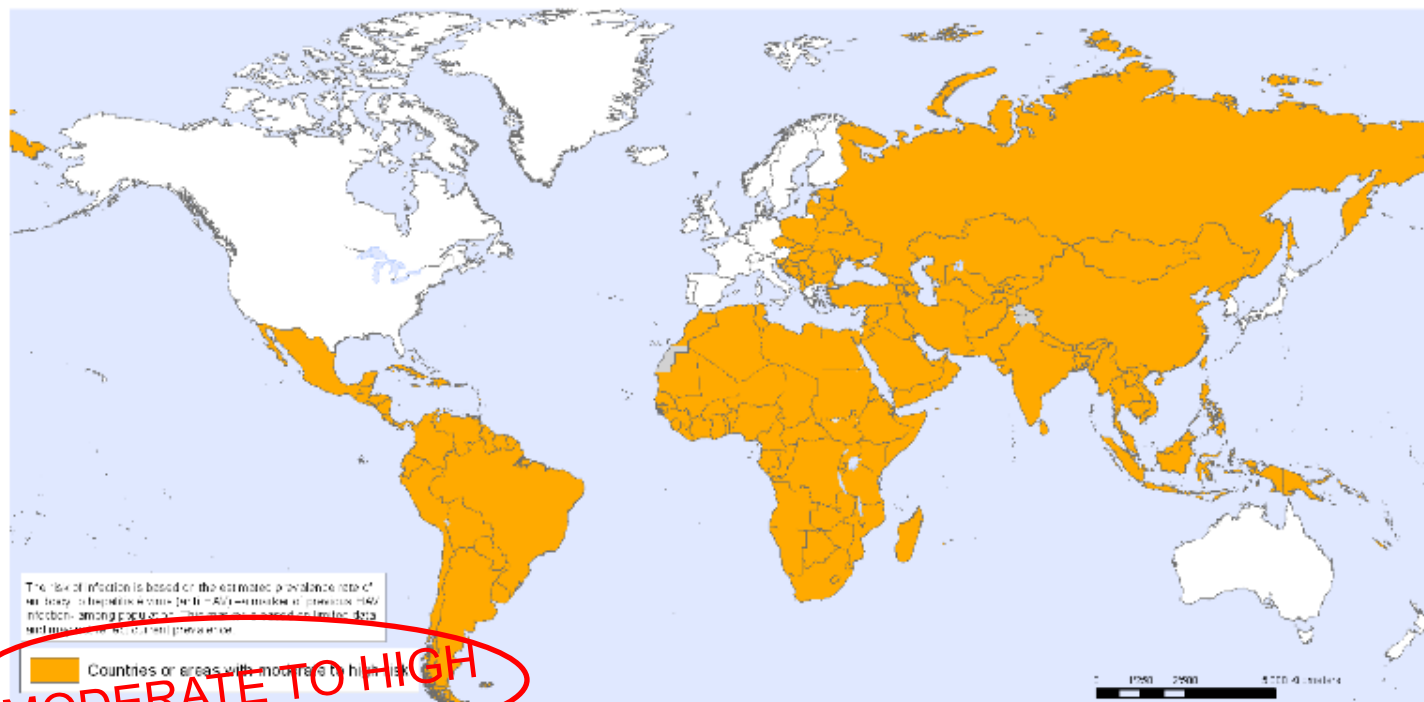
EU/EEA countries recommending hepatitis A virus vaccination to groups defined by the WHO as at high risk for exposure or at risk of serious clinical outcome, 2013 (n = 30*)



EEA: European Economic Area; EU: European Union; HAV: hepatitis A virus; HIV: human immunodeficiency virus; WHO: World Health Organization.

WHO ITH 2018

Hepatitis A, countries or areas at risk



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Data Source: World Health Organization, Jacobson KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1980 and 2006. Vaccine 2010 Sep;28(41):6653-7
 Map Production: Public Health Information and Geographic Information Systems (GIS) World Health Organization



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Hepatitis A and travel

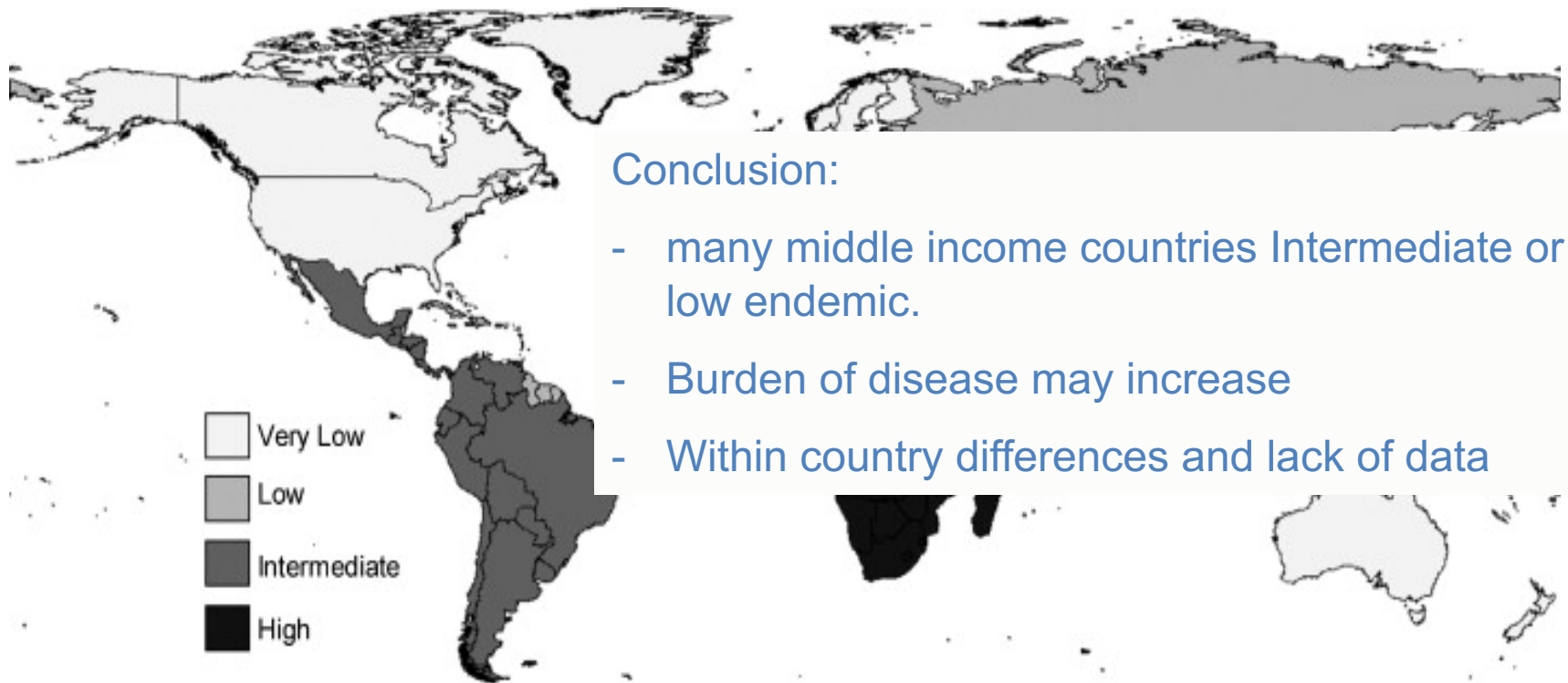


Fig. 1. Estimated prevalence of hepatitis A virus, 2005.

Contents

261 WHO position paper
on hepatitis A vaccines –
June 2012

Sommaire

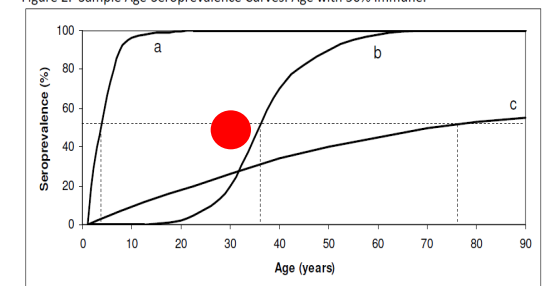
**WHO position paper on
hepatitis A vaccines – June
2012**

**Note de synthèse: position
de l'OMS concernant les
vaccins contre l'hépatite A –
Juin 2012**

Level of endemicity by age-related seroprevalence anti-HAV:

