Hepatitis B Virus
A Global Perspective

Lausanne, January 10, 2013

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HBV infection in a nutshell

- 2 billion persons have been into contact with HBV
- 240,000,000 are chronic HBsAg carriers
- Most new infections occur in high endemicity countries *via* the mother-to-child route
- 25% die because of long-term sequelae of chronic hepatitis B (cirrhosis and/or hepatocellular carcinoma)
- Vaccination may reduce mortality by >85%

HBV infection

- The changing epidemiology in the West
- The health burden
- HBV vaccination

HBV infection

- The changing epidemiology in the West
- The health burden
- HBV vaccination

Global HBsAg prevalence (%)

(source: WHO, CDC)

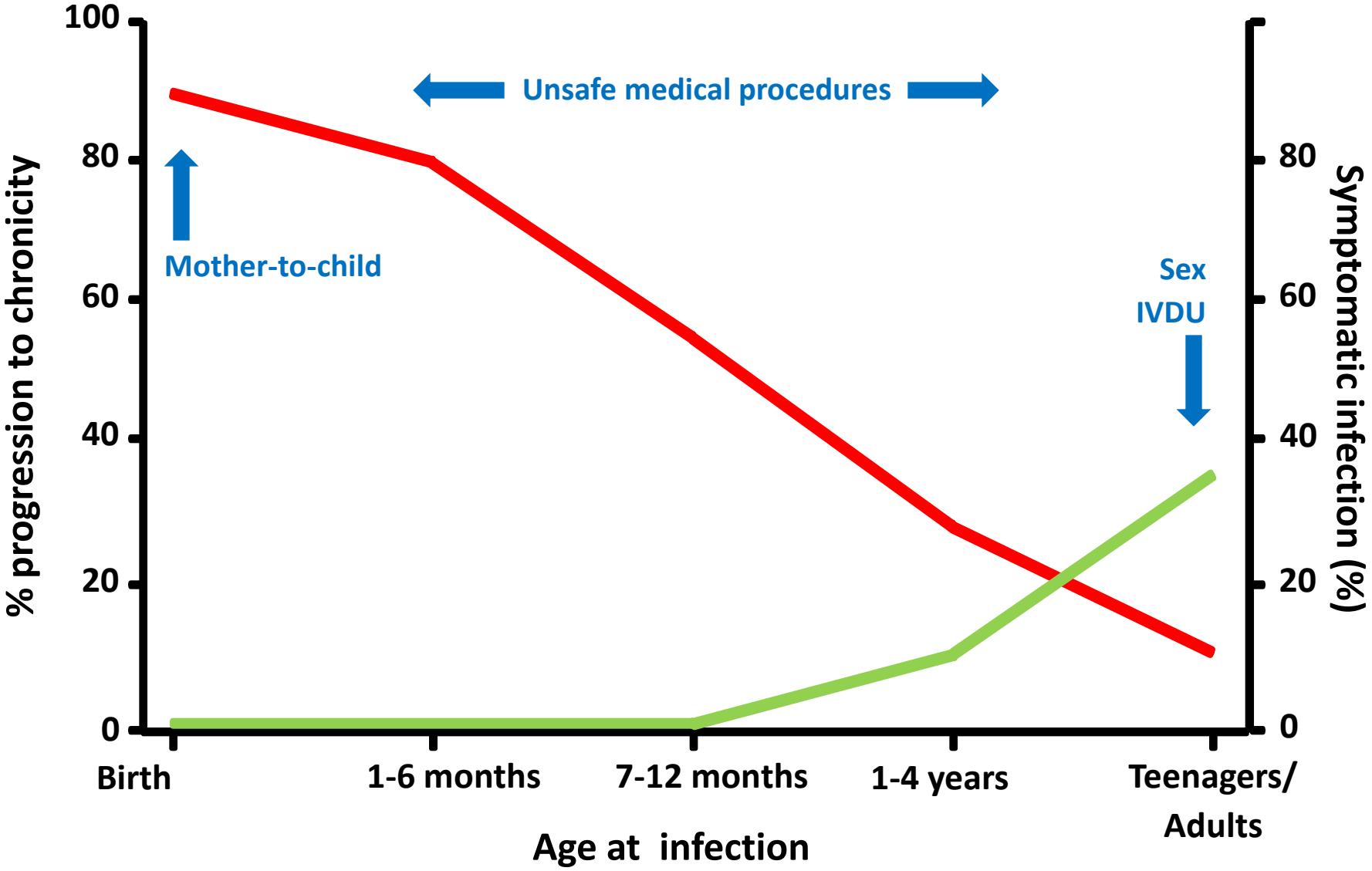
	Males	Females	All
1990	118 million (4.4)	105 million (4.0)	223 million (4.2)
2005	127 million (3.9)	113 million (3.5)	240 million (3.7)

OTT *et al,* Vaccine 2012;30:2212-9

Concentration of HBV in different biological fluids

High	Moderate	Weak or undetectable
blood	sperm	urines
serum	vaginal	feces
wound	secretions	sweat
exudates	saliva	tears
		milk

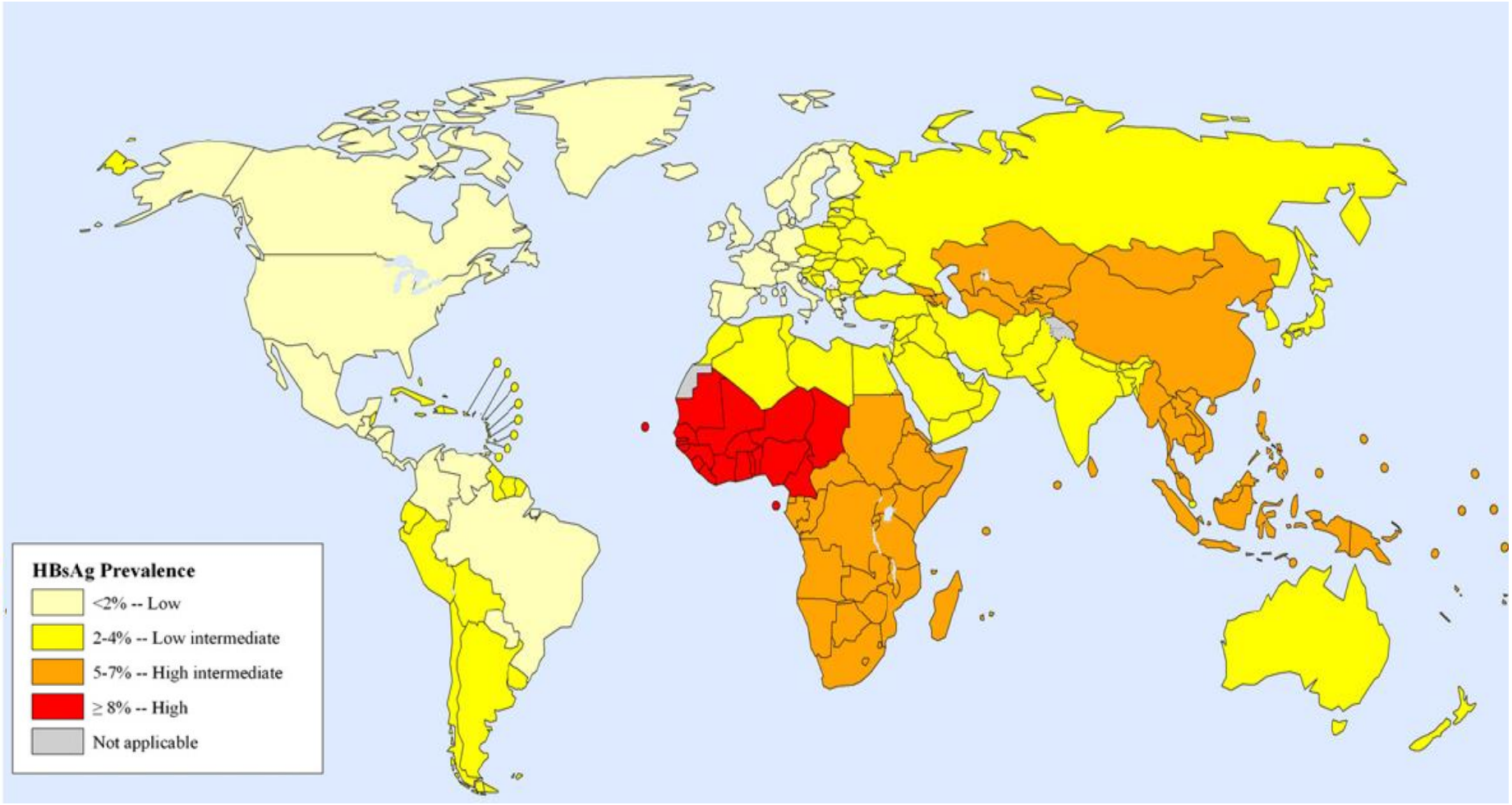
Progression of HBV infection to chronicity depends on the age at infection



Levels of endemicity of HBV

- **High** (>8%): 45% of infections globally
  - Frequently acquired at birth or during early infancy
- **Intermediate** (2%-8%): 43% globally
  - Infections occur throughout life
- **Low** (<2%): 12% globally
  - Frequent in high-risk adults

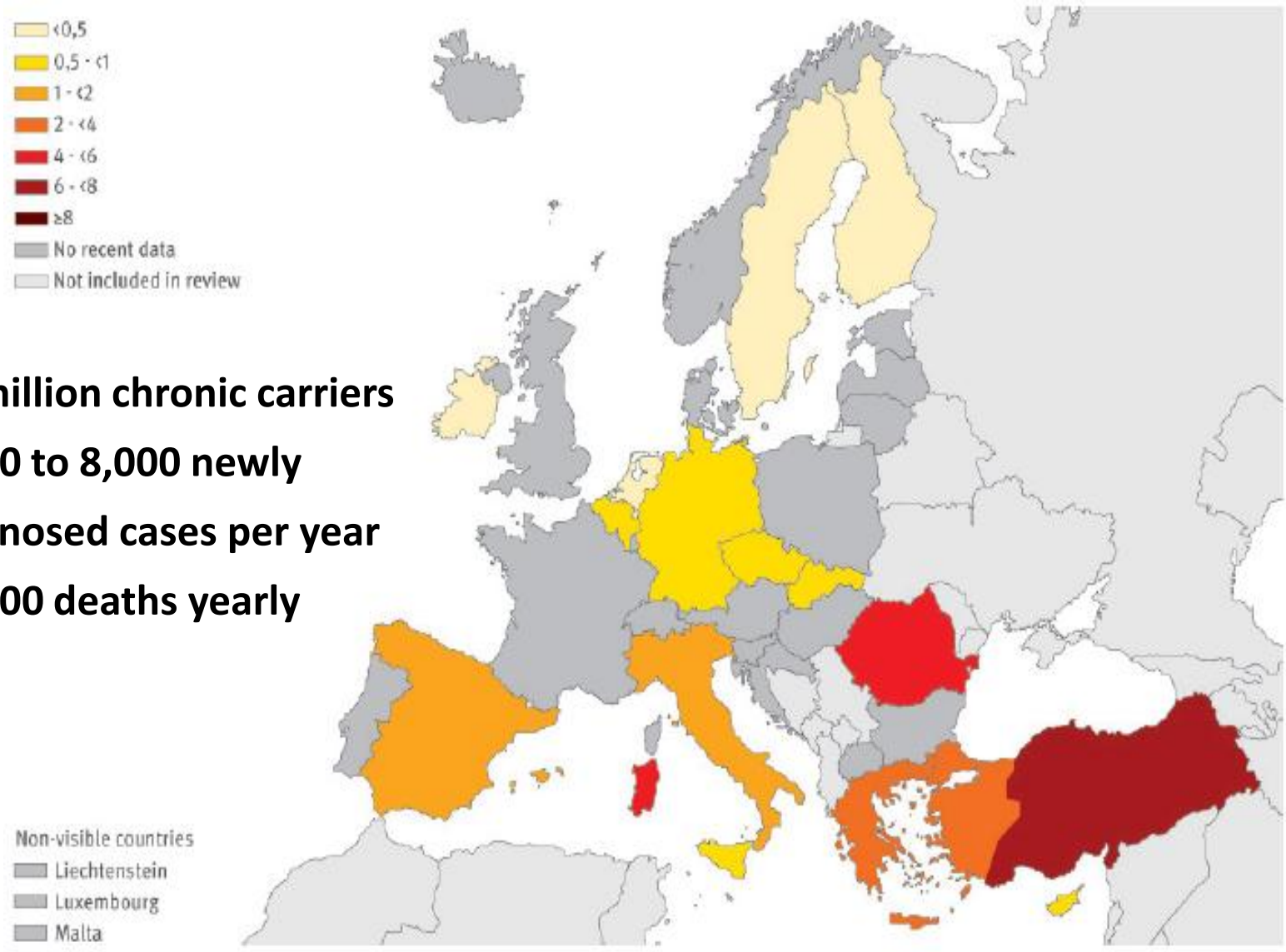
Prevalence of HBV infection (adults, 19-49 years, 2005)



OTT *et al,* Vaccine 2012;30:2212-9

www.ecdc.europa.eu

HBsAg Prevalence in Europe



- **14 million chronic carriers**
- **7,000 to 8,000 newly diagnosed cases per year**
- **36,000 deaths yearly**

