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Overview of surveillance and epidemiology of hepatitis in Luxembourg

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Viral hepatitis epidemics in Luxembourg

July 2015: 569 604 inhabitants

285 583 men

284 021 women

2 586 km²

HAV, HBV and HCV are notifiable diseases in Luxembourg ,data sent to ECDC

- ✓ Currently notification is done by clinicians only
- ✓ Clinical notification likely to be underestimate
  - known for other infectious diseases (e.g. Salmonella) where isolate data available

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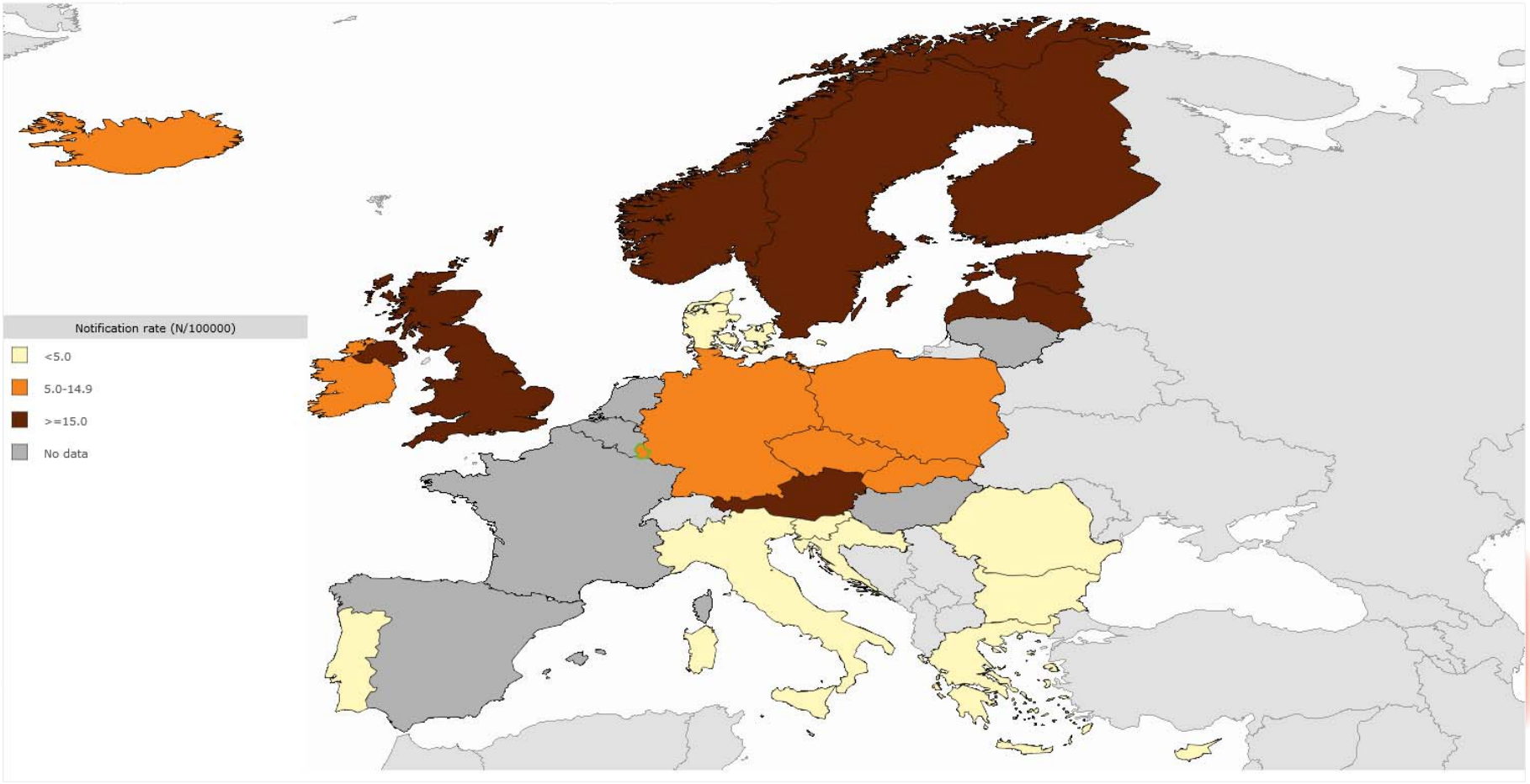
European reporting of hepatitis C in 2015