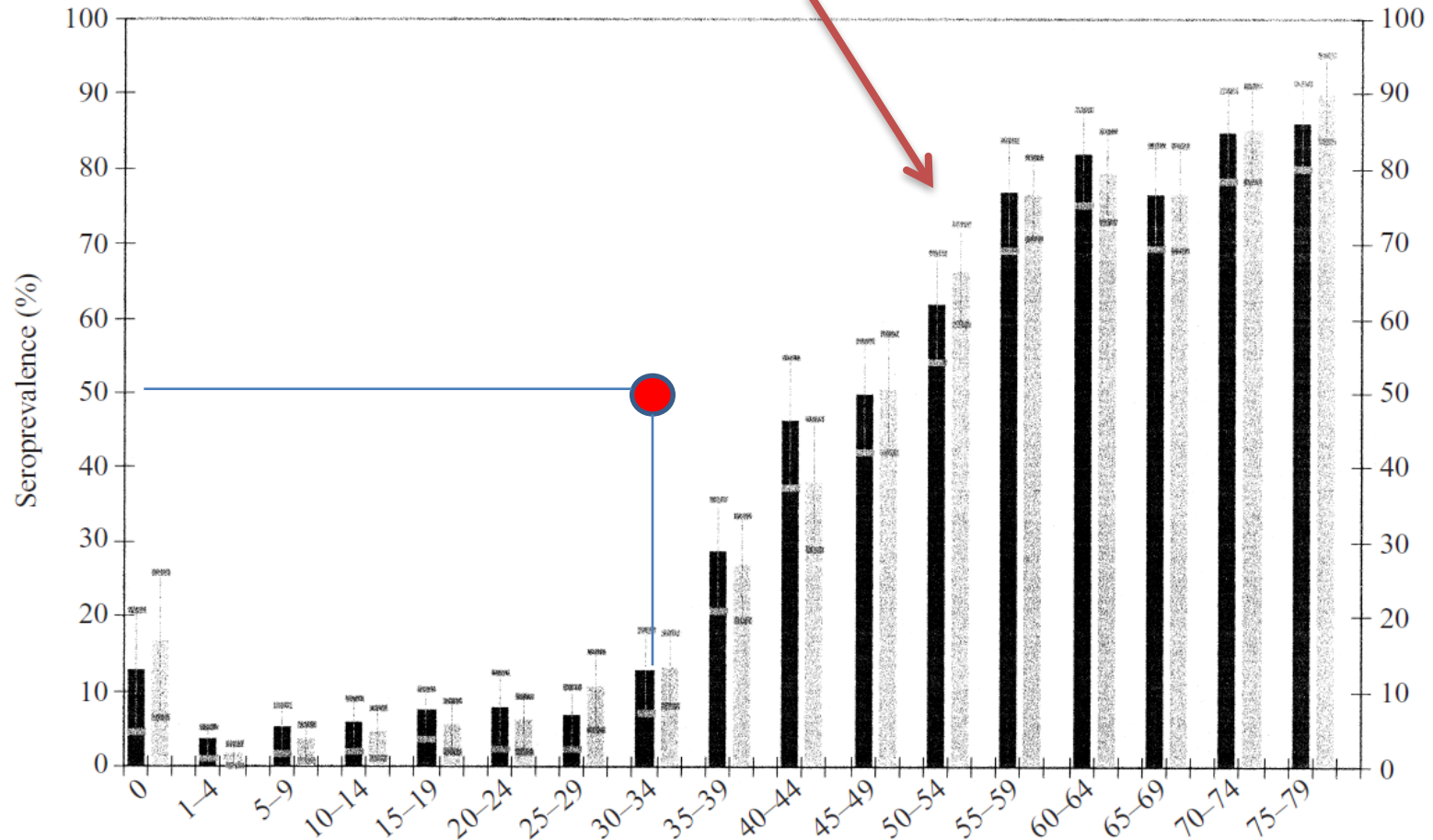
- HIGH: > 90% by age 10
- INTERMEDIATE: > 50% by age 15; <90% by age 10
- LOW: > 50% by age 30; < 50% by age 15
- VERY LOW: < 50% by age 30

Figure 2. Sample Age-Seroprevalence Curves: Age with 50% Immune.



Age related seroprevalence NL

Born 1945

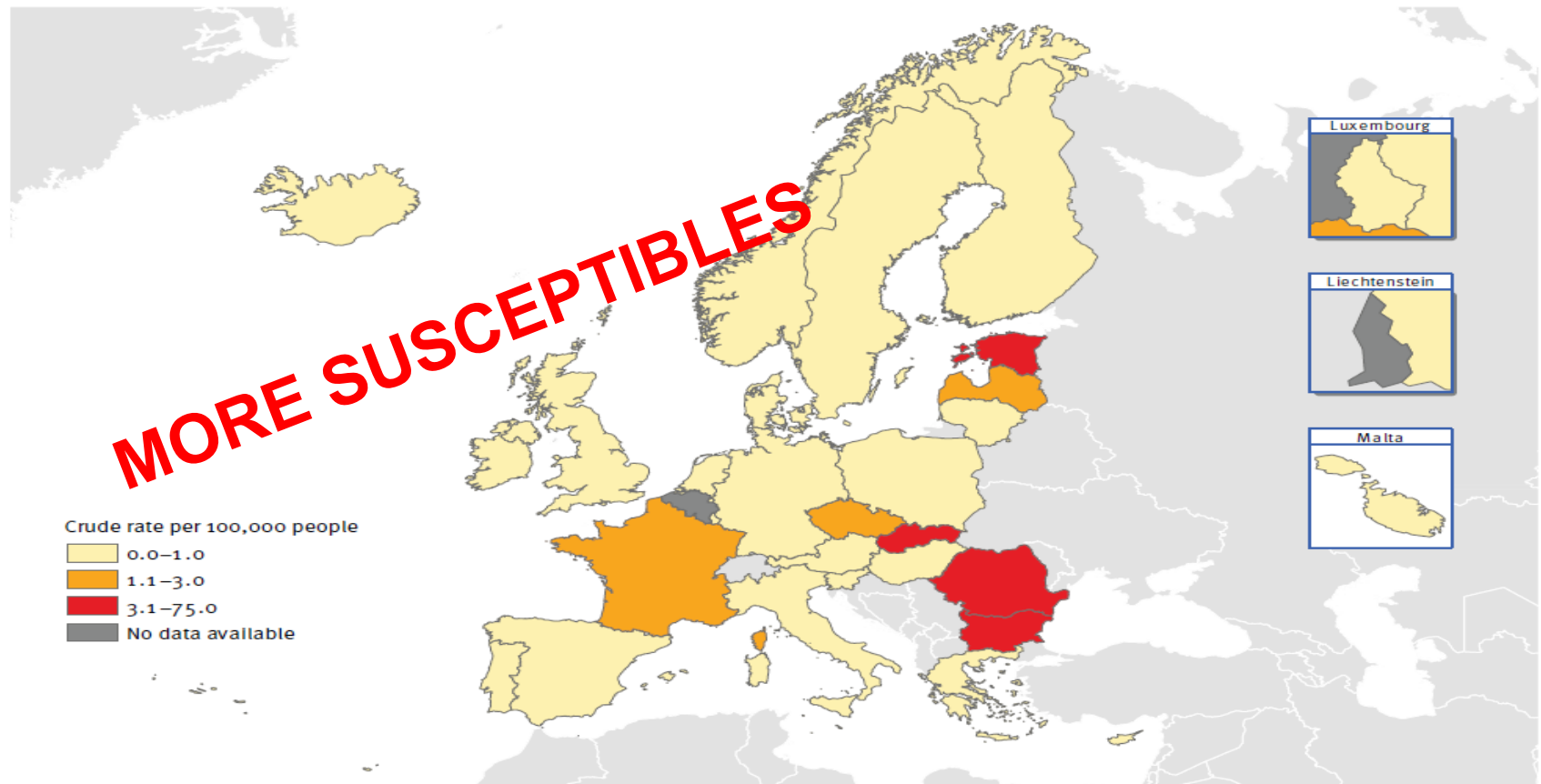


Termorshuizen et al. Epid Inf 2000
 (samples 1995-96)

Changing hepatitis A epidemiology in the European Union: new challenges and opportunities

C M Gossner (Celine.Gossner@ecdc.europa.eu)^{1,2,3}, E Severi^{1,3}, N Danielsson¹, Y Hutin⁴, D Coulombier¹

Distribution of hepatitis A crude notification rates in EU/EEA countries, 2011



EEA: European Economic Area; EU: European Union.

Hepatitis A vaccine shortage 2017



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 Map Production: Public Health Information
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 World Health Organization



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Hepatitis A vaccine shortage 2017



European Centre for Disease Prevention
An agency of the European Union

Infectious diseases & public health

Home > News & events > Epidemiological update: hepatitis A outbreak in the EU/EEA mostly affecting men who have sex with men

Epidemiological update: hepatitis A outbreak in the EU/EEA mostly affecting men who have sex with men

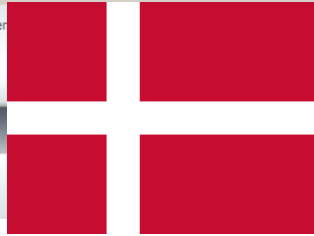
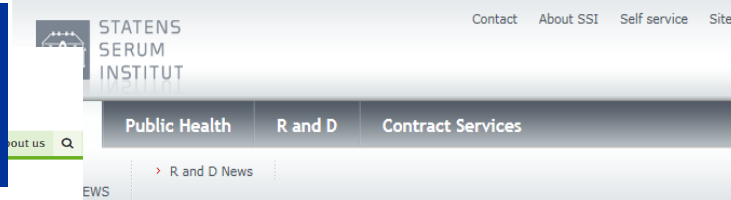
Vaccination

The main prevention EU is currently limited (and Sweden) while reported any **shortage** vaccine **shortages**, promoted and offer hepatitis A-infected implementation of t

Shortage: Austria, Denmark, Italy, Portugal, Spain and Sweden

No shortage: Belgium, Czech Republic, Estonia, Finland, Germany, Iceland, Ireland, Luxembourg and Slovenia

Shortage in some areas: Malta and the Netherlands



Search in news:

Søg

Shortage of vaccines against hepatitis A

2 November 2017

Several European countries are currently experiencing a shortage in particular of monovaccines for protection against hepatitis A, for children as well as for adults.

The shortage has arisen, among others, after one of the main manufacturers needed to discard a substantial number of hepatitis A vaccine batches two years ago. Increased consumption due to ongoing outbreaks of the disease in Europe, in men who have sex with men (MSM), among others, may also have contributed.