ECDC Technical Report: Hepatitis B and C in the EU neighborhood, 2010

Hepatitis B in Switzerland

- **Prevalence of HBsAg among pregnant women (37.3% foreign-born): 61/9006 (0.67%)**

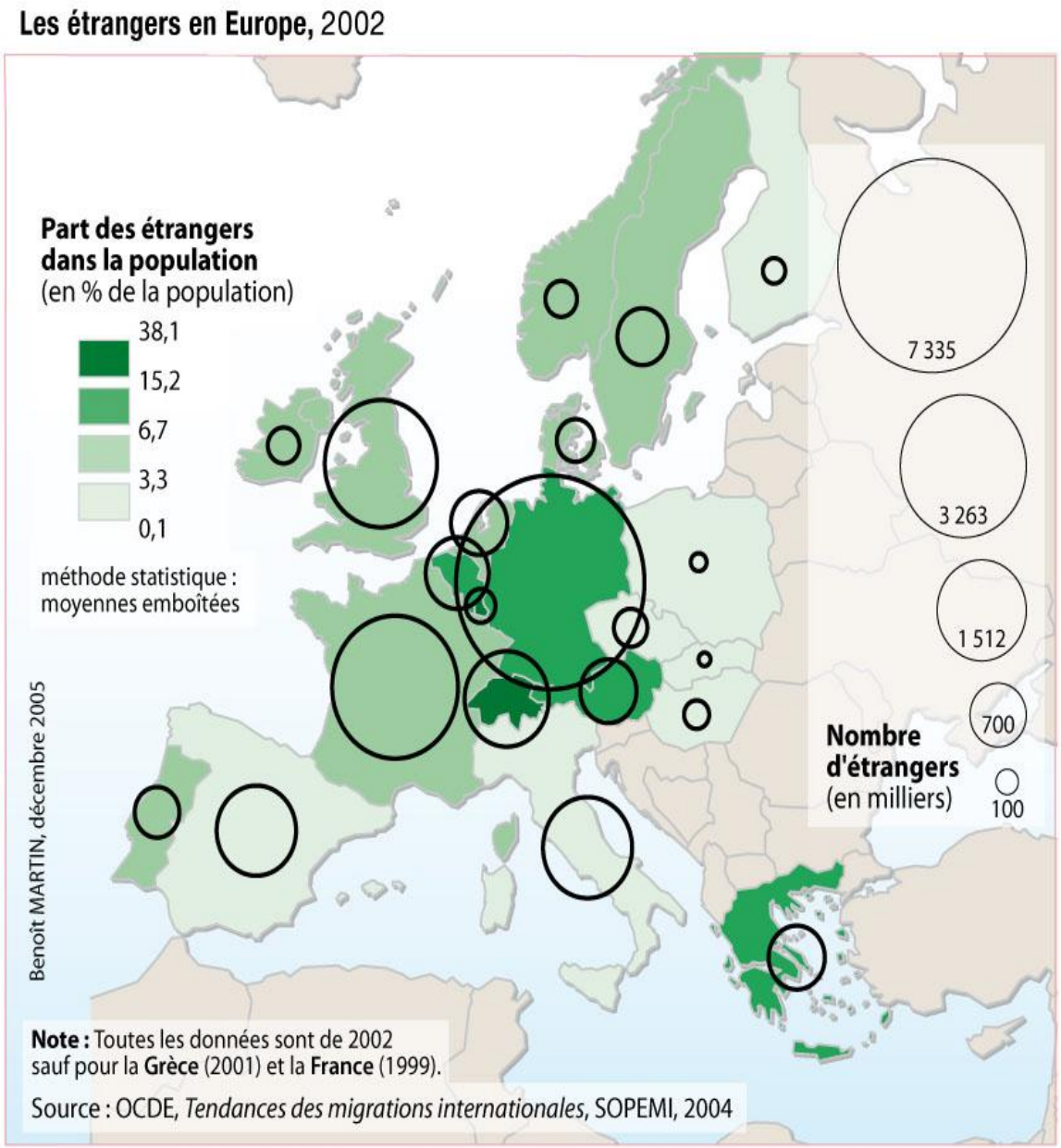
  BART *et al*, Liver 1996;16:110-6

- **Infections reported at the BAG**
  - **1990-95: 1600 – 4000 / year**
  - **1998-02: 600 – 1600 / year**
- **New cases mostly affecting 20 - 30 years old persons**
- **New cases mostly transmitted through sex**

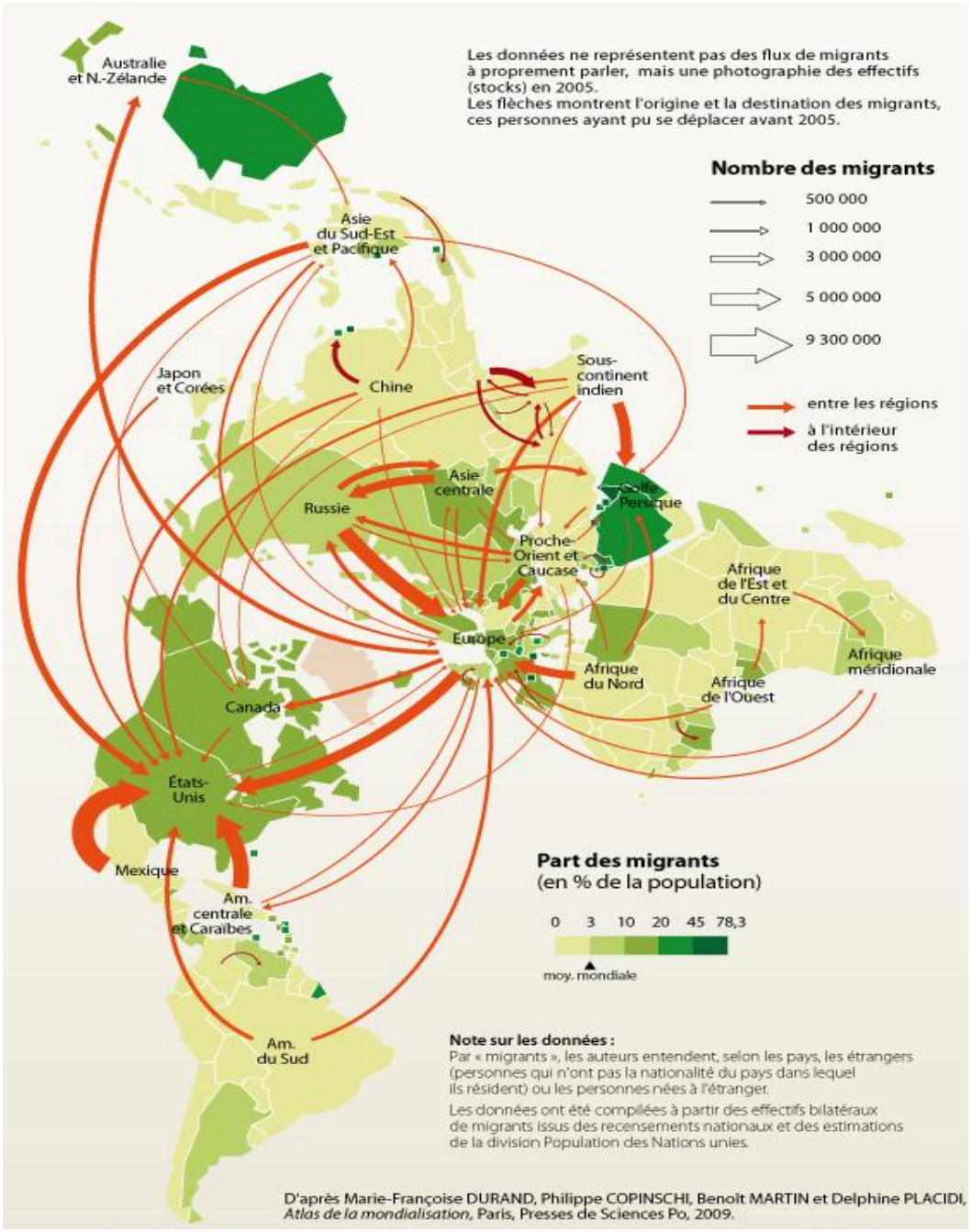
Proportion of foreign-born persons in Geneva, Switzerland

	%
Resident population (2008)	52
HBsAg-positive	94
Anti-HCV-positive	72

Foreigners in Europe (2002)



In Marie-Françoise DURAND, Benoît MARTIN, Delphine PLACIDI, Marie TORNQUIST-CHESNIER, *Atlas de la mondialisation*, Presses de Sciences Po, Paris, 2007, 2ème édition



Migrants

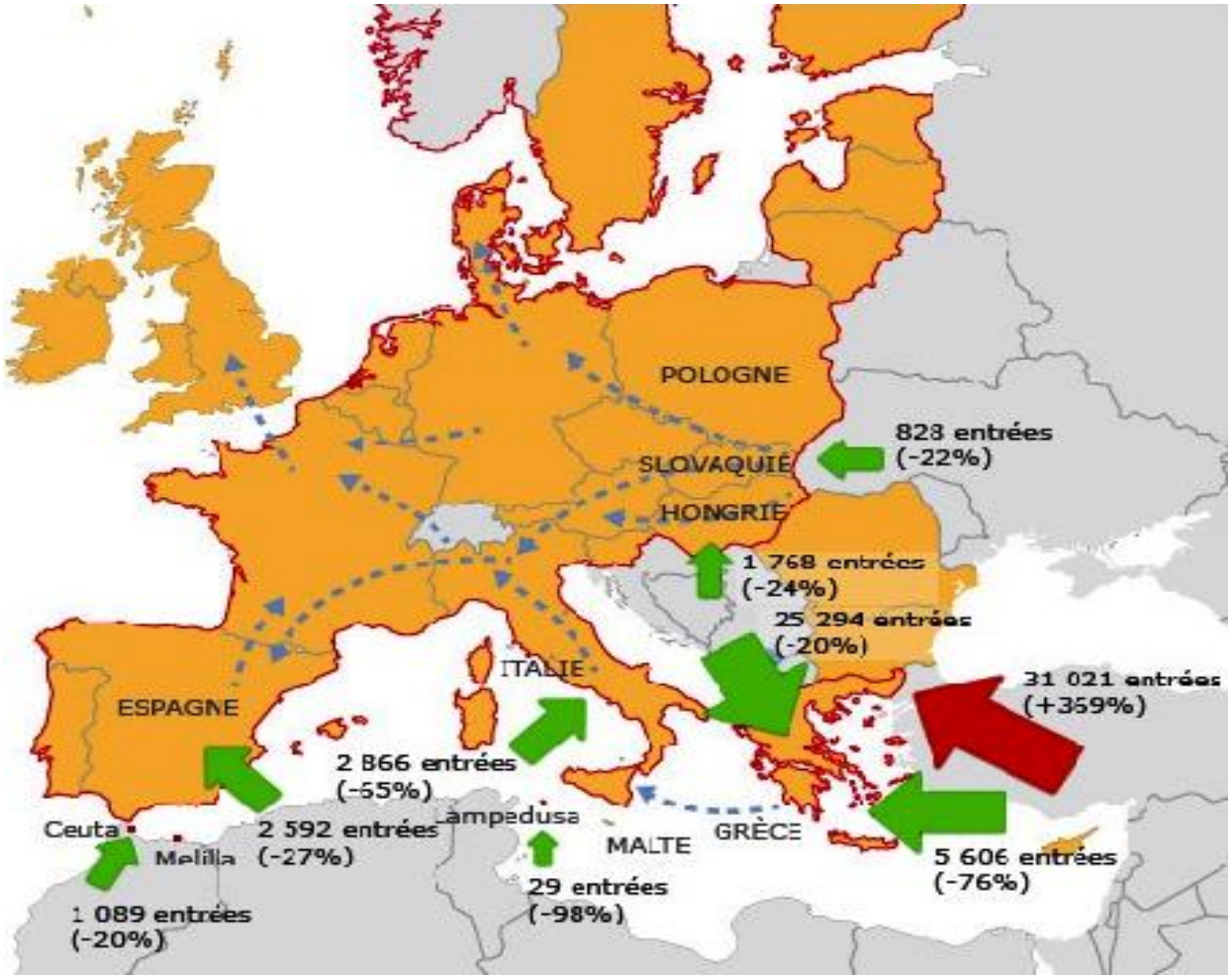
(persons living in a country other than that where they were born):