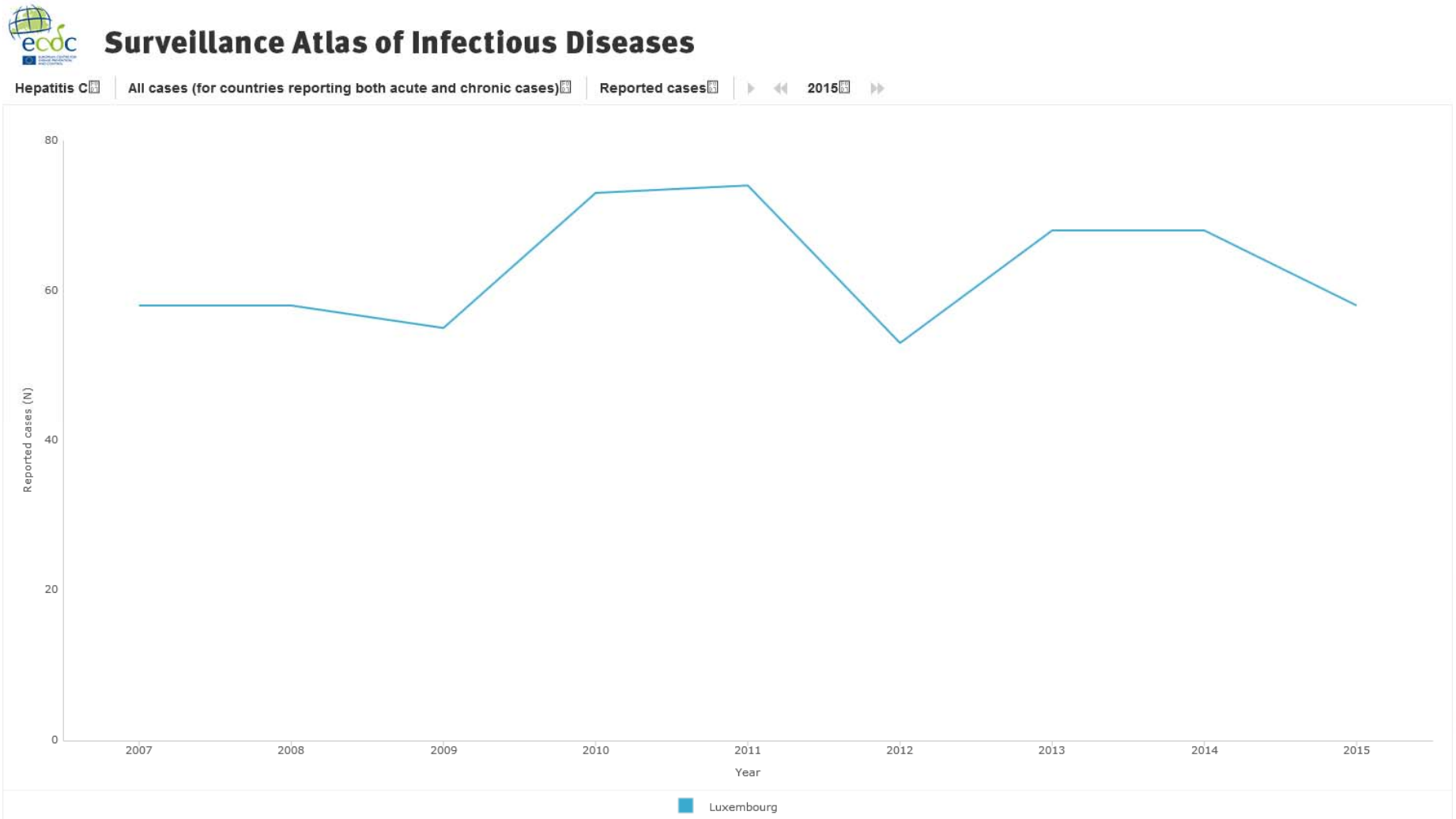
ecdc **Surveillance Atlas of Infectious Diseases**

Hepatitis C | All cases (for countries reporting both acute and chronic cases) | Notification rate | 2015



- ✓ Number of notifications similar in Luxembourg to Germany, but lower than in Northern countries with better infectious disease registries