Hepatitis A is the type of infection of the liver you can get via contaminated food and drinking water, but it may also, in some cases, be transmitted

hepatit en vaccinbrist

FiercePharma

QUESTEX

PHARMA MANUFACTURING MARKETING PHARMA ASIA ANIMAL HEALTH DRUG DELIVERY VACCINES

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Vaccines

Merck, GlaxoSmithKline face hepatitis A vaccine shortage amid U.S. outbreaks

by Angus Liu | Nov 14, 2017 2:31pm



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Large lack of Hepatitis A vaccine

SWEDEN

There is a serious lack of hepatitis A vaccine in Sweden. The healthcare is now using replacement treatment while the supplier promises immediate delivery. "This is a big challenge I can say," says Leif Dotevall, Deputy Infection Surgeon in Västra Götaland.



Vaccine shortage worldwide

CNN

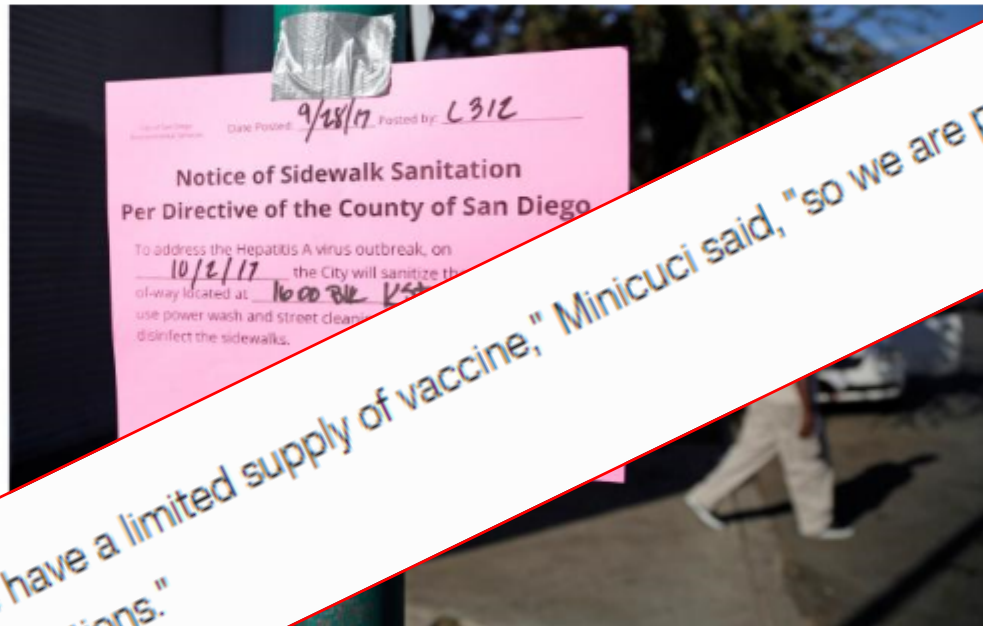
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International Edition + 🔍 ☰

During a hepatitis A emergency, there's a nationwide shortage of vaccine

by Sandee LaMotte, CNN

🕒 Updated 2230 GMT (0630 HKT) January 12, 2018



"We have a limited supply of vaccine," Minicuci said, "so we are prioritizing delivery to high-risk populations."

(CNN) — The battle against hepatitis A outbreaks across

McGregor
after bus incident



Americans urged to carry
opioid overdose antidote
naloxone



Situation Netherlands

In February 2017: shortage of hepatitis A
Adult → temporarily 2 child hepA or
combined hepA/hepB vaccine even
without hepB indication

On March 3rd: shortage of hepB vaccine;
prioritize for those most risk

In April: shortage of both hepA adult and
child





Prioritising high risk

RIVM: national center for disease control:
prioritise MSM outbreak

LCR: prioritise travelers at highest risk
restrict use of vaccin:

- Low endemicity
- Popular destinations among Dutch travelers

**The Global Prevalence of Hepatitis A
Virus Infection and Susceptibility:
A Systematic Review**

WHO 2010

www.who.int/vaccines-documents/

Age related seroprevalence Thailand

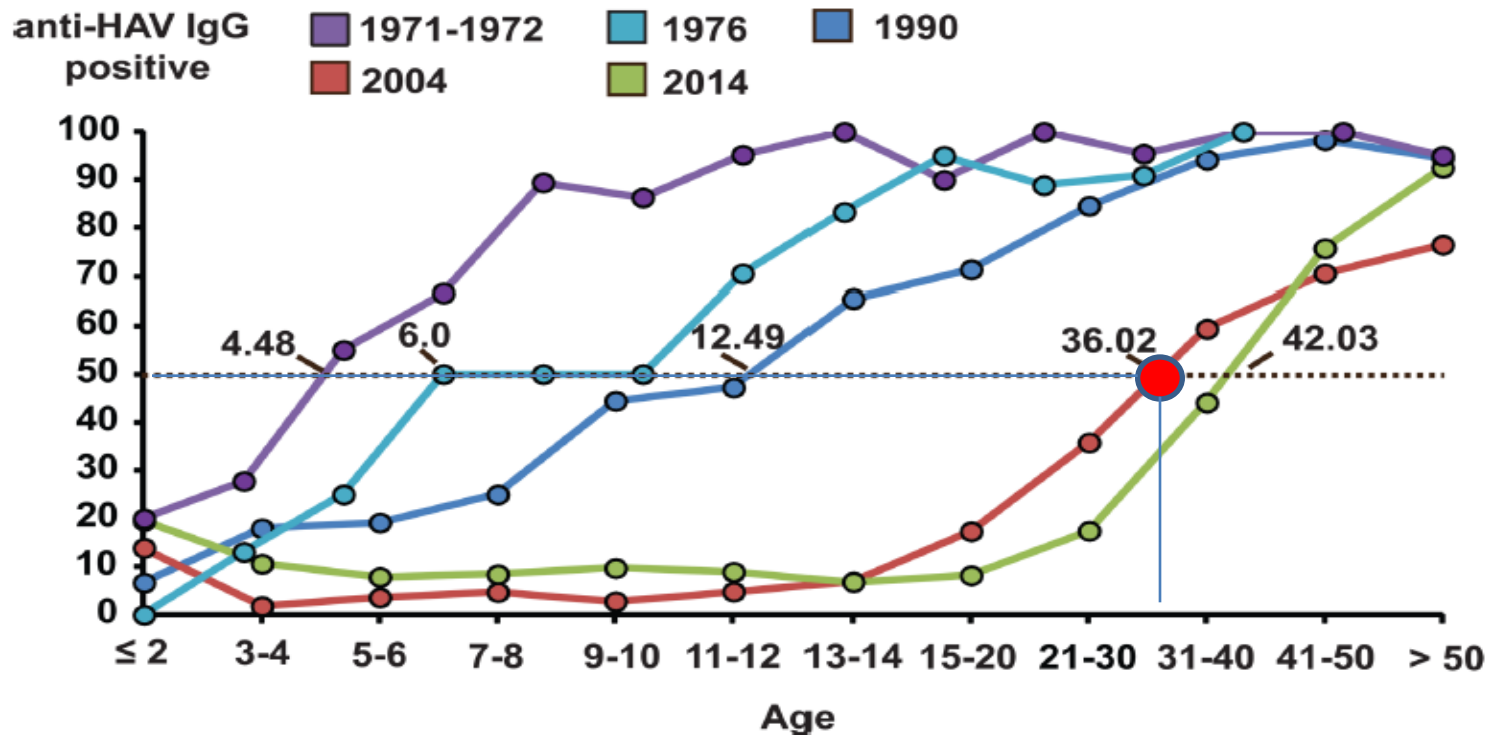


Fig 3. Comparison of anti-HAV IgG positivity from 1971 to 2014. Seroprevalence data from this and other studies were plotted as line charts. The dotted line denotes 50% anti-HAV IgG positivity. Intersection with the seroprevalence curve indicates the mean age at which 50% of the individuals in the population possessed anti-HAV IgG (denoted by the numbers on the line graphs) [16–18].