214 Million (world)

75 Million (Europe)

http://cartographie.sciences-po.fr

Illegal migrants to Europe



EU countries

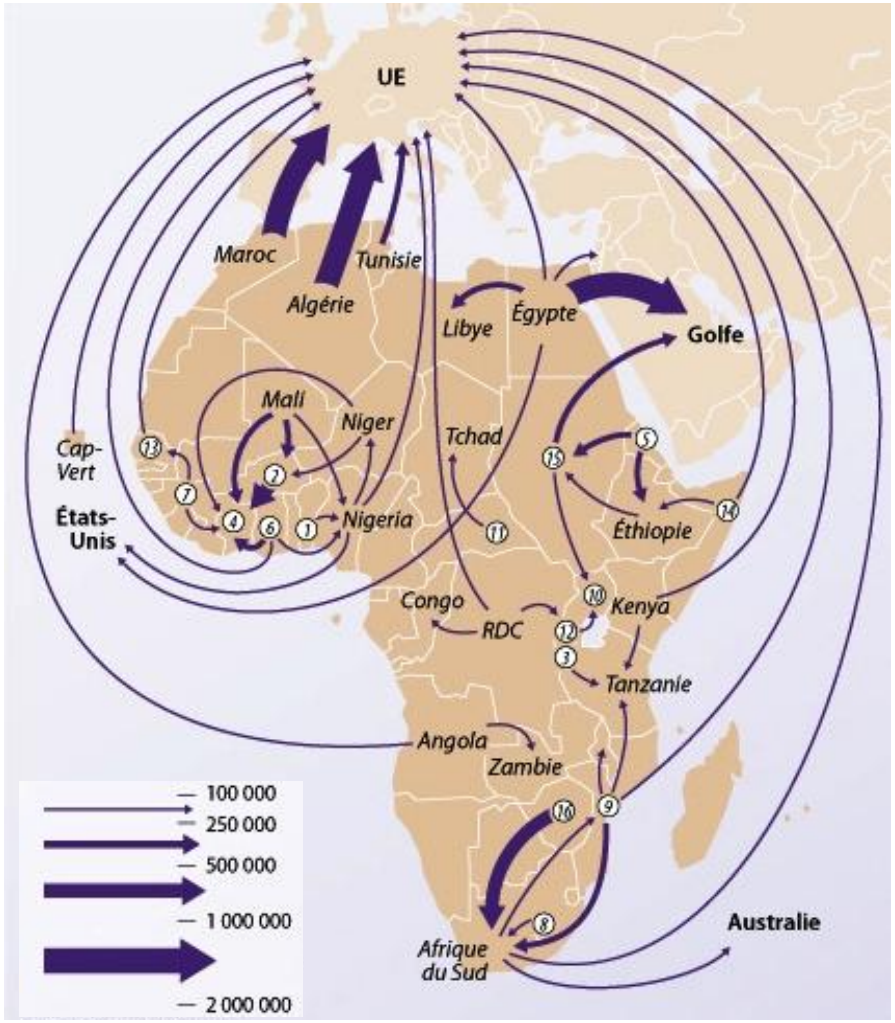
Schengen space

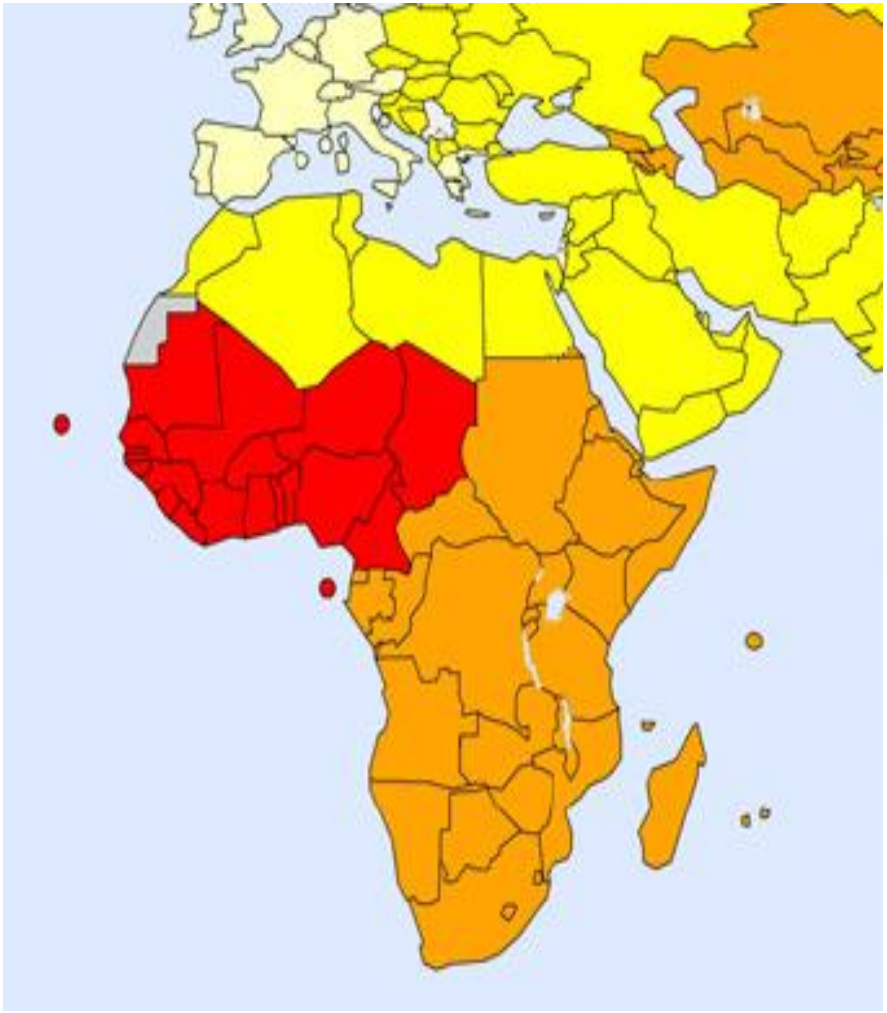
Decreased with respect to 2009

Increased with respect to 2009

Source: Frontex

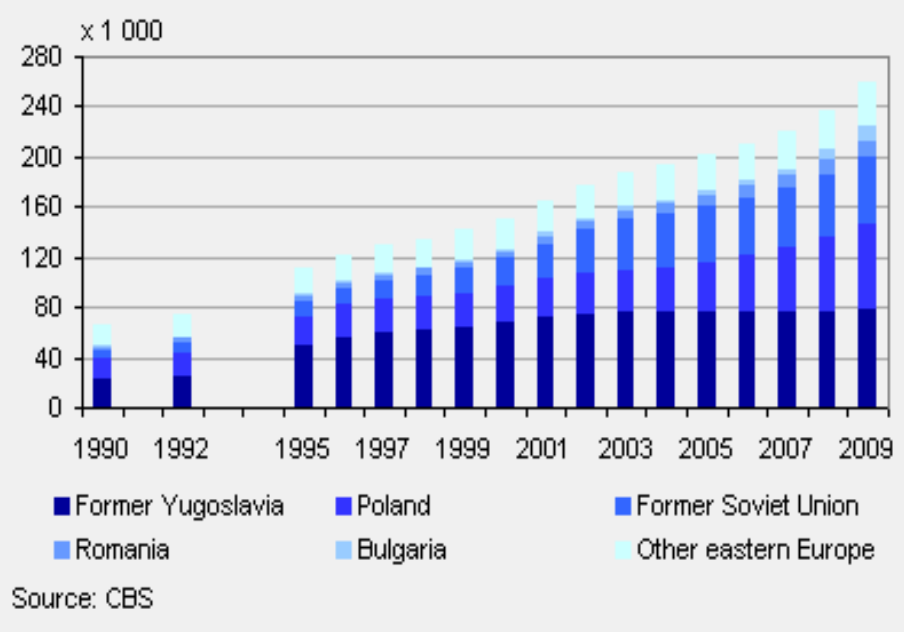
Migration from Africa



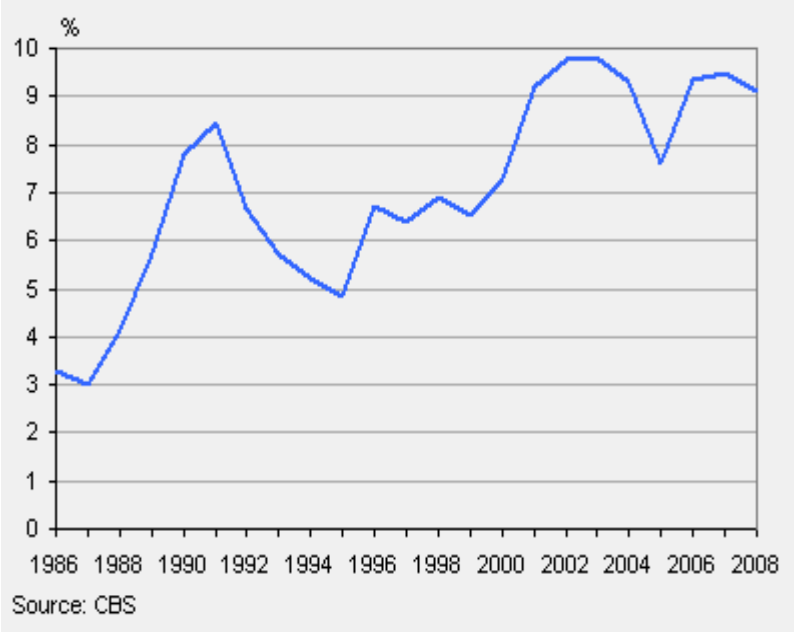


Sources: University of Sussex, World Bank, WHO and Institut d'études politiques (Paris)

Migration from Eastern Europe



Number of people from Eastern Europe in the Netherlands, on January 1st, by country



Proportion of Eastern Europeans in total German immigration, 1986-2008

Source: http://www.cbs.nl

Prevalence of HBsAg in some Eastern European countries

Country	HBsAg+	Author(s)
Albania (blood donors)	**6.7%**	Durro (2010)
Albania (refugees)	**11.7 - 13.6%**	Milionis (2010), Chironna (2000)
Bosnia & Herzegovina (blood donors)	**0.8%**	Petrovic (2011)
Bulgaria (blood donors)	**0.9 – 5.1%**	Gubev (1987)
Croatia (blood donors)	**0.07%**	Grgicevic (2000)
Croatia (pregnant women)	**0.75%**	Ivic (1999)
Croatia (general population)	**1.8%**	Jelic (1994)
Hungary (prison staff)	**0.38%**	Treso (2012)
Kosovo (blood donors)	**4.2%**	Fejza (2009)
Kosovo (refugees)	**2.9%**	Chironna (2001)
Poland (medical students)	**0.7%**	Jablkowski (2002)
Poland (elderly)	**1.12%**	Hartleb (2012)
Romania (general population)	**4.4%**	Gheorghe (2013)
Russia (general population, Moscow)	**2%**	Iashina (1992)

Year
2005

Issue
51/52: Weihnachtsheft
50: 2876-2914
49: 2817-2852
48: 2753-2790
47: 2693-2728
46: Hypertonie
45: 2555-2598
44: 2495-2528

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Dtsch med Wochenschr 2005; 130(48): 2753-2758
DOI: 10.1055/s-2005-922067

Originalien

Gastroenterologie / Epidemiologie

Erhöhen Migrationen aus hohen und mittleren Endemiegebieten die Hepatitis B-Prävalenz in Deutschland?

Epidemiologische Schätzung der HBsAg-Prävalenz bei verschiedenen erwachsenen BevölkerungsgruppenDoes migration from high and intermediate endemic regions increase the prevalence of hepatitis B infection in Germany?

T. Marschall[1], A. Krämer[1], L. Prüfer-Krämer[2], R. Mikolajczyk[1], M. Kretzschmar[1]

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Further Information

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Zusammenfassung

Hintergrund und Fragestellung: Deutschland gehört zu den Niedrigendemiegebieten für Hepatitis B. Die in Deutschland lebenden 7,3 Millionen Ausländer und 3,2 Millionen Aussiedler stammen zum Großteil aus Gebieten mit mittlerer und hoher HBsAg-Prävalenz. Das Ziel dieser Arbeit war es, die HBsAg-Prävalenz bei erwachsenen Ausländern und Aussiedlern im Vergleich zu Erwachsenen ohne Migrationshintergrund zu bestimmen.

Migrants and HBsAg prevalence in Germany

- Germany is a low prevalence country for HBV
- 7.3 million migrants in 2003
- 84% of migrants are from countries with moderate to high HBV endemicity
- Of the estimated ~500,000 HBsAg carriers, 42% have a migratory background, although migrants represents only 12.7% of the whole population
- Foreigners have a 4.3-fold higher risk of being HBsAg+ than the German population

MARSCHALL *et al,* Dtsch Med Wochenschr 2005;130:2753-8

OPEN ACCESS Freely available online

PLOS ONE

Seroprevalence of Chronic Hepatitis B Virus Infection and Prior Immunity in Immigrants and Refugees: A Systematic Review and Meta-Analysis

Carmine Rossi[1,2]*, Ian Shrier[1,2], Lee Marshall[1], Sonya Cnossen[1], Kevin Schwartzman[2,3], Marina B. Klein[2,4], Guido Schwarzer[5], Chris Greenaway[1,2,6]

1 Centre for Clinical Epidemiology and Community Studies of the Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada, **2** Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada, **3** Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada, **4** Division of Infectious Diseases, McGill University Health Centre, McGill University, Montreal, Canada, **5** Institute of Medical Biometry and Medical Informatics, University of Freiburg, Freiburg, Germany, **6** Division of Infectious Diseases, Jewish General Hospital, McGill University, Montreal, Canada

- **110 studies on migrants from intermediate or high HBV prevalence countries arriving in low prevalence countries**
- **209,822 immigrants and refugees**
- **Factors independently associated with HBsAg+**

ROSSI *et al,* PLoS ONE 2012;7: e44611

Prevalence of HBsAg and prior immunity to HBV (95% CI) among immigrants

	HBsAg	Anti-HBs
Overall	**7.2% (6.3 – 8.2)**	**39.7% (35.7 – 43.9)**
East Asia/ Pacific	**11.3% (10.3 – 12.4)**	**50.2% (45.8 – 54.6)**
Sub-Saharan Africa		**41.7% (37.6 – 45.9)**
Eastern Europe/ Central Asia/ South Asia	**5.8% (4.3 – 7.9)**	**NA**
Latin America/ Caribbean/ Middle East/ North Africa	**1.7% (1.1 – 2.7)**	**NA**

ROSSI *et al,* PLoS ONE 2012;7: e44611

HBV among migrants and refugees

- **Refugees** have greater odds of being HBsAg+ compared to immigrants (OR 1.42, 95% CI 1.01 – 1.99)
- **Migrants in studies from the 1990s** have greater odds of being HBsAg+ compared to migrants of studies reported in the 1980s (OR 1.58, 95% CI 1.03 – 2.43)

ROSSI et al, PLoS ONE 2012;7: e44611

Country-specific estimates of HBsAg prevalence in migrants in some traditional immigrant-receiving countries

Country	Immigrants	Estimated number of infected immigrants (%)
Canada	**4,271,500**	285,000 (6.7)
United States	**35,500,500**	1,607,000 (4.5)
Austria	**993,000**	58,000 (5.8)
Belgium	**411,000**	22,500 (5.5)
France	**2,348,000**	113,500 (4.8)
Germany	**4,784,000**	284,000 (5.9)
Israel	**1,148,000**	54,000 (4.7)
Italy	**3,684,500**	201,500 (5.5)
Netherlands	**1,395,000**	73,500 (5.3)
Spain	**3,487,000**	128,500 (3.7)
Sweden	**965,500**	52,500 (5.4)
Switzerland	**691,000**	41,000 (5.9)
United Kingdom	**3,002,000**	193,500 (6.4)
New Zealand	**491,500**	47,500 (9.7)
Australia	**2,141,000**	176,000 (8.2)

ROSSI *et al,* PLoS ONE 2012;7: e44611

HBV among migrants and refugees

- The seroprevalence of chronic HBV infection is high in migrants from most world regions, particularly among those from East Asia, Sub-Saharan Africa and Eastern Europe
- More than 50% are susceptible to HBV
- Targeted screening and vaccination of international migrants can become an important component of HBV disease control efforts in immigrant-receiving countries

ROSSI *et al,* PLoS ONE 2012;7: e44611

Cost-effectiveness of screening for HBV

- It is cost effective to screen if seroprevalence is as low as 1%

HUTTON DW et al, Ann Intern Med 2007;147:460-9

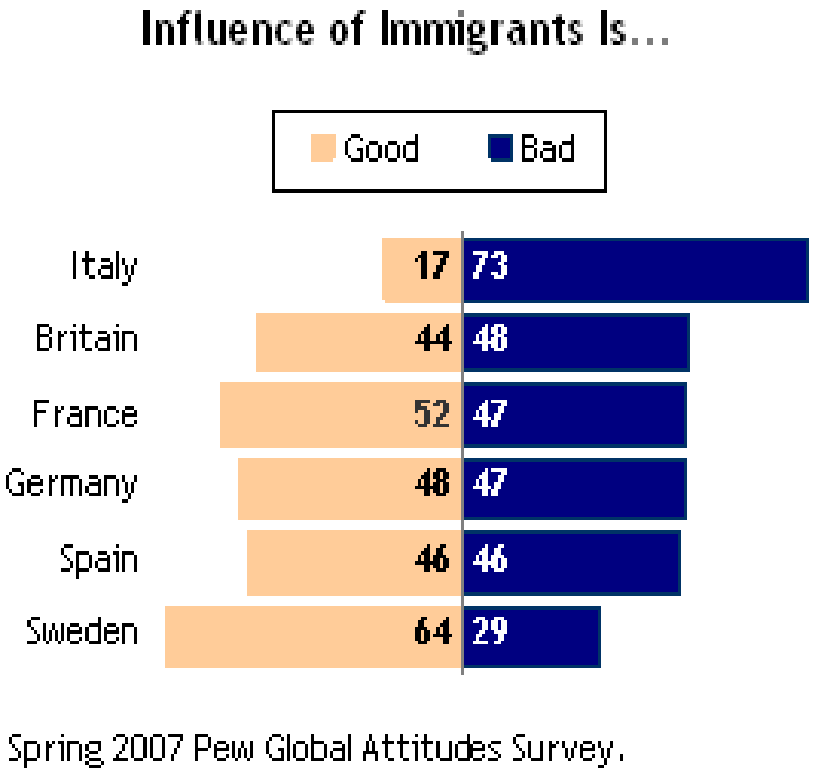
VELDHUIJZEN IK et al, Gastroenterology 2010;138:522-30

ECKMAN MH et al, Clin Infect Dis 2011;52:1294-306

WONG WW et al, Liver Int 2011;31:1179-90

- Screening may allow also identifying persons susceptible to infection, hence implementing vaccination programs

Unfortunately, implementing policies targeting migrants *is not easy*



Spring 2007 Pew Global Attitudes Survey.

The health burden of HBV: willing to pay now or later ?

Persons at risk of HBV infection

- Persons with chronic liver disease
- History of hemodialysis
- HIV, HCV, other STD
- Recipients of organs / blood products
- Before/during immunosuppression/chemotherapy
- Household members/sex partners of HBV +
- MSM, IDU, high risk sex, victims of rape
- Persons and migrants born or having lived during childhood in geographic regions with HBsAg prevalence ≥ 2%
- Long-term travellers to geographic regions with HBsAg prevalence ≥ 2%
- Newborns of HBsAg+ mothers
- Residents of institutions for the mentally disabled
- History of imprisonment
- HCW

FRETZ *et al* (submitted)

HBV infection

- The changing epidemiology in the West
- The health burden
- HBV vaccination

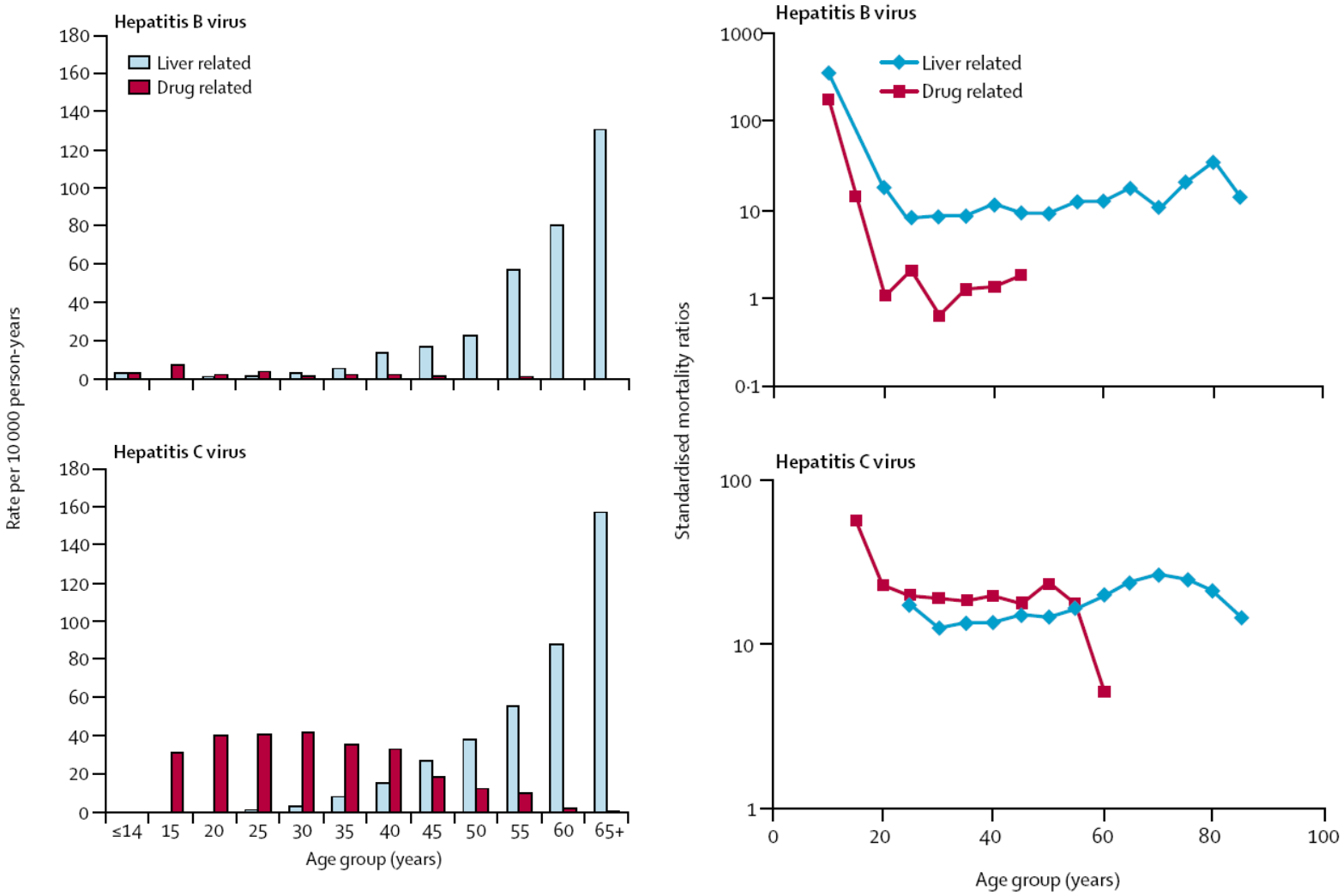
10 Leading Causes of Infectious Disease Deaths Worldwide (Year 2000)

Disease	Deaths x Year
Lower respiratory tract infections	~ 3.5 million
HIV/AIDS	~ 3.0 million
Diarrheal diseases	~ 2.2 million
Tuberculosis	~ 2.0 million
Malaria	~ 1-3 million
Measles	~ 888,000
Hepatitis B	~ 750,000
Pertussis	~ 355,000
Neonatal tetanus	~ 300,000
Hepatitis C	~ 250,000

WHO. Hepatitis B. 2002. Maynard JE, et al. In: Viral Hepatitis and Liver Disease. New York: Alan R. Liss, Inc. 1988
CDC. Epidemiology & prevention of vaccine-preventable diseases. The Pink Book. 8th ed. CDC. MMWR. 2001;50:RR-11

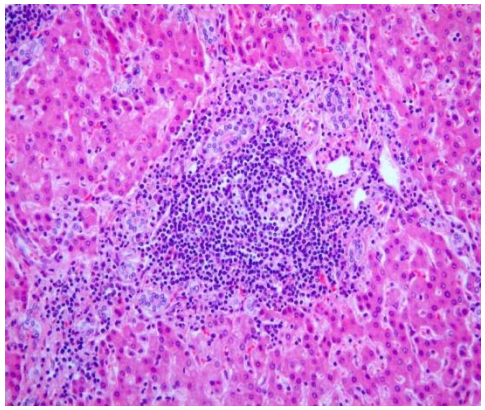
Hepatitis B and C: what do patients die of?