Age related seroprevalence Thailand

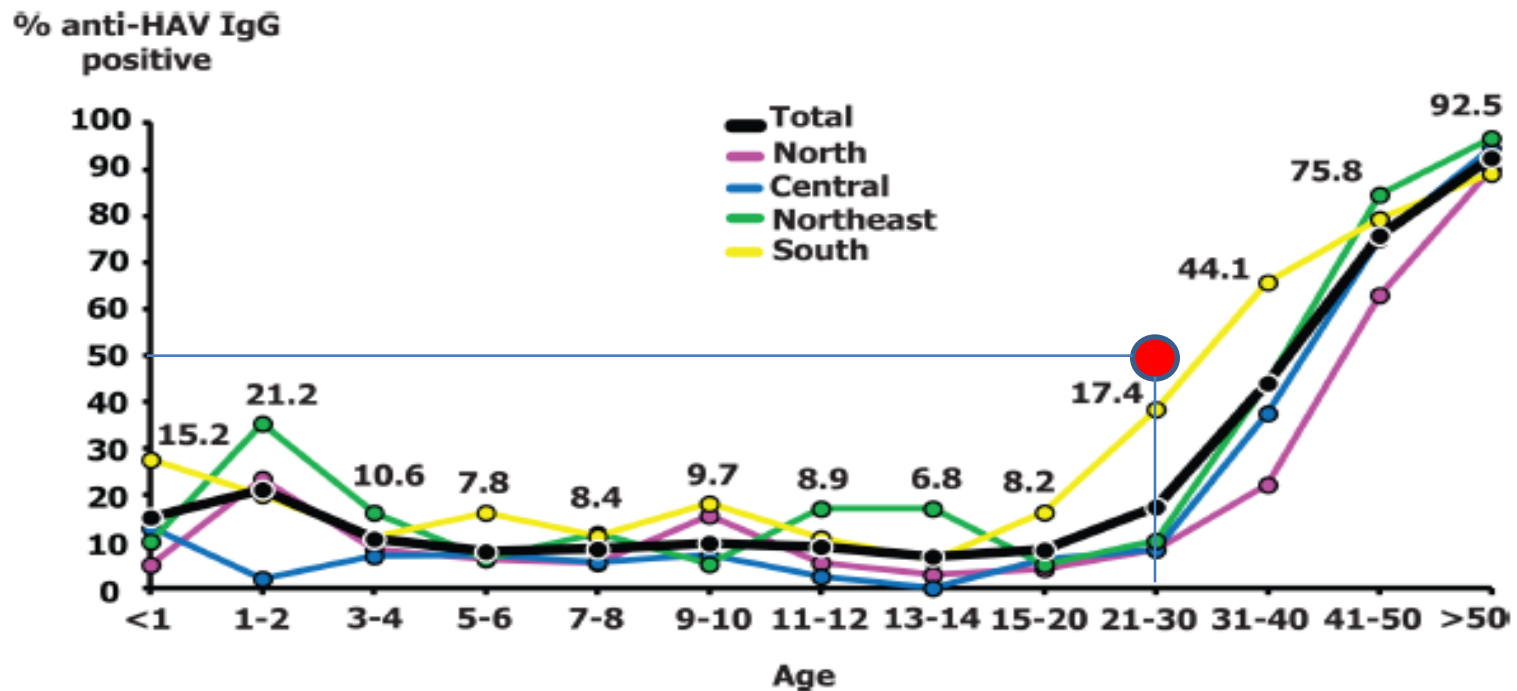
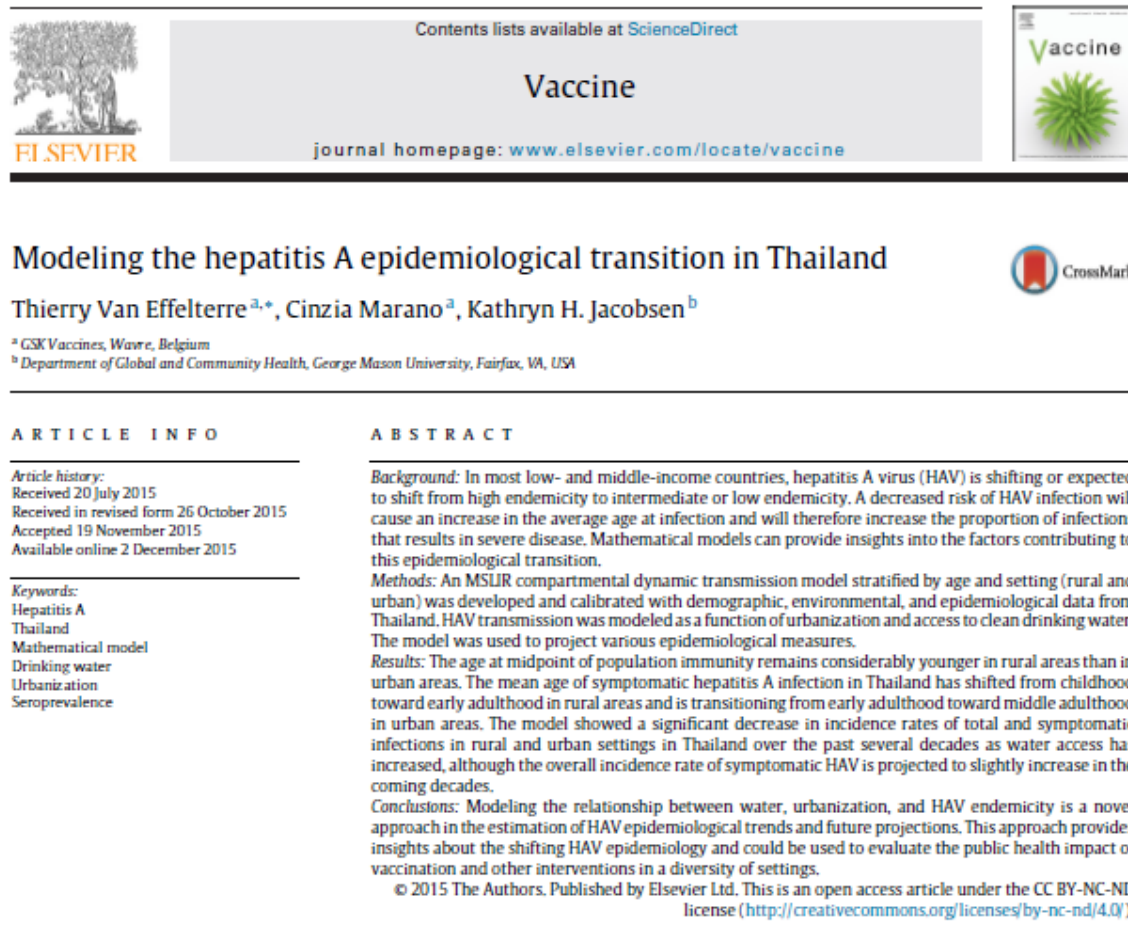


Fig 2. The frequency of anti-HAV IgG positivity in each age group. Numbers above the line charts indicate the total seroprevalence for each age group.

Modeling studies



Modeling the relationship between water, urbanization, and HAV endemicity is a novel approach in the estimation of HAV epidemiological trends and future projections

Hepatitis A virus epidemiology in Turkey as universal childhood vaccination begins: seroprevalence and endemicity by region

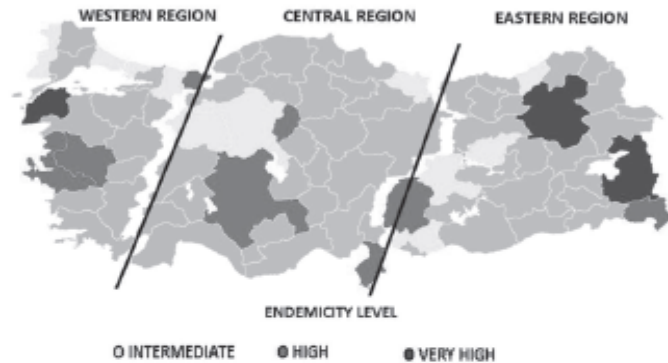
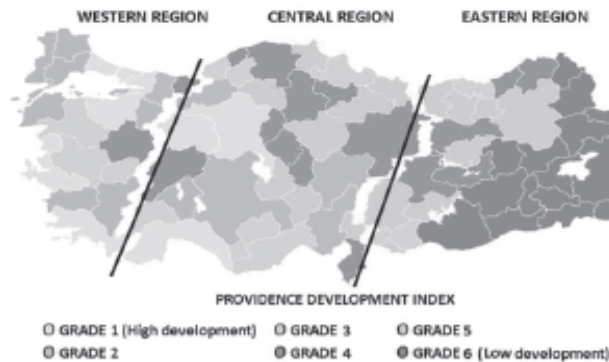


Fig. 2. Map of province development index (PDI) levels across Turkey.

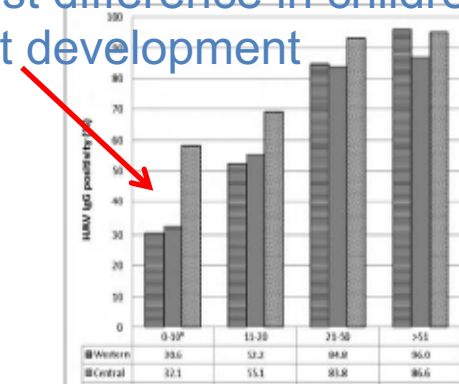


Province Development Index PDI shows clearer trend than HAV endemicity

Access to water and sanitation not significantly associated with endemicity, nor are urbanization and PDI

Migration to cities are of influence

Largest difference in children < 10: recent development





RESEARCH ARTICLE

Open Access

Vaccination coverage of children aged 12-23 months in Gaziantep, Turkey: comparative results of two studies carried out by lot quality technique: what changed after family medicine?

Birgul Ozcirpici^{1,4*}, Neriman Aydin¹, Ferhat Coskun², Hakan Tuzun³ and Servet Ozgur¹

Coverage 84-93%

“Hepatitis A and Varicella vaccines are going to be added to schedule in 2013. All routine EPI vaccines are financed by government.”

18 April 2017

Temporary change in LCR guideline:

- No hepatitis A vaccination for travelers to Turkey, Thailand (and South Africa)
- Delay boosters until 3 years after first hepatitis A vaccine (instead of 1 year)





Travel to Turkey, Thailand, South Africa?

Imported cases Netherlands (notified)

Turkey	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	5	5	8	3	0	2	1	1	1	3

Turkey 248.000 travellers in 2016-2017*

Thailand	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	-	-	-	0	0	0	0	1	0	0

Thailand 49.000 travellers 2016-2017*

South	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Africa	-	-	-	1	0	1	0	1	0	1

South Africa 52.000 travellers 2016-2017*

*Kantar market research commissioned by GSK

Vaccine shortage UK



PHE recommends that all MSM without reliable evidence of previous vaccination or infection attending GUM and HIV clinics should be opportunistically offered hepatitis A vaccination.