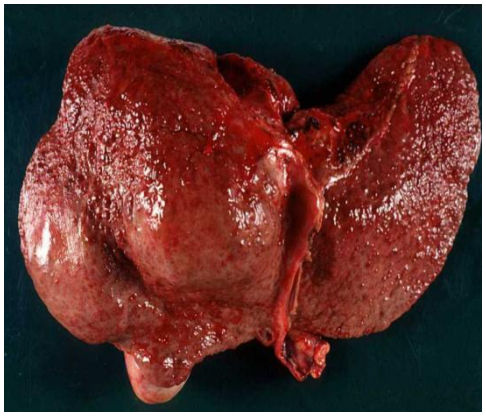
A retrospective study linking notified cases of HBV and HCV infection to the Australian Death Notification Index (n=117547, 65% HCV monoinfected, 2.2% HBV/HCV coinfected)

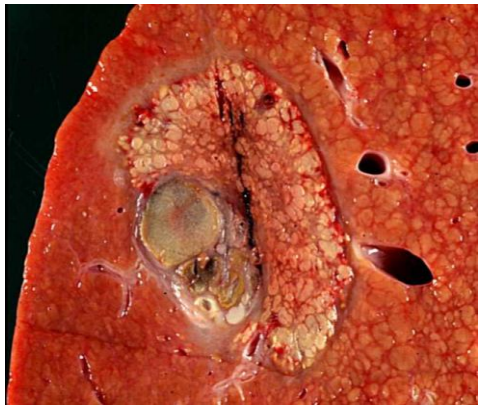


AMIN *et al,* Lancet 2006;368:938-945

Natural history of hepatitis B







HBeAg+ = 2-5% yearly

Anti-HBe+ = 8-10% yearly

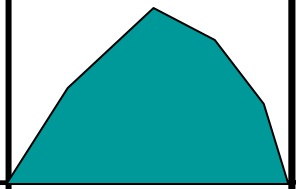
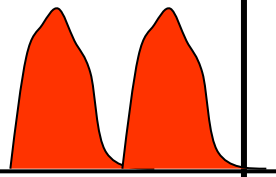
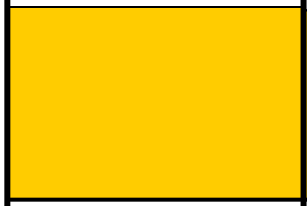
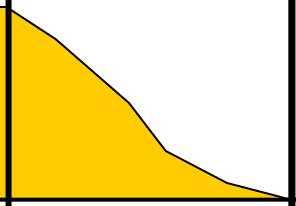
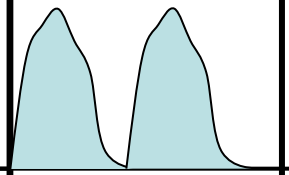
~2-6% yearly

HIV, HDV, age, activity, alcohol

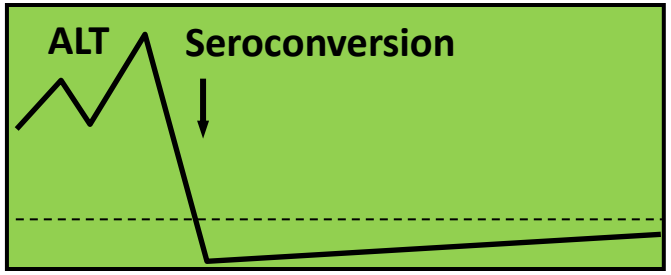
Male sex, age

BRUNETTO *et al,* J Hepatol 2002

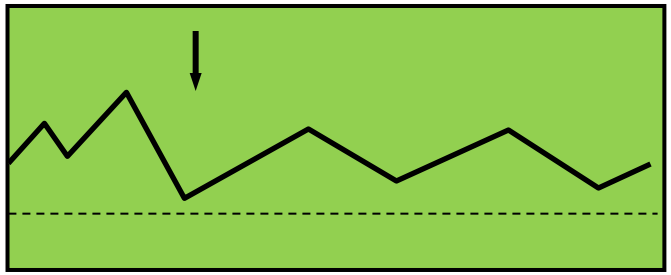
Natural history of HBV infection

	Immune Tolerant	Immune Reactive	Inactive Carrier	HBeAg-CHB	Recovery
ALT	Normal		Normal		Normal
HBV DNA			($<10^4$ copies/ml, or <2,000 IU/ml)		-
HBeAg	+	+/-	-	-	(anti-HBs+)
Liver Histology	Mild or No Activity	Hepatitis	Residual Fibrosis	Hepatitis	Residual Fibrosis

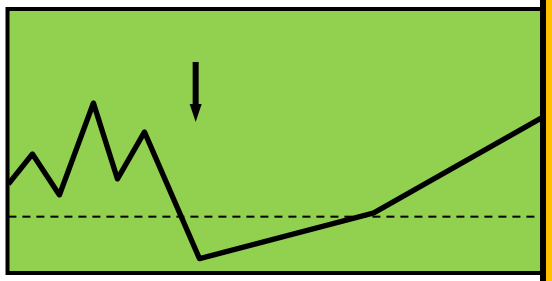
Outcome after spontaneous HBeAg seroconversion



% Patients	Hepatitis
85	sustained remission



% Patients	Hepatitis
5	sustained active



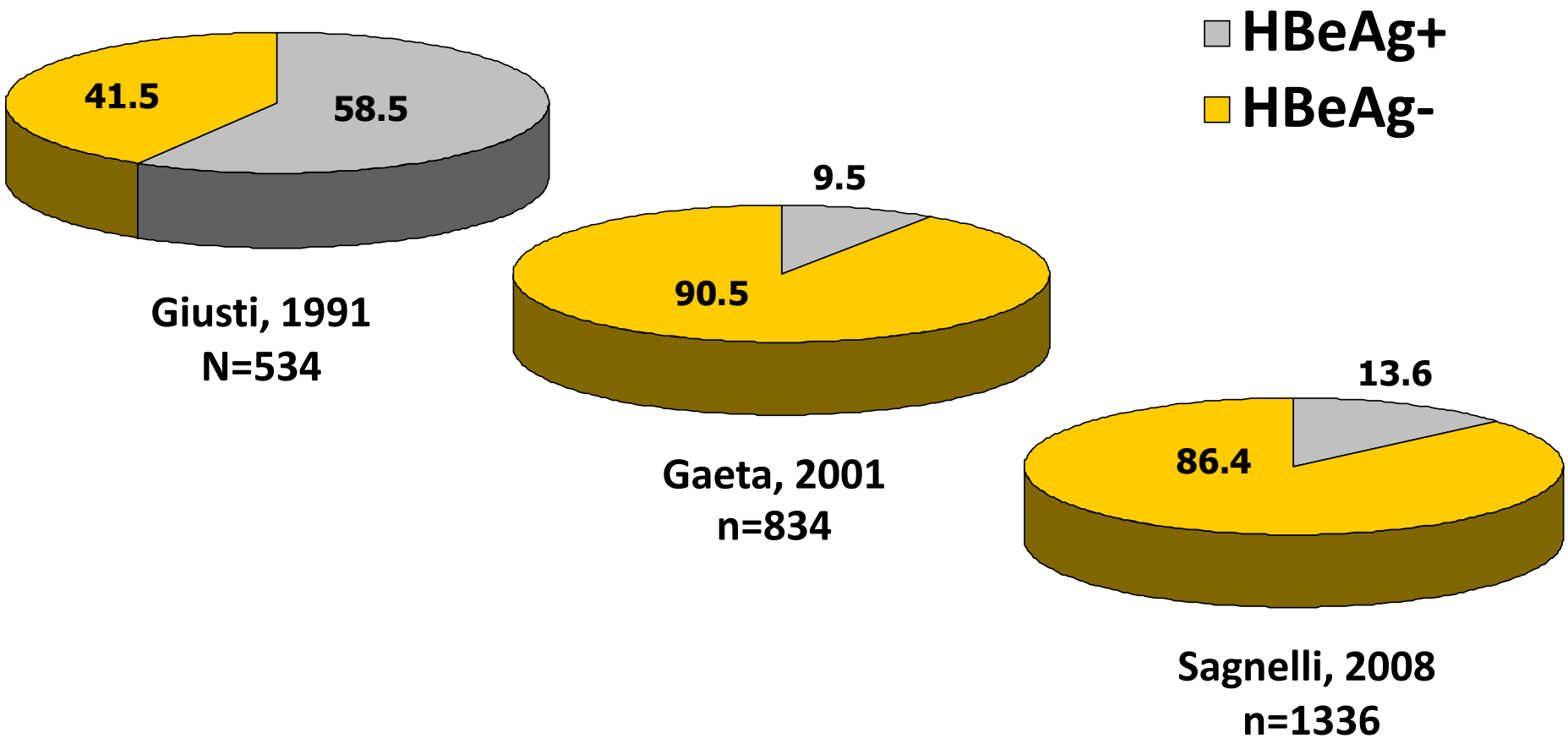
Yearly rates of spontaneous seroconversion:

- **children and adults with elevated ALT 8 - 15 %**
- **children with normal ALT**
  - **2 % before 3 years of age**
  - **4 - 5 % after 3 years of age**

FATTOVICH *et al,* Hepatology 1986; 6: 167-72

BORTOLOTTI *et al,* J Hepatol 1998; 29: 184-90

Evolution of the prevalence of HBeAg-positive cases in Italy



Chronic Hepatitis B in Europe

A 2006 survey from France, Germany, Italy and Spain

200 physicians provided data on 2023 chronic HBV infected patients

Chronic hepatitis B patients in Europe have distinct features:

- 64% HBeAg-negative
- 53% with significant liver disease
- 86% with serum HBV DNA >10^4 copies/ml

BERG *et al,* J Viral Hepat 2010;17:624-30

Relative proportion of anti-HCV and HBsAg in cirrhotic patients

Country	n	anti-HCV+	HBsAg+	Reference
Italy	4125	61%	11%	Stroffolini et al, 2004 Sagnelli et al, 2005
Spain	451	32%	10%	Aoufi et al, 2008
Turkey	505	11%	64%	Ozer et al, 2003 Bayan et al, 2007

ECDC Technical Report: Hepatitis B and C in the EU neighborhood, 2010

Number of new cancer cases in 2008 attributable to infection, by infectious agent and development status

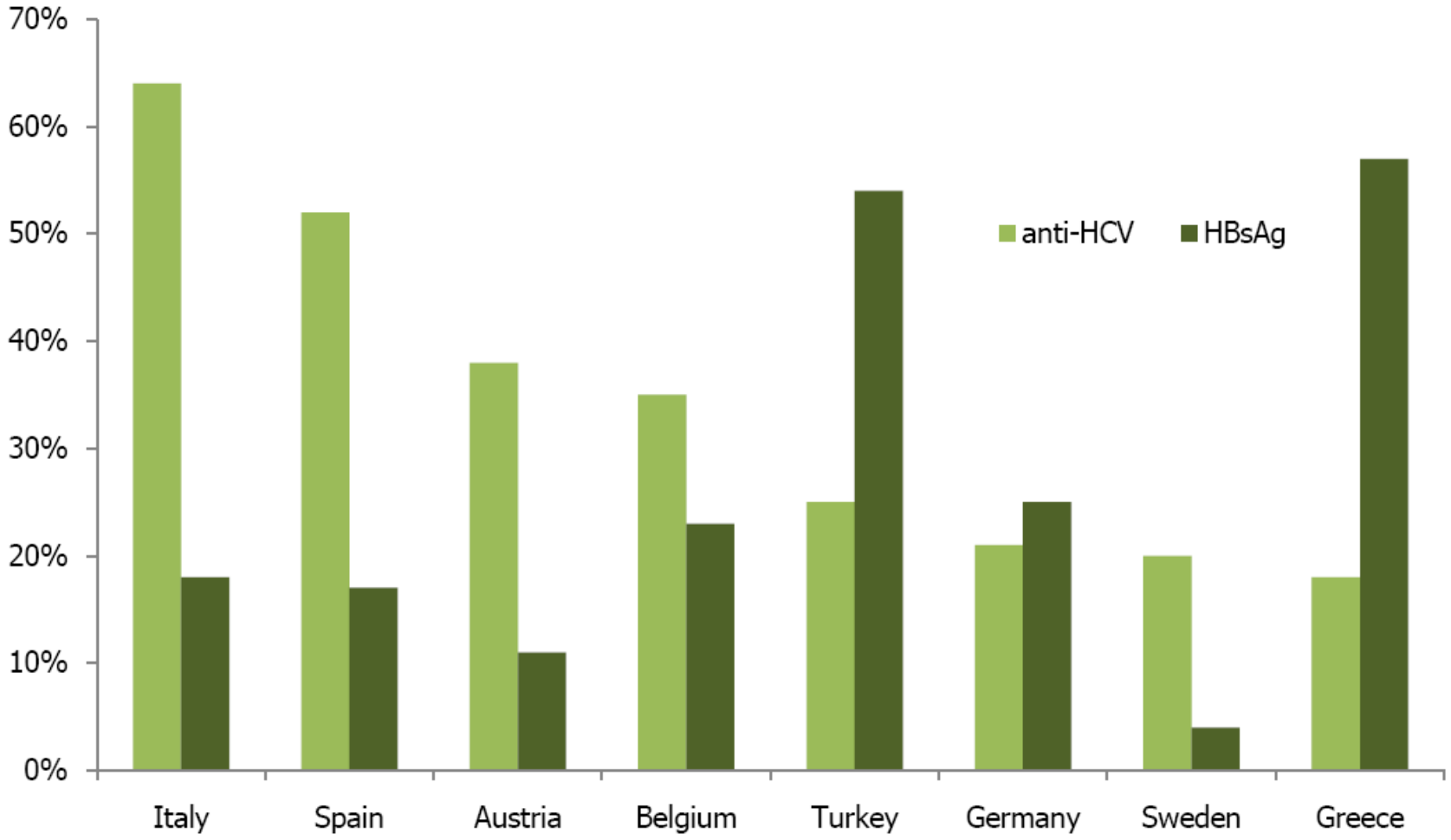
(n = 2,000,000, or 16.1% of the total 12.7 million new cases estimated for 2008)

	Less developed regions	More developed regions	World
Hepatitis B and C viruses	520 000 (32·0%)	80 000 (19·4%)	600 000 (29·5%)
Human papillomavirus	490 000 (30·2%)	120 000 (29·2%)	610 000 (30·0%)
Helicobacter pylori	470 000 (28·9%)	190 000 (46·2%)	660 000 (32·5%)
Epstein-Barr virus	96 000 (5·9%)	16 000 (3·9%)	110 000 (5·4%)
Human herpes virus type 8	39 000 (2·4%)	4100 (1·0%)	43 000 (2·1%)
Human T-cell lymphotropic virus type 1	660 (0·0%)	1500 (0·4%)	2100 (0·1%)
Opisthorchis viverrini and *Clonorchis sinensis*	2000 (0·1%)	0 (0·0%)	2000 (0·1%)
Schistosoma haematobium	6000 (0·4%)	0 (0·0%)	6000 (0·3%)
Total	1 600 000 (100·0%)	410 000 (100·0%)	2 000 000 (100·0%)

”Application of existing public health methods for infection prevention, such as vaccination, safer injection practice, or antimicrobial treatments, could have a substantial effect on the future burden of cancer worldwide”

DE MARTEL *et al,* Lancet Oncol 2012;13:607-15

Estimated anti-HCV and HBsAg prevalence in HCC patients, by country



ECDC Technical Report: Hepatitis B and C in the EU neighborhood, 2010

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The Impact of Infection on Population Health: Results of the Ontario Burden of Infectious Diseases Study

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KWONG *et al*, PLoS One 2012;7:e44103

Number and proportion of average annual HALY* by infectious disease or pathogen, 2005–07, Ontario, Canada

Rank	Pathogen	Years of life lost	Year-equivalents of reduced functioning	HALY	% of total HALYs
1	HCV	8823	983	9807	11.02%
2	*S. pneumoniae*	6669	1601	8270	9.30%
3	*E. coli*	7485	341	7826	8.80%
4	HPV	6191	1418	7609	8.55%
5	HBV	6918	86	7004	7.87%
6	HIV	5036	1312	6349	7.14%
7	*S. aureus*	3740	400	4140	4.65%
8	Influenza virus	2482	1076	3558	4.00%
9	*Cl. difficile*	3216	107	3323	3.74%
10	Rhinoviruses	125	1615	1740	1.96%

*Health-adjusted life years

KWONG *et al,* PLoS One 2012;7:e44103

HBV infection

- The changing epidemiology in the West
- The health burden
- HBV vaccination

The vaccine against HBV: a success story

- Early 1970's: plasma derived vaccines are developed by Merck and Institute Pasteur
- Late 1970's: clinical trials are completed

CROSNIER *et al,* Bull Acad Natl Med 1980;164:764-6

MAUPAS *et al,* Lancet 1981;1:289-92

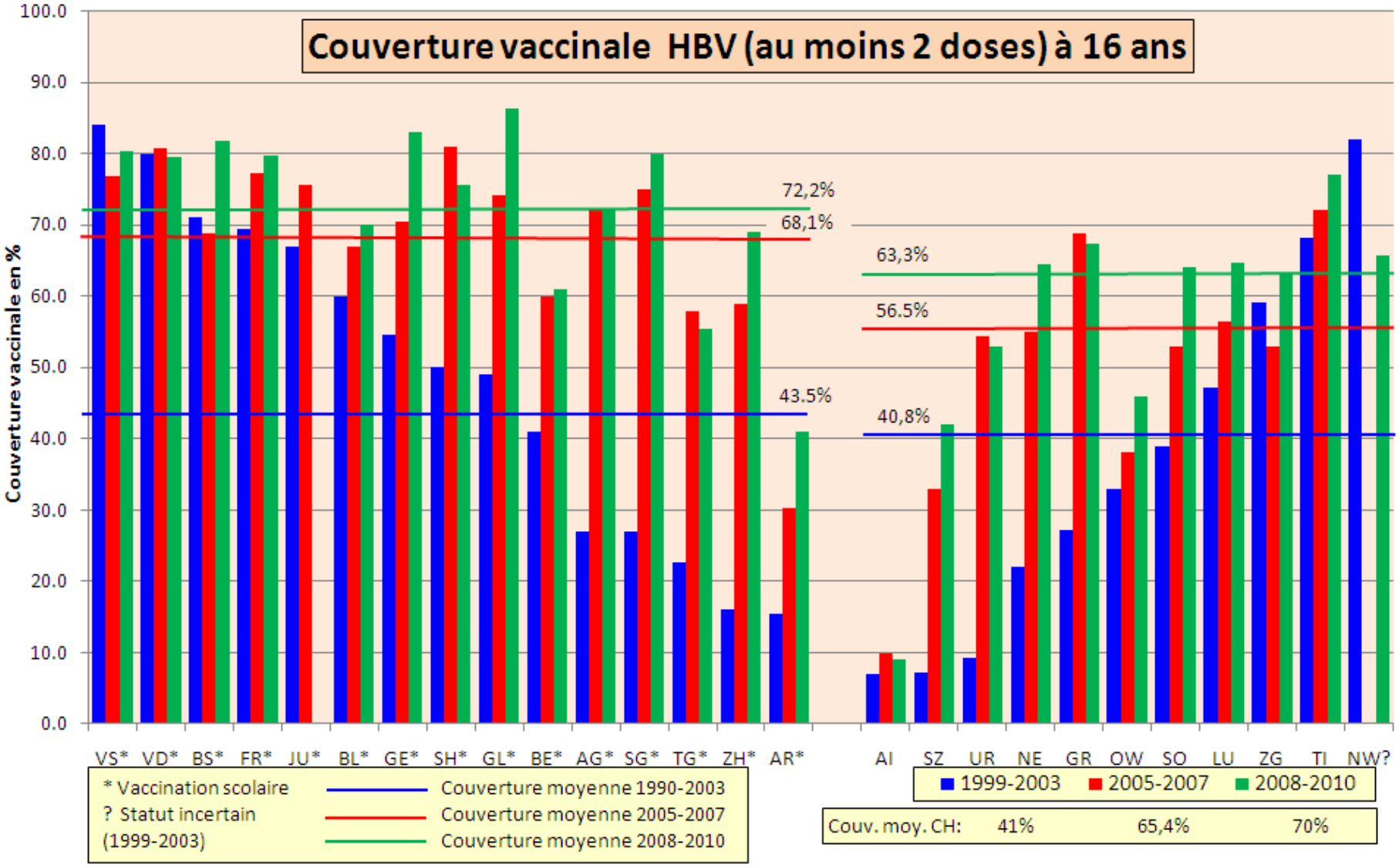
SZMUNESS *et al,* N Eng J Med 1980;303:833-41

- 1981: first plasma-derived vaccine licensed by FDA
- Mid-1980's: introduction of recombinant DNA vaccines (HBV genotype A2)
- 2001: combined vaccine (HBV + HAV) approved by FDA

The path to universal vaccination against HBV

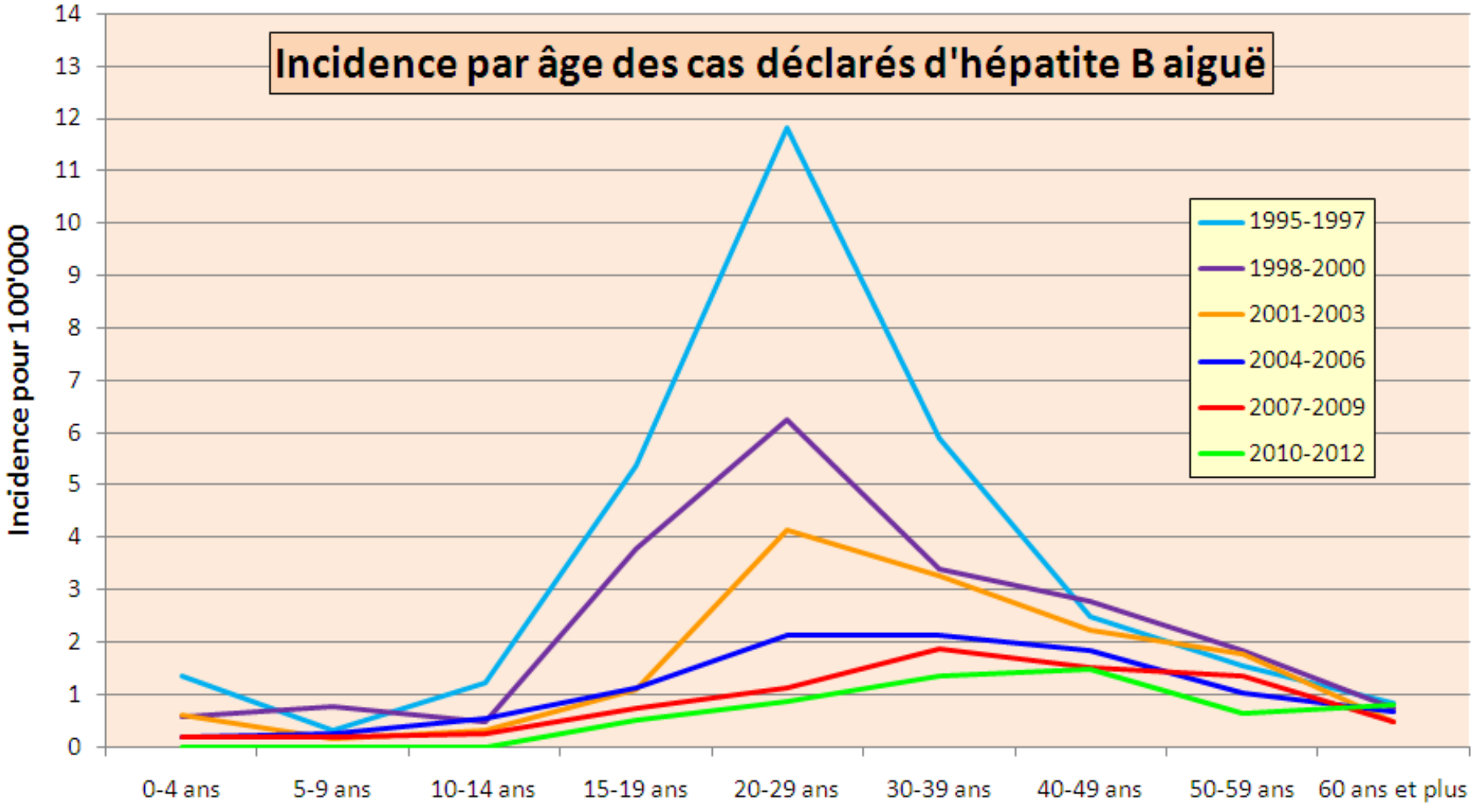
- July 1984: all newborns to HBsAg mothers (Taiwan)
- July 1986: all newborns (Taiwan)
- July 1987: all preschool children (Taiwan)
- 1991: vaccination of all newborns is recommended in the US
- May 1992: WHO endorses the integration of HBV vaccine into national immunization programs within:
  - 1995 for countries with HBsAg prevalence ≥ 8%
  - 1997 for all other countries
- 1994: WHA calls for a 80% reduction of new HBV carrier children by 2001
- By 2006, only 60% of infants globally have received three doses

The Swiss situation - 1



(courtesy of V. Masserey-Spicher, SFOPH)

The Swiss situation - 2



(courtesy of V. Masserey-Spicher, SFOPH)

Reduction of HBsAg carrier rates in children and teenagers following vaccination programmes

Country	Before vaccination	After vaccination	Reference
Taiwan	9.8%	0.5%	NI *et al*, 2007
Alaska	16%	0%	NAMGYAL, 2003
Samoa	7%	0.5%	
Micronesia	12%	3%	
Gambia	10%	0.6%	VIVIANI *et al*, 1999

HBV-associated hepatocellular carcinoma is a vaccine preventable cancer

Table 1. Incidence of Hepatocellular Carcinoma in Boys and Girls Aged 6 to 14 Years in Taiwan, 1981-1996

	Boys			Girls		
Year of Diagnosis*	No. of Cases	Population	Incidence†	No. of Cases	Population	Incidence†
1981-1984	56	5 182 103	1.08	12	4 897 529	0.24
1984-1990	94	10 753 818	0.87	33	10 143 281	0.32
1990-1996	51	10 396 566	0.49	25	9 769 501	0.26

*1981-1984, July 1981 to June 1984; 1984-1990, July 1984 to June 1990; and 1990-1996, July 1990 to June 1996.
†Number per 100 000 population.