1.2 Dose-sparing vaccine advice

The advice is based on a broad assessment considering the following criteria:

- risk of acquiring infection
- risk of complications of infection
- immune response to vaccine products of varying antigen content
- availability and number of doses required
- fit with vaccine schedule
- in settings
- already being immune

Hepatitis A vaccination in adults- temporary recommendations

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15 Jun 2017



CHANGES TO THE COUNTRY INFORMATION PAGES: HEPATITIS A VACCINE RECOMMENDATIONS

NaTHNaC has reviewed and updated the hepatitis A country specific information and vaccine recommendations to provide up-to-date recommendations for travellers and travel health professionals

Advice for health professionals

HAV is usually a sub-clinical infection (without symptoms) in young children. However, the disease becomes more serious with advancing age, with an approximate mortality (death) rate of two percent in those over 50 years of age.

Vaccination is recommended for most travellers to countries with a high burden of HAV.

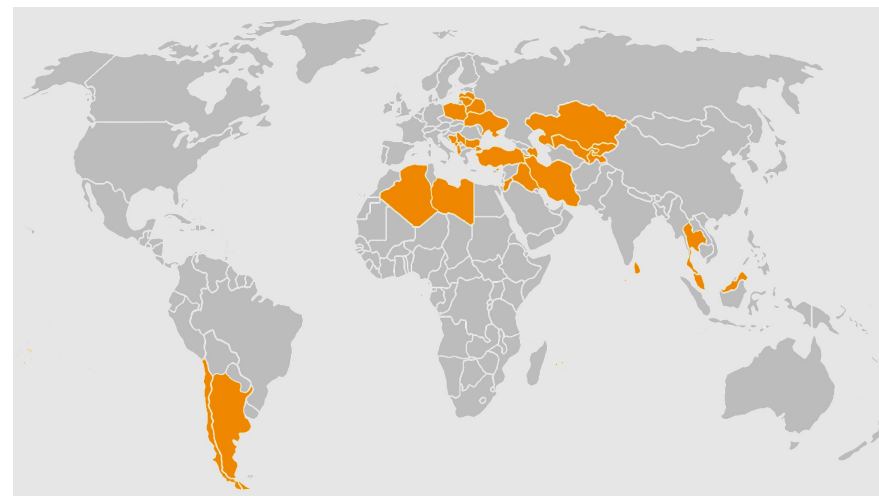
In countries where there is a lower risk of HAV factors such as access to improved sanitation, travel plans, activities, and medical conditions should be considered in the risk assessment.

Travellers who may be at increased risk of hepatitis A infection include:

- those staying with or visiting the local population
- frequent/long-stay travellers to areas where sanitation and food hygiene are likely to be poor
- adventure travellers visiting rural areas and staying in basic accommodation
- those with existing medical conditions such as liver disease or haemophilia
- men who have sex with men
- people who inject drugs
- those going to areas of hepatitis A outbreaks who have limited access to safe water and medical care

Based on this review:

Country specific vaccine recommendations have been updated for the following countries: Albania, Algeria, Argentina, Azerbaijan, Belarus, Belize, Bosnia and Herzegovina, Bulgaria, Chile, Cuba, Fiji, Guyana, Iran, Iraq, Jordan, Kazakhstan, Kyrgyzstan, Latvia, Libya, Lithuania, Malaysia, Maldives, Mauritius, Montenegro, Palau, Poland, Réunion (France), Samoa, Serbia, Sri Lanka, Tajikistan, Thailand, Tonga, Turkey, Ukraine, and Uzbekistan.





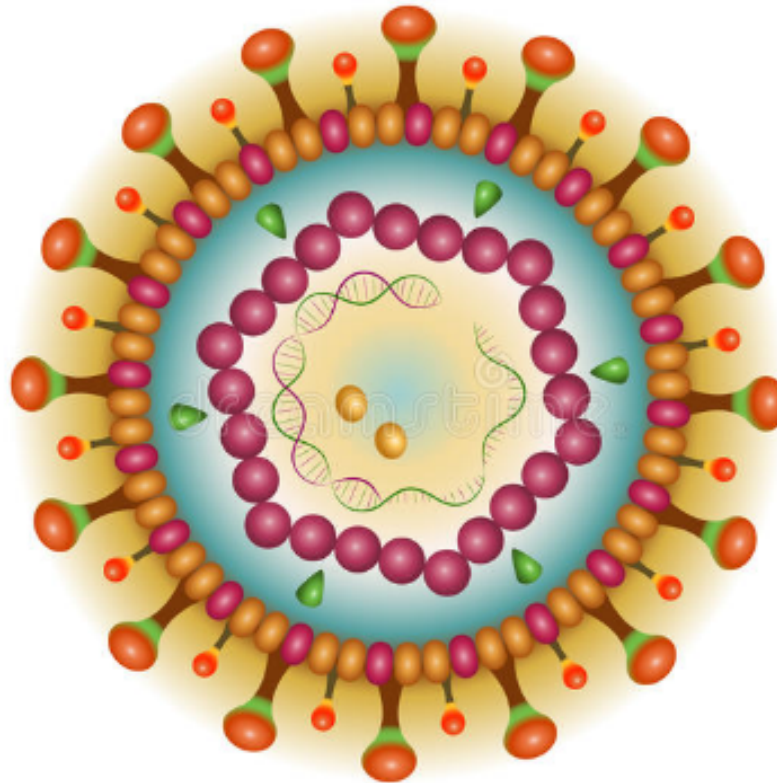
Conclusions hepatitis A

- Worldwide vaccine shortages have suddenly urged us to reconsider indication for travelers; vaccine has been prioritised for highest risk groups

Hepatitis A endemicity is changing rapidly as a result of growing economies, risks for travelers decline

- Seroprevalence and modelling studies become more widely available in the last few years
- This leads to different recommendations between (European) countries

Hepatitis B





Hepatitis B and travel

Relation hepatitis B and travel less obvious than hepatitis A

- Longer incubation/wider range up to 6 months
- High-risk destinations did not correlate with the destination country's prevalence of hepatitis B surface antigen*
- More related to behavior than hepatitis A / different exposure



Hepatitis B and travel

Behavioral studies: 33-76% at risk

Zuckerman JTM 2000 Connor JTM 2006 Streeton JTM 2006

Prospective study: 2/7887 infections in
travelers of which 2/97 worked abroad and
0/7317 vacationers

Steffen JID 1987

Retrospective study: risk for tourists very
low; immigrants (VFR) significantly higher
irrespective of travel

Sonder JTM 2009

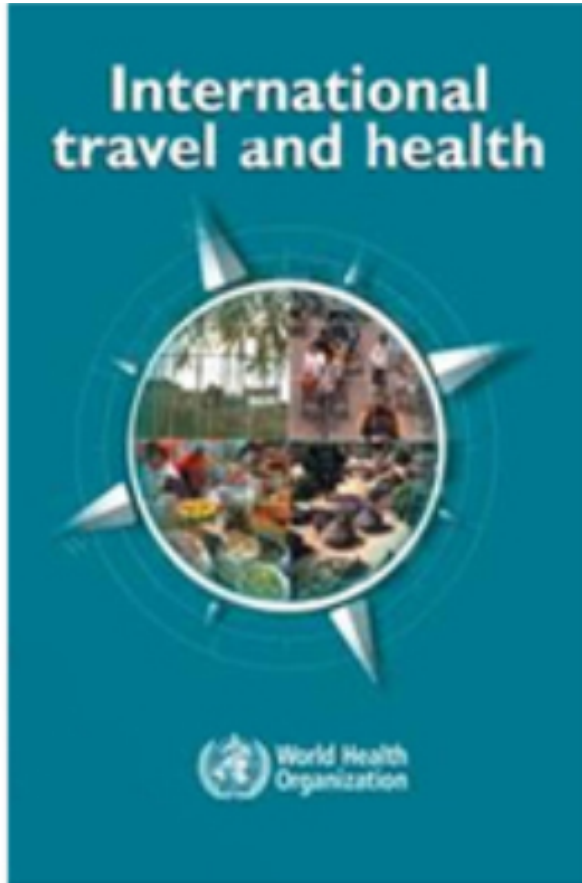


Hepatitis B and travel

Case control study: risk increases with journey length and travel alone or with friends instead of partner