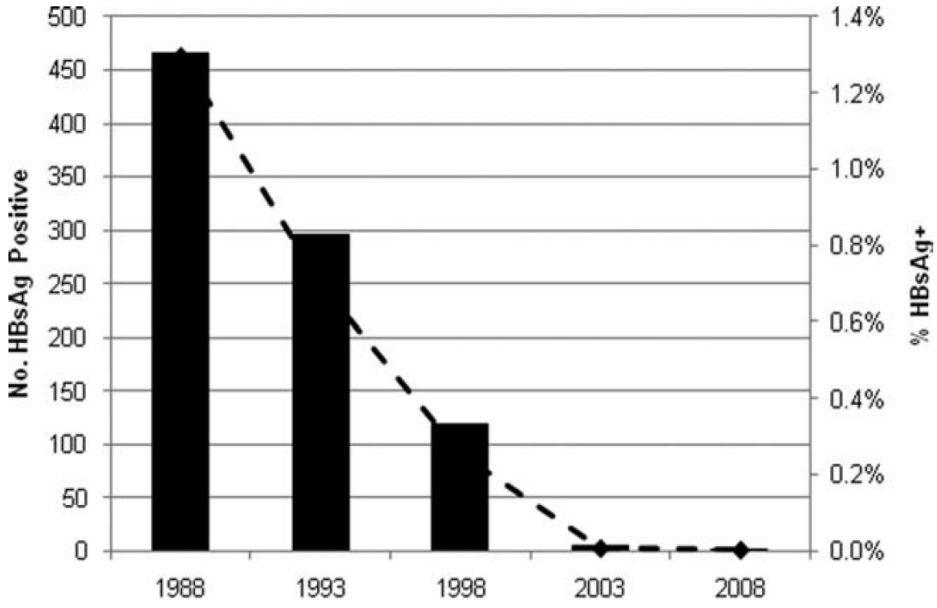
Table 2. Effect of Birth Year on the Development of Childhood Hepatocellular Carcinoma by Sex*

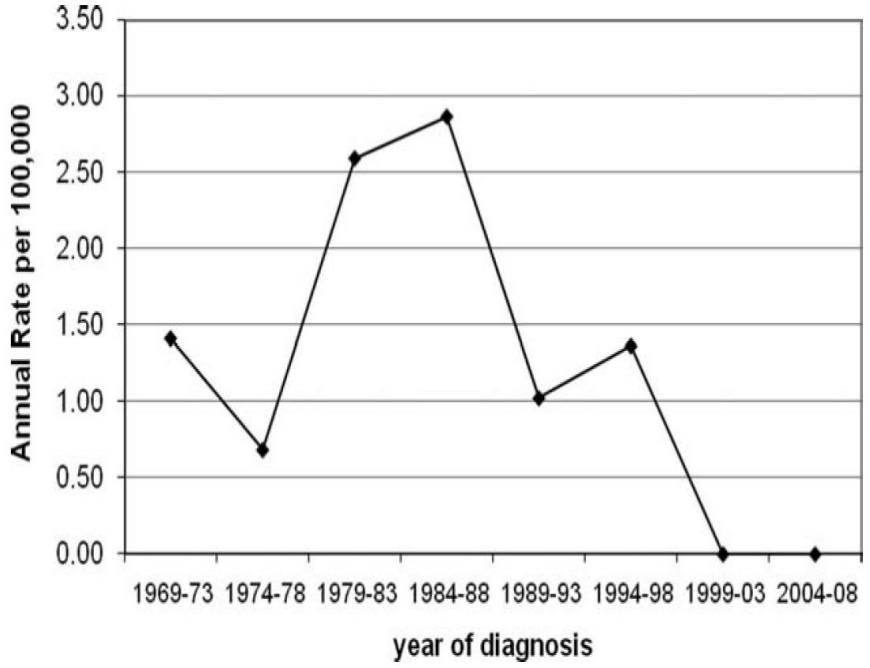
	Boys		Girls	
Birth Year	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
1966-1977	1.00 (Referent)		1.00 (Referent)	
1978-1983	0.83 (0.71-0.96)	.02	1.02 (0.79-1.30)	.90
1984-1989	0.72 (0.59-0.89)	.002	0.77 (0.52-1.15)	.20

*RR indicates relative risk; CI, confidence interval.

CHANG *et al,* JAMA 2000;284:3040-2

Elimination of HBsAg carriers and HCC in <25 years old persons in Alaska





MCMAHON *et al,* Hepatology 2011;54:801-7

HBV vaccination: the hurdles

- Acceptability / safety concerns
- Maternal viral load
- HBV heterogeneity
- Escape mutants

What Other Side Effects are Associated with Hep B Vaccine?

Common reactions include fatigue, muscle weakness, fever, headache, irritability, and joint pain. But there have been reports of disabling neurological and immunological disorders that have developed following hepatitis B vaccinations as well, including:

Multiple sclerosis (MS)	Guillain Barre syndrome	Bell's Palsy
Diabetes	Rheumatoid arthritis	Lupus
Idiopathic Thrombocytopenia purpura	Convulsions and brain disorders such as encephalitis (brain swelling) and brain demyelination	Immune dysfunction
Visual and hearing impairments, including optic neuritis	Pancreatitis	Autism spectrum disorders

A study published September 2009 in Annals of Epidemiology also found that giving hepatitis B vaccine to infant boys more than tripled their risk for an autism spectrum disorder. This was doubly concerning because an earlier study by the same researcher group, *using a different database*, found the same results.

For all of these serious risks, what is your baby getting in return?

Consider that not only do infants and children *rarely acquire hepatitis B*, but vaccines only confer temporary, partial immunity and the length of time you are protected from hepatitis B after receiving the vaccine series has gotten shorter and shorter as studies have revealed antibody levels decline much more rapidly than vaccine developers and policymakers expected.

http://articles.mercola.com/sites/articles/archive/2011/05/19/us-government-concedes-hep-b-vaccine-causes-systemic-lupus-erythematosus.aspx (accessed January 4, 2013)

Safety of vaccination: the importance of 'negative' studies

The New England Journal of Medicine

VOLUME 344 FEBRUARY 1, 2001 NUMBER 5

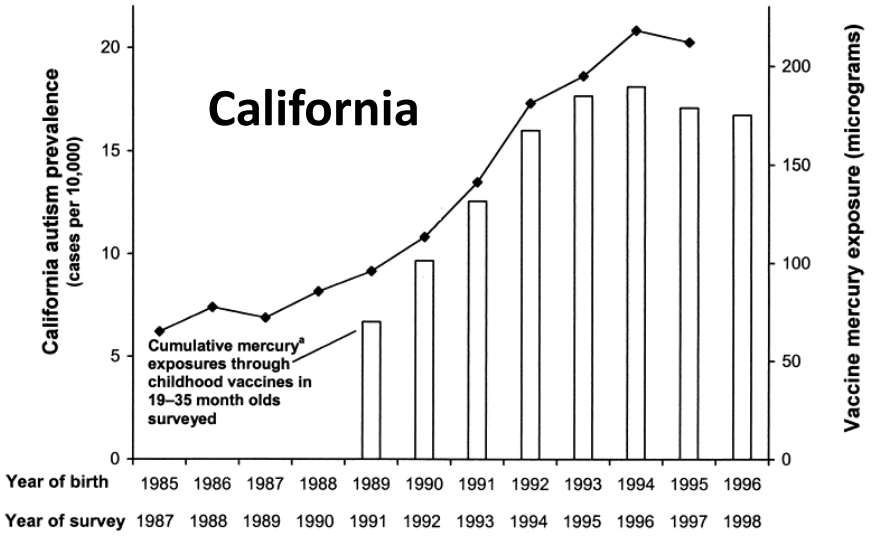
VACCINATIONS AND THE RISK OF RELAPSE IN MULTIPLE SCLEROSIS

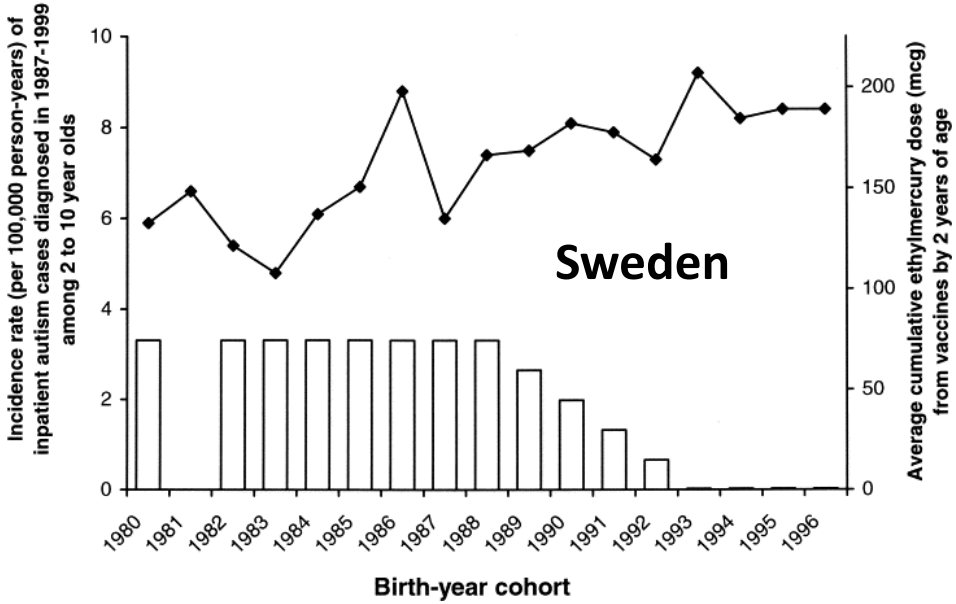
CHRISTIAN CONFAVREUX, M.D., SAMY SUISSA, PH.D., PATRICIA SADDIER, M.D., PH.D., VALÉRIE BOURDÈS, M.D., M.P.H., AND SANDRA VUKUSIC, M.D., FOR THE VACCINES IN MULTIPLE SCLEROSIS STUDY GROUP*

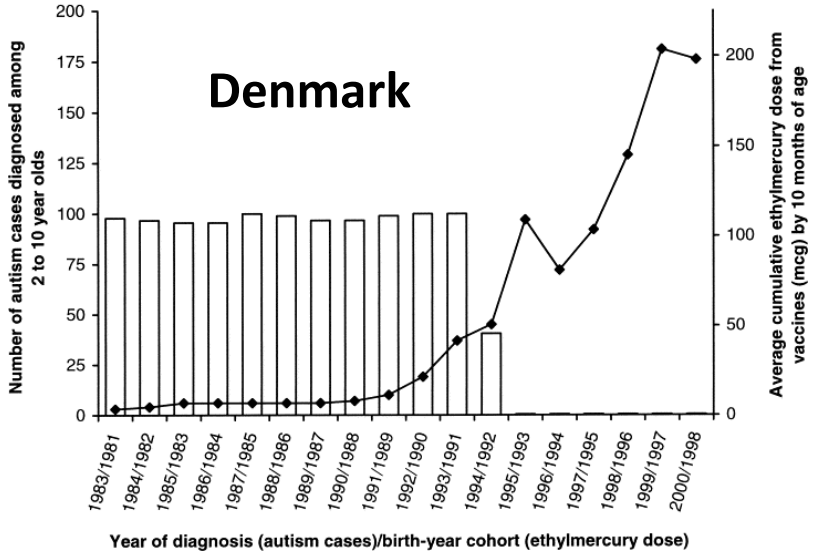
HEPATITIS B VACCINATION AND THE RISK OF MULTIPLE SCLEROSIS

ALBERTO ASCHERIO, M.D., DR.P.H., SHUMIN M. ZHANG, M.D., SC.D., MIGUEL A. HERNÁN, M.D., DR.P.H., MICHAEL J. OLEK, M.D., PAUL M. COPLAN, SC.D., KIMBERLY BRODOVICZ, M.P.H., AND ALEXANDER M. WALKER, M.D., DR.P.H.

Thiomersal exposure and autism







STEHR-GREEN *et al,* Am J Prev Med 2003;25:101-6

'A number of peer-reviewed studies have found a relationship between the hep B vaccination and infant deaths'

http://www.naturalnews.com/032579_hepatitis_B_vaccines.html

Neonatal Deaths After Hepatitis B Vaccine

The Vaccine Adverse Event Reporting System, 1991-1998

Manette T. Niu, MD; Marcel E. Salive, MD, MPH; Susan S. Ellenberg, PhD

Objective: To evaluate reports of neonatal deaths (aged 0-28 days) after hepatitis B (HepB) immunization reported to the national Vaccine Adverse Event Reporting System (VAERS).

Design: Case series; review of autopsy reports.

Setting: Voluntary reports submitted to VAERS, a passive surveillance system, from the US population.

Patients: All US neonates (0-28 days of age) whose deaths after HepB vaccination given alone were reported to VAERS, occurring from January 1, 1991, through October 5, 1998.

Intervention: None (observational database).

Results: Of 1771 neonatal reports, there were 18 deaths in 8 boys and 9 girls (1 patient unclassified). The mean age at vaccination for these 18 cases was 12 days (range, 1-27 days); median time from vaccination to onset of symptoms was 2 days (range, 0-20 days); and median time from symptoms to death was 0 days (range, 0-15 days). The mean birth weight of the neonates (n = 15) was 3034 g (range, 1828-4678 g). The causes of death for the 17 autopsied cases were sudden infant death syndrome for 12, infection for 3, and 1 case each of intracerebral hemorrhage, accidental suffocation, and congenital heart disease.

Conclusion: Few neonatal deaths following HepB vaccination have been reported, despite the use of at least 86 million doses of pediatric vaccine given in the United States since 1991. While the limitations of passive surveillance systems do not permit definitive inference, these data suggest that HepB immunization is not causing a clear increase in neonatal deaths.

Arch Pediatr Adolesc Med. 1999;153:1279-1282

The negative attitude towards vaccines is also supported by health care providers

- In a survey conducted in 2004 in France among GPs and pediatricians:
  - 88% were unsure about the safety of HBV vaccine
  - 60% doubted its usefulness
  - 30% did not follow recommendations

'Adverse events can occur later in life'

'The pharmaceutical industry falsifies the data'

'I lack the confidence in health authorities'

BALINSKA, J Clin Virol 2009;46:202-5

Universal vaccination of children: a difficult decision for parents

- Consider freedom of choice but also the collective responsibility (i.e. those who refuse vaccination still profit from others being vaccinated)
- Choices may be affected by specificities/medical conditions (for example, the child of a parent with MS)
- The 'anticipated regret' plays a major role (people feel less guilty if they have not intervened and a problem occurs, than if they ***do*** intervene and a problem occurs)
- It is difficult for parents to imagine their child as a possible risk-taking teenager or young adult

BALINSKA, J Clin Virol 2009;46:202-5

Explaining the benefits of vaccines: a major challenge for clinical scientists

- Do rigourous science
- Improve access to data for practitioners
- Improve long-term pharmacovigilance
- Learn how to explain the risk-to-benefit ratio
- Ask the collaboration of media to translate science into understandable language

Preventing vaccine failure in babies born to highly viremic HBsAg+ mothers

- Maternal HBV DNA >10^8 copies/ml is associated with ~10% risk of immunoprophylaxis failure

BURK *et al,* J Infect Dis 1994;170:1418-23

VAN ZONNEVELD *et al,* J Viral Hepat 2003;10:294-7

WISEMAN *et al,* Med J Aust 2009;190:489-92

- In utero/transplacental transmission may occur

XU *et al,* J Med Virol 2002;67:20-6

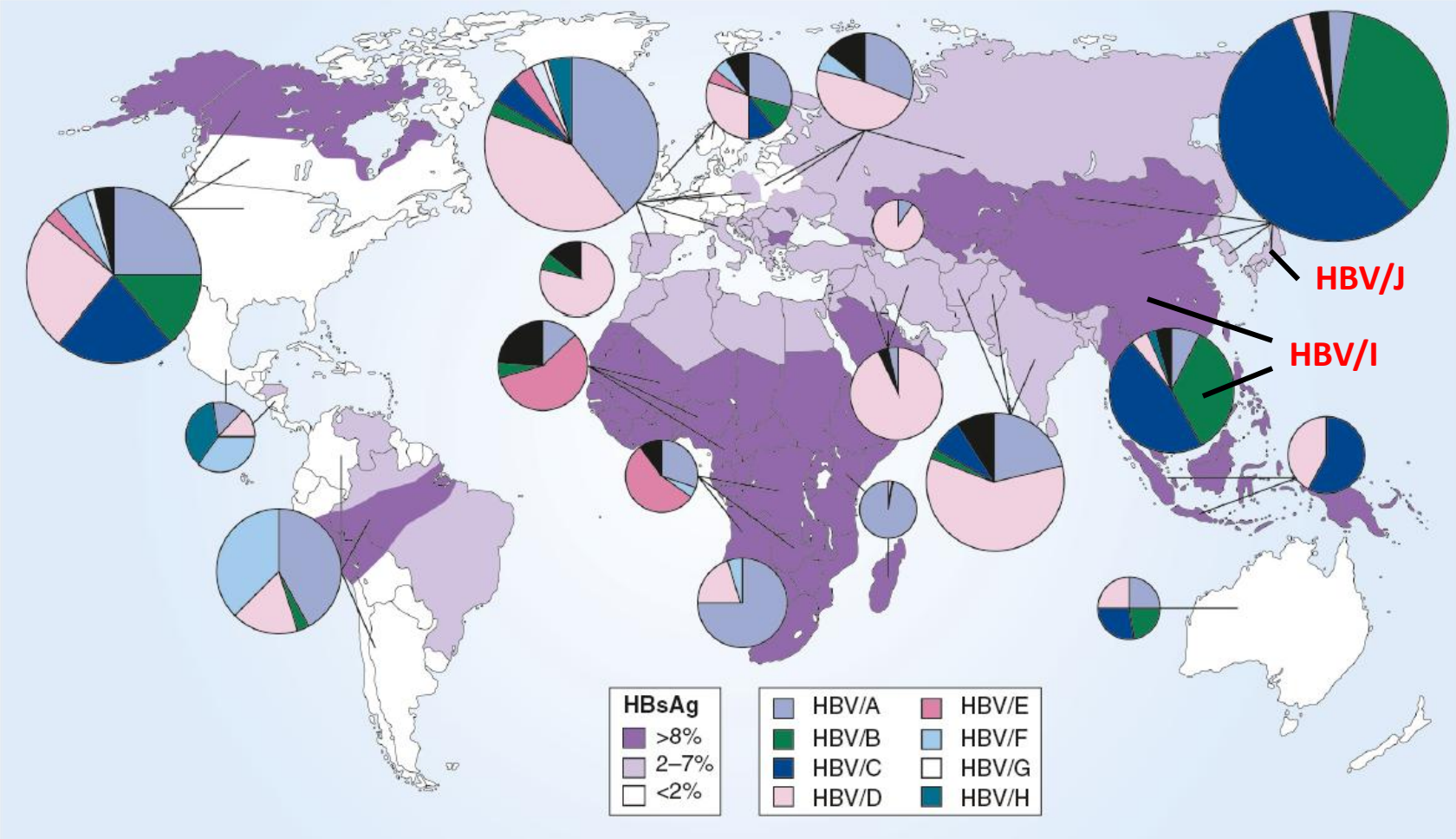
SHAO *et al,* J Med Virol 2011;83:791-5

Lowering maternal viremia reduces immunoprophylaxis failure

Antiviral	HBsAg+ children born to treated mothers (%)*	HBsAg+ children born in placebo group (%)*	Reference
Lamivudine	10/56 (18)	23/59 (39)	XU *et al,* 2009
Telbivudine	3/135 (2.1)	12/94 (13)	HAN *et al,* 2011
Tenofovir	0/11 (0)	na	PAN *et al,* 2012

*Intention to treat analyses

HBV genotypes A to J



KURBANOV *et al,* Hepatol Res 2010;40:14-30; CASSIDY *et al,* Expert Rev Vaccines 2011;10:1709-13
YU *et al,* PLoS One 2010;5:e9297; JUTAVIJITTUM et al, Proc. HBV Meeting, Rome 2007
TRAN *et al,* J Virol 2008;82:5657-63; TATEMATSU *et al,* J Virol 2009;83:10358-47
TONG *et al,* J Med Virol 2012;84:866-70

HBV genotypes and serotypes

Genotype	Serotype	Geographical distribution
A	*adw2, ayw1*	NW Europe, US, Central Africa, India
B1	*adw2*	Indonesia, China
B2	*ayw1*	Vietnam
C	*adw2* *adrq+* *adrq-, ayr, adr*	East Asia Korea, China, Japan, Taiwan Polynesia, Korea, China, Japan Australia, US, Vietnam
D	*ayw2, ayw3* *ayw4*	Mediterranean area, Middle East, India, Russia, US
E	*ayw4*	West Africa
F	*adw4q-* *adw2, ayw4*	Polynesia, US (rare) Central and South America
G		Europe, US (rare)
H	*adw4*	Central and South America
I		Laos, Vietnam, Sichuan (China)
J		Japan

Adapted from WEBER, J Clin Virol 2005;32:102-12

Since all HBV vaccines are genotype A2, serotype *adw*, is HBV heterogeneity an obstacle to immunization?

- The '*a*' determinant is common to all HBV genotypes and serotypes
- After vaccination, >90% of anti-HBs antibodies have anti-*a* specificity

HAUSER *et al*, Postgrad Med J 1987;63(suppl 2):S83-91

- 97% of B-cell lines isolated from vaccinated persons are *a*-specific

SHOKRGOZAR *et al*, Vaccine 2002;20:2215-20

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nucleic Acid Testing to Detect HBV Infection in Blood Donors

Susan L. Stramer, Ph.D., Ulrike Wend, Daniel Candotti, Ph.D., Gregory A. Foster, B.A., F. Blaine Hollinger, M.D., Roger Y. Dodd, Ph.D., Jean-Pierre Allain, M.D., and Wolfram Gerlich, M.D.

- Out of ~3.7 million donors, 9 were HBV DNA+
- Viremia was transient and very low level
- 6/9 had been vaccinated (4 had 'protective' levels of anti-HBs+)
- HBV genotypes were A2, C2, F1, B2, D-A2 and D-A4-A2/D

STRAMER *et al,* N Eng J Med 2011;364:236-47

HBV heterogeneity *is not* an obstacle to immunization

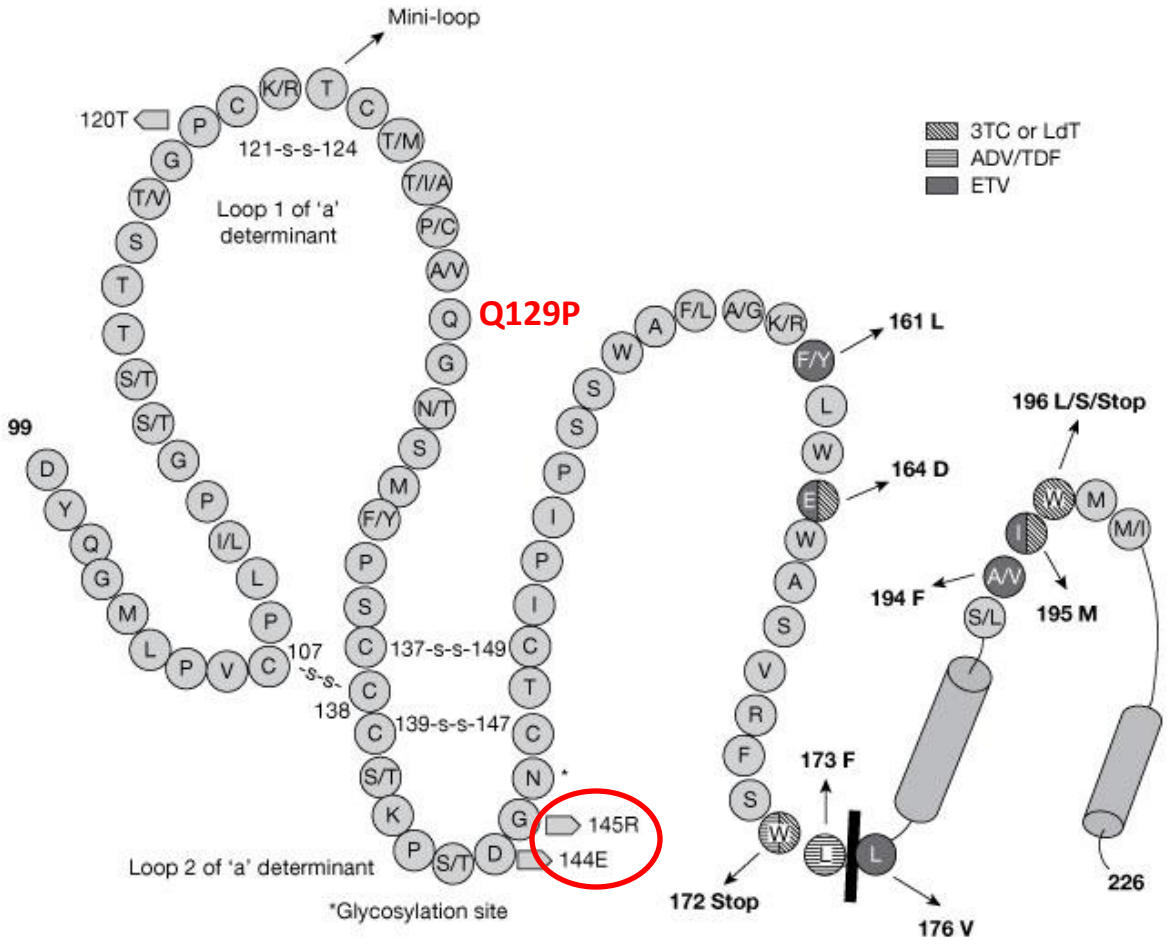
- Cross-serotype protection has been shown in chimpanzees after monoclonal Ab prophylaxis or vaccination

SCHELLEKENS *et al,* Postgrad Med J 1987;63(suppl 2):93-6

- Vaccination with A2-derived vaccines has resulted in significant reduction of carrier rates in areas where infections are due to genotypes A1, B, C, D, E

CHANG *et al,* J Natl Cancer Inst 2009;101:1348-55
DONG *et al,* J Med Virol 2009;81:1517-24
CHONGSRISAWAT *et al,* Trop Med Int Health 2006;11:1496-502
POOVORAWAN *et al,* J Viral Hepat 2011;18:369-75
VIVIANI *et al,* Vaccine 1999;17:2946-50
BHIMMA *et al,* Arch Pediatr Adolesc Med 2003;157:1025-30

Escape mutants may arise from mutations within the ‘a’ determinant of the HBsAg



LOCARNINI & YUEN, Antiviral Ther 2010;15:451-61

Immune escape mutants of HBV

- Escape mutants may arise from low-level, replicative HBV upon immune selective pressure:
  - in vaccine recipients (<1% - 8%)

CARMAN *et al,* Lancet 1990;336:325-9
NGUI *et al,* J Infect Dis 1997;176:1360-5
NAINAN *et al,* J Med Virol 2002;68:319-27
McMAHON *et al,* Ann Intern Med 2005;142:333-41

  - in liver transplant recipients receiving immunoprophylaxis

PROTZER & SCHALLER, Vaccine 2000;21:27-37
ROCHE *et al,* Liver Transpl 2010;16:885-94

- They may evade detection by common ELISAs

GERLICH, J Clin Virol 2006;36(suppl 1):S18-S22

Further studies on the natural history of immune escape mutants are needed!

Conclusions

- The HBV epidemiology is changing (especially in the traditionally low endemicity countries) due to migration
- HBV remains a major cause of excess (mostly liver-related) deaths globally
- Vaccine is effective, but its uptake has to be improved