Nielsen J Inf 2012

WHO ITH

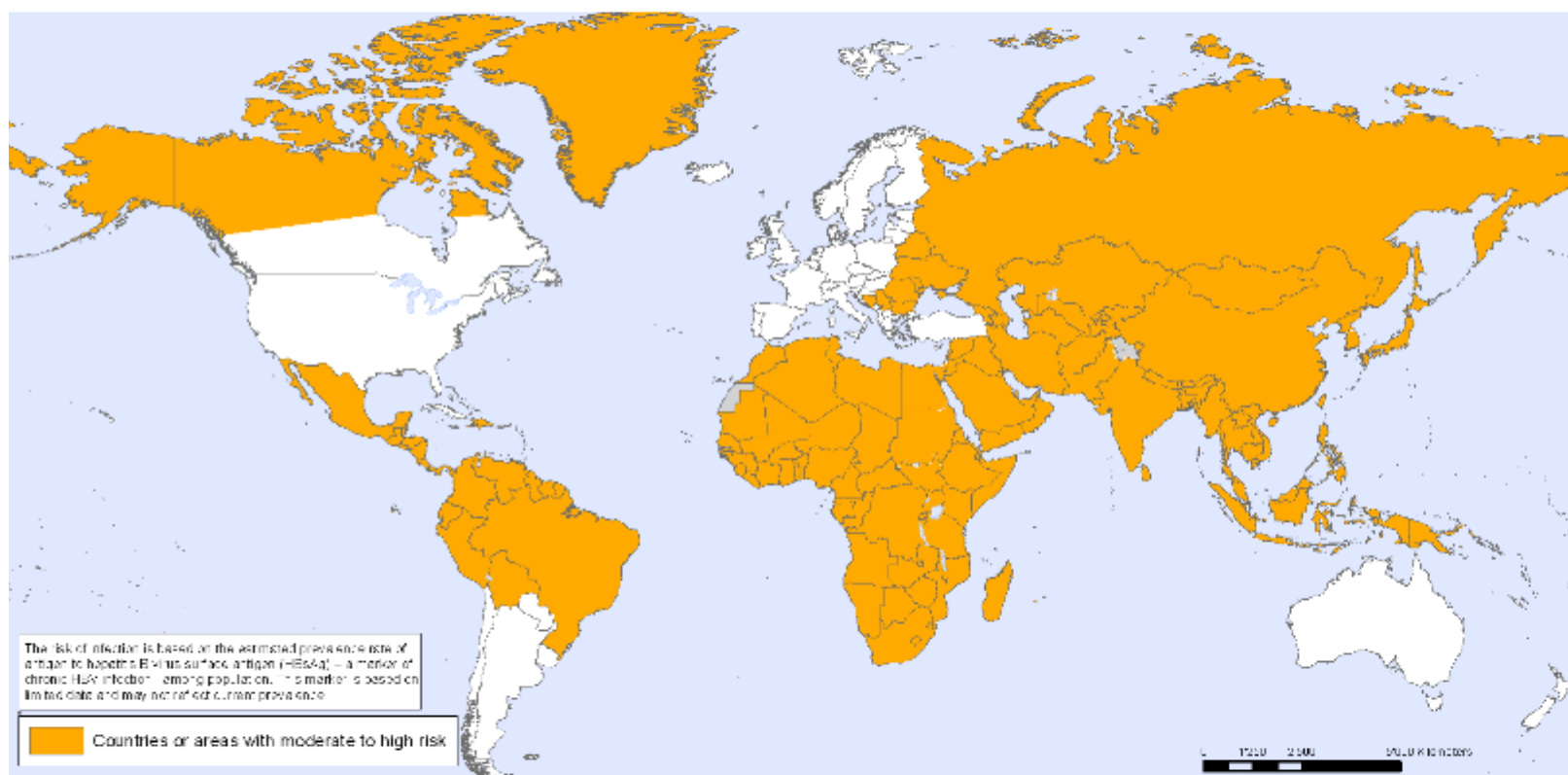


-depends mainly on personal risk taking behaviour and the prevalence of HBsAg

-hepatitis B is unlikely to be increased for the average traveller.

Hepatitis B and travel

Hepatitis B, countries or areas at risk



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Data Source: World Health Organization/CDC
 Map Production: Public Health Information
 and Geographic Information Systems (GIS)
 World Health Organization

Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013

Aparna Schweitzer, Johannes Horn, Rafael T Mikolajczyk, Gérard Krause, Jödis J Ott

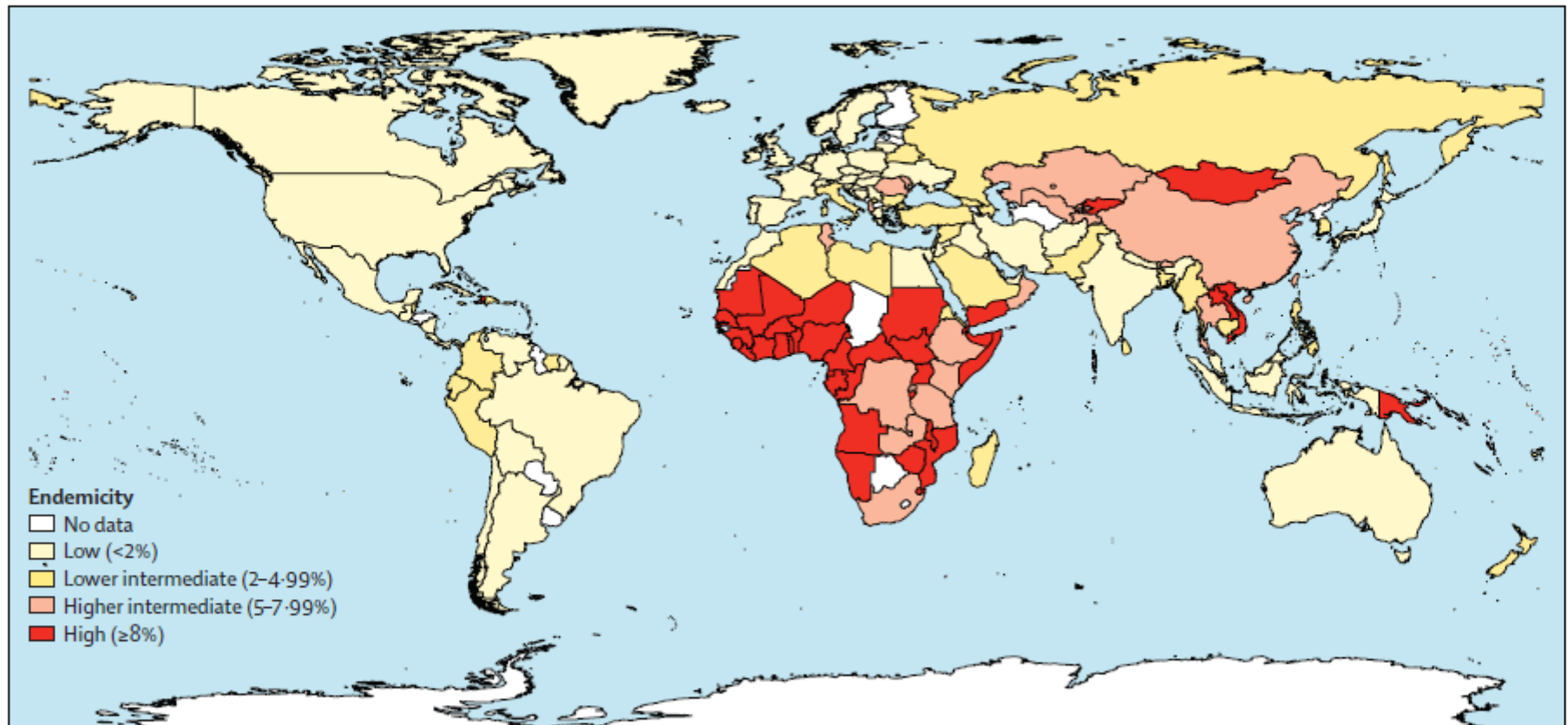


Figure 2: Global HBsAg endemicity (1957-2013)

Schweitzer et al. Lancet 2015



Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013

Aparna Schweitzer, Johannes Horn, Rafael T Mikolajczyk, Gérard Krause, Jödis J Ott

Conclusions:

- HBsAg prevalence worldwide: 3,61%
- Estimated 248 million HBV carriers
 - » 74 million China; 17 million India; 15 million Nigeria
- Decrease in prevalence in several countries
 - » Thailand, India, China, S Korea, Malaysia, Singapore
- Prevalence may increase in low endemic countries by immigration

Limitation:

- most individuals 16-50 year, *recent vaccination effects missing*



Introduction HBV vaccine Asia

Table 1 Prevalence of chronic hepatitis B and coverage of expanded program on HBV immunization in Asian countries receiving a high number of travelers [10, 12, 14]

Arrival Country	International traveler's arrivals per year (2014)	Estimated prevalence of chronic hepatitis B infection ^a	Estimated HBsAg positive population	Implement of Expanded program of immunization (EPI) for HBV (Year)	Complete HBV vaccination at year 2014 (%)	Population age after EPI deployed at year 2016
China	55,622,000	5.49 %	74,601,204	2000	99	16
Malaysia	27,437,000	0.74 %	208,540	1989	96	27
Thailand	24,780,000	6.42 %	4,260,008	1992	99	24
Saudi Arabia	15,098,000	3.18 %	866,675	1990	98	26
South Korea	14,202,000	4.36 %	2,111,914	1995	99	21
Japan	13,413,000	1.02 %	1,294,431	No	No	0
Singapore	11,858,000	4.09 %	207,943	1990	97	26
Indonesia	9,435,000	1.86 %	4,468,684	1992	78	24
India	7,703,000	1.46 %	17,553,389	2004	70	12
Vietnam	7,874,000	10.79 %	9,607,438	2003	95	13
Philippines	4,833,000	4.63 %	4,326,212	1995	79	21
Cambodia	4,503,000	4.05 %	581,596	2006	97	10
Jordan	3,990,000	1.86 %	119,919	1995	98	18
Myanmar	3,081,000	3.40 %	1,765,643	2003	75	13
Laos	2,510,000	8.74 %	558,710	2003	88	13

Estimated at year 2015 based on data on prevalence of chronic HBV infection published between Jan 1, 1965, and Oct 23, 2013^a

Introduction HBV vaccine

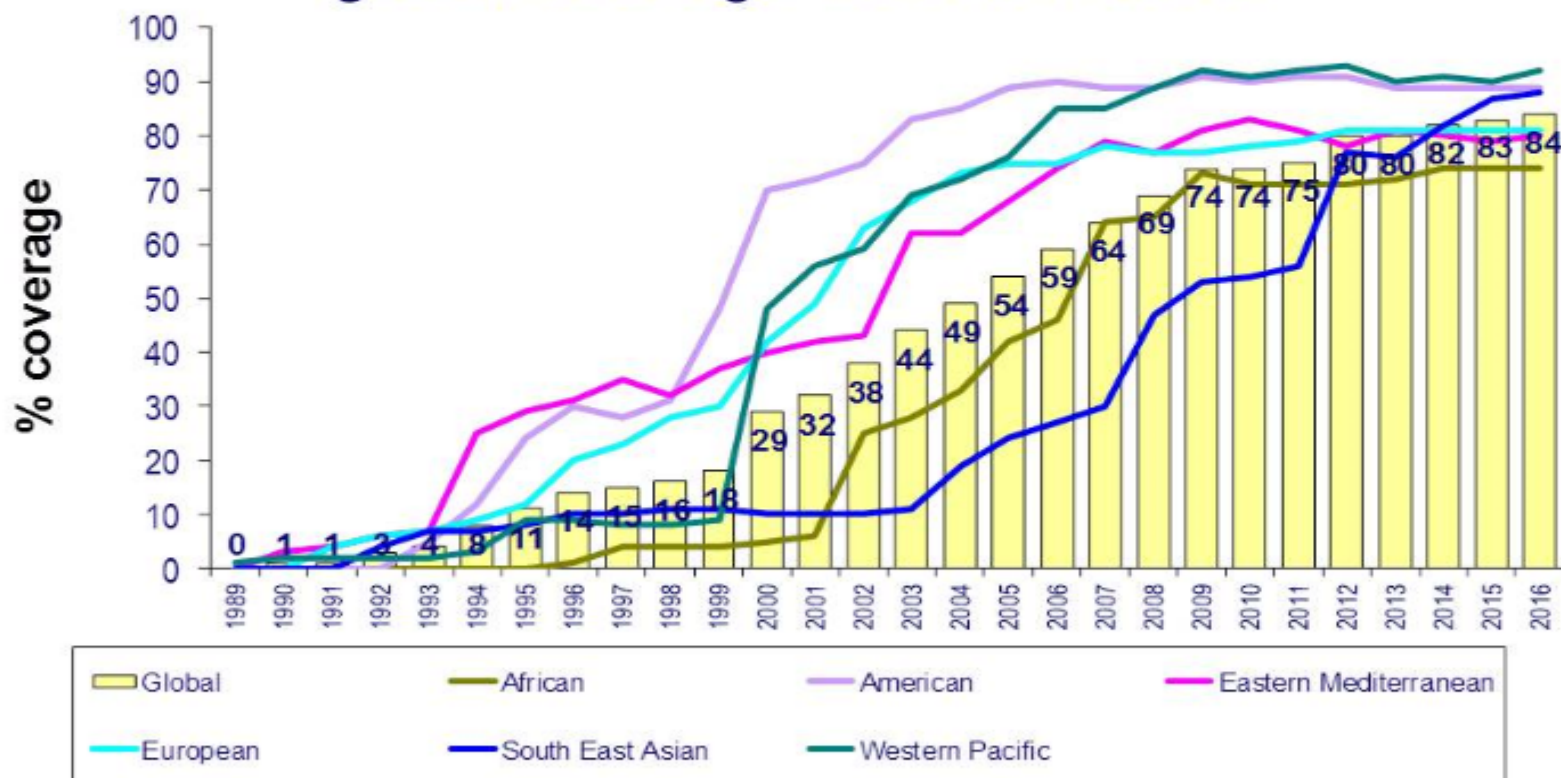
Table 2 Prevalence of CHB and coverage of expanded program on HBV immunization in international traveler's to Asia departure countries outside Asia [12–14]

Region	Country	International traveler's departures per year (2013)	Estimated prevalence of chronic hepatitis B infection ^a	Estimated HBsAg positive population	Start of Expanded Program of Immunization (EPI) for HBV (Year)	Complete HBV vaccination (%)	Number of years since EPI deployed, at year 2016
N. America	USA	61,569,000	0.27 %	843,724	1993	90	23
	Canada	32,977,000	0.76 %	260,865	2003	75	13
S. America	Mexico	15,911,000	0.20 %	237,858	2000	84	16
	Argentina	7,544,000	0.77 %	312,806	2002	94	14
Europe	United Kingdom	58,510,000	0.01 %	3,300	Not started	N/A	N/A
	Russia	54,069,000	2.73 %	3,926,499	2001	97	15
	Italy	27,798,000	2.52 %	1,533,546	1991	84	25
	France	26,243,000	0.01 %	1,533,546	1991	84	25
	Ukraine	23,761,000	0.01 %	1,533,546	1991	84	25
	Netherlands	18,094,000	0.01 %	1,533,546	1991	84	25
	Hungary	15,997,000	0.01 %	1,533,546	1991	84	25
	Sweden	15,917,000	0.01 %	1,533,546	1991	84	25
Oceania	Spain	11,246,000	0.01 %	1,533,546	1991	84	25
	Australia	8,768,000	0.01 %	1,533,546	1991	84	25
	New Zealand	2,193,000	4.11 %	179,357	1992	93	24
Africa	South Africa	5,168,000	6.70 %	3,445,477	1997	74	19
	Uganda	378,000	9.19 %	3,123,886	2002	78	14

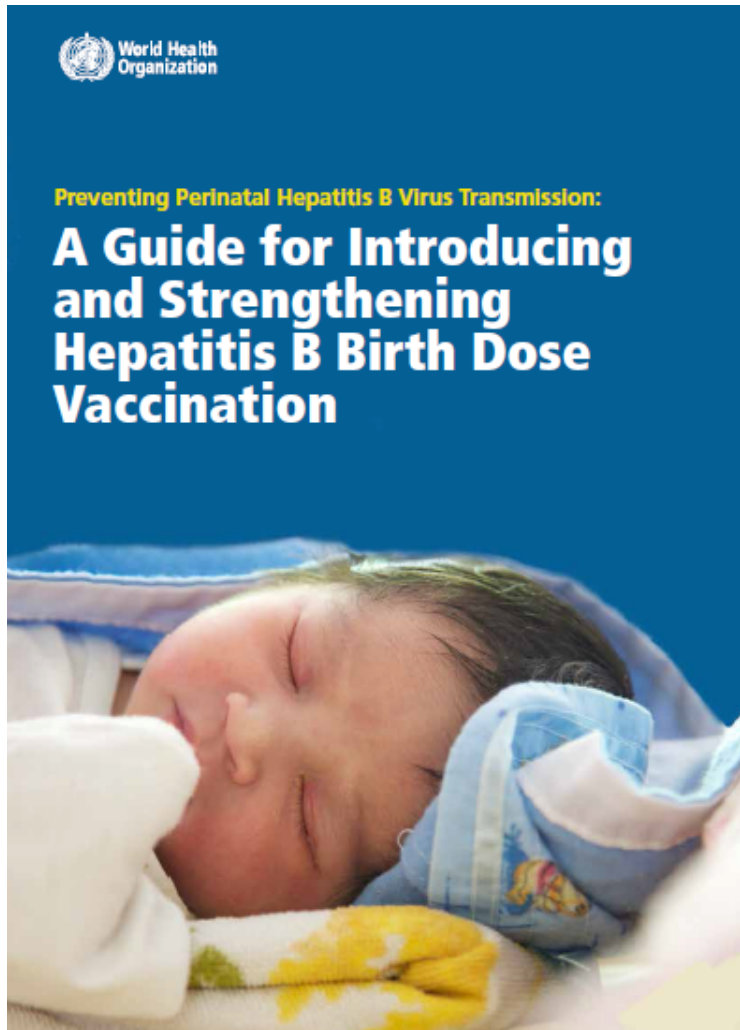
Conclusion: Vaccination should be considered for travelers to Asia, especially those engaging in casual sex, tattoos, piercings, medical procedures, those who travel longer, and those who are born after implementation of HBV vaccination in their country

^a Estimated at year 2015 based on data on prevalence of chronic HBV infection published between Jan 1, 1965, and Oct 23, 2013

Global Immunization 1989-2016, 3rd dose of Hepatitis B (HepB3) coverage in infants global coverage at 84% in 2016



Vertical transmission



Vaccination < 24 hours

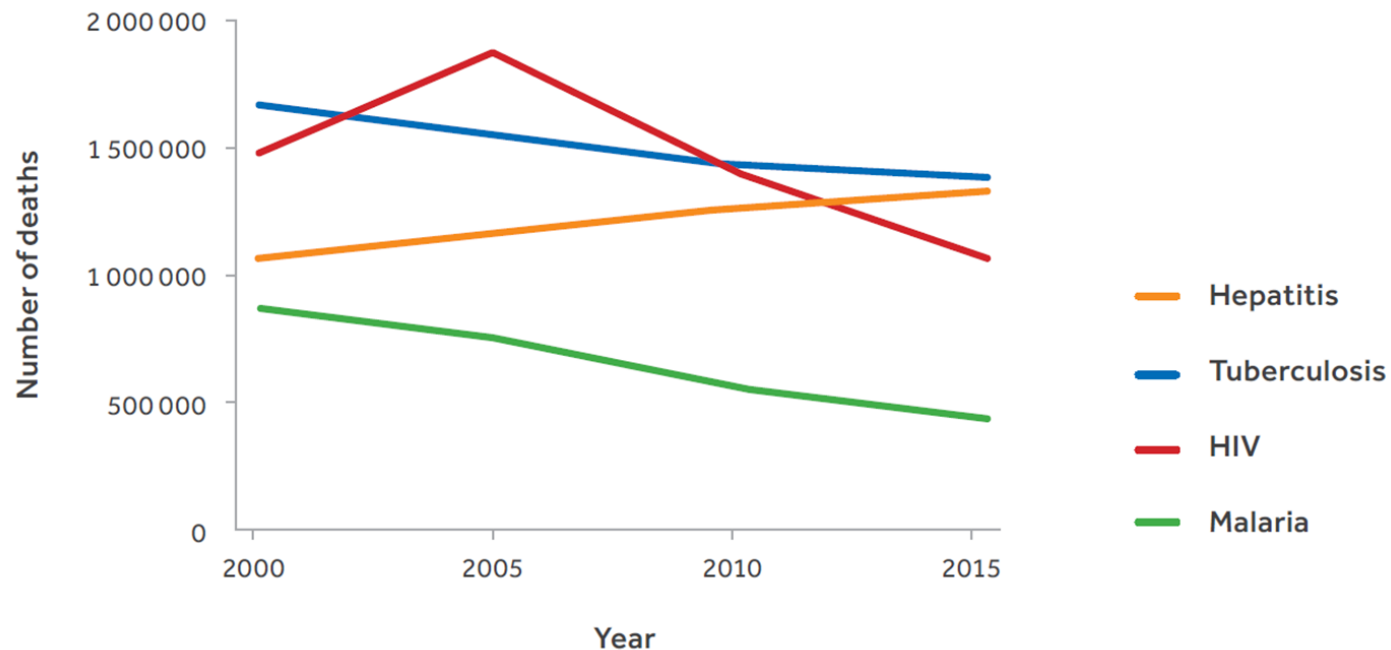
Pregnancy screening in low endemic countries (in NL since 1989)

Worldwide < 5 year old children infected

4.7% ➡ 1.3%

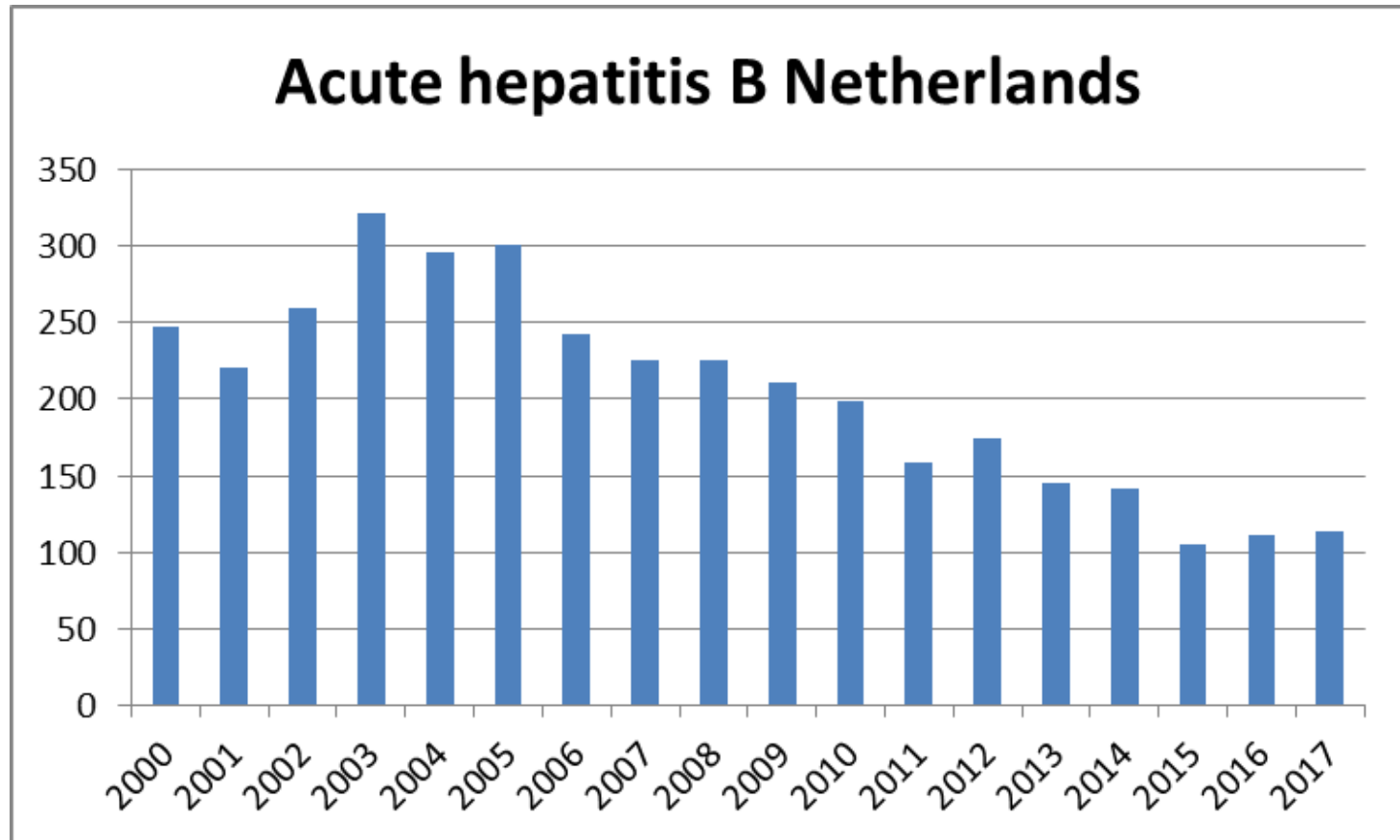
Mortality viral hepatitis

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

Acute hepatitis B NL



Source: RIVM 2018

Disease data from the ECDC Surveillance Atlas

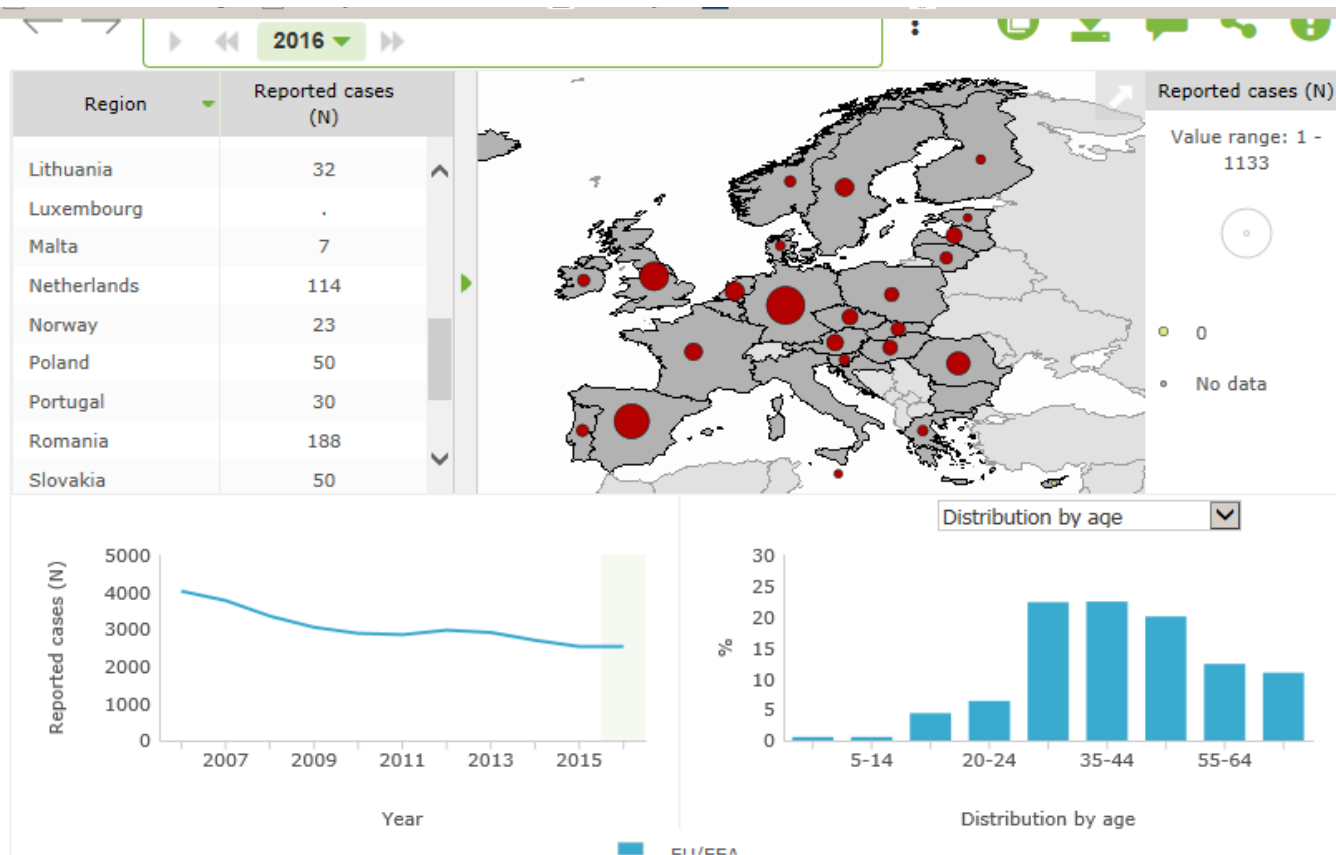
See the latest available data on hepatitis B

[Go to the Atlas](#)

Disease data from the ECDC Surveillance Atlas

World Hepatitis Day

European Test Finder





Hepatitis B vaccine shortage

Open Access News Government News Health & Social Care News

Global Shortage of hepatitis B vaccine caused by manufacturing process

March 2, 2018

Health pro
manufactu
hepatitis B

Current update

**Prioritise within countries
for highest risk groups**

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News story

Current global shortage of hepatitis B vaccine

There is currently a global shortage of hepatitis B vaccine which has been caused by problems in the manufacturing process.

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symptom of chronic neglect?

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Private market hepatitis B shortage





Conclusions

Hepatitis A and B epidemiology are changing rapidly

Vaccine shortages have forced countries to adjust guidelines

Differences in recommendations between countries have probably increased

'Prioritize those at highest risk' coordination necessary and possible?