National Reporting of hepatitis C



- ✓ Number of notifications constant over past decade (~70 cases/year = incidence of 12 per 100,000)

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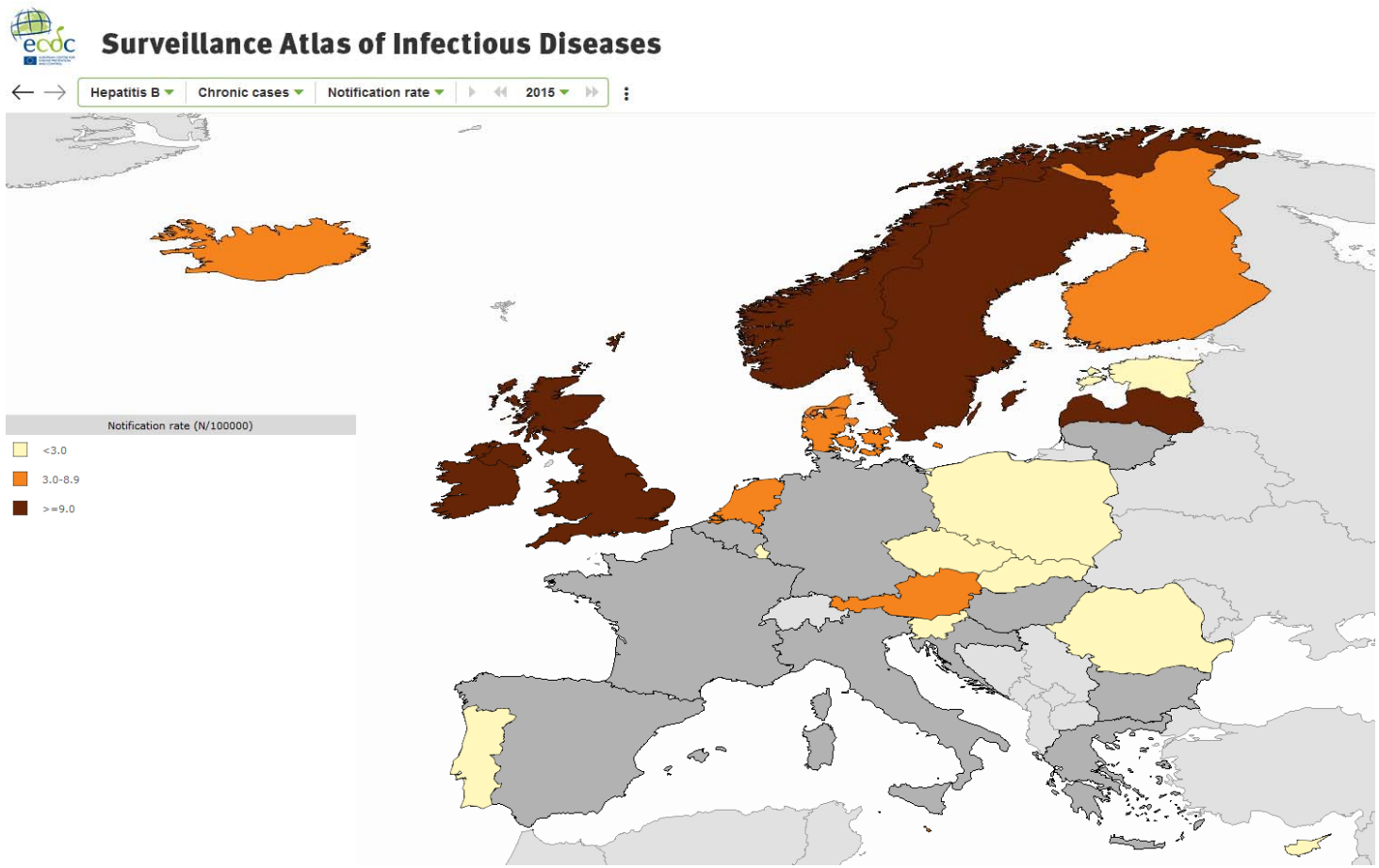
National Reporting of hepatitis B in 2015



- ✓ Universal hepatitis B vaccination programmes, very high coverage in infants , proposed in IDUs and refugees (higher proportion of HBV in migrant these past years)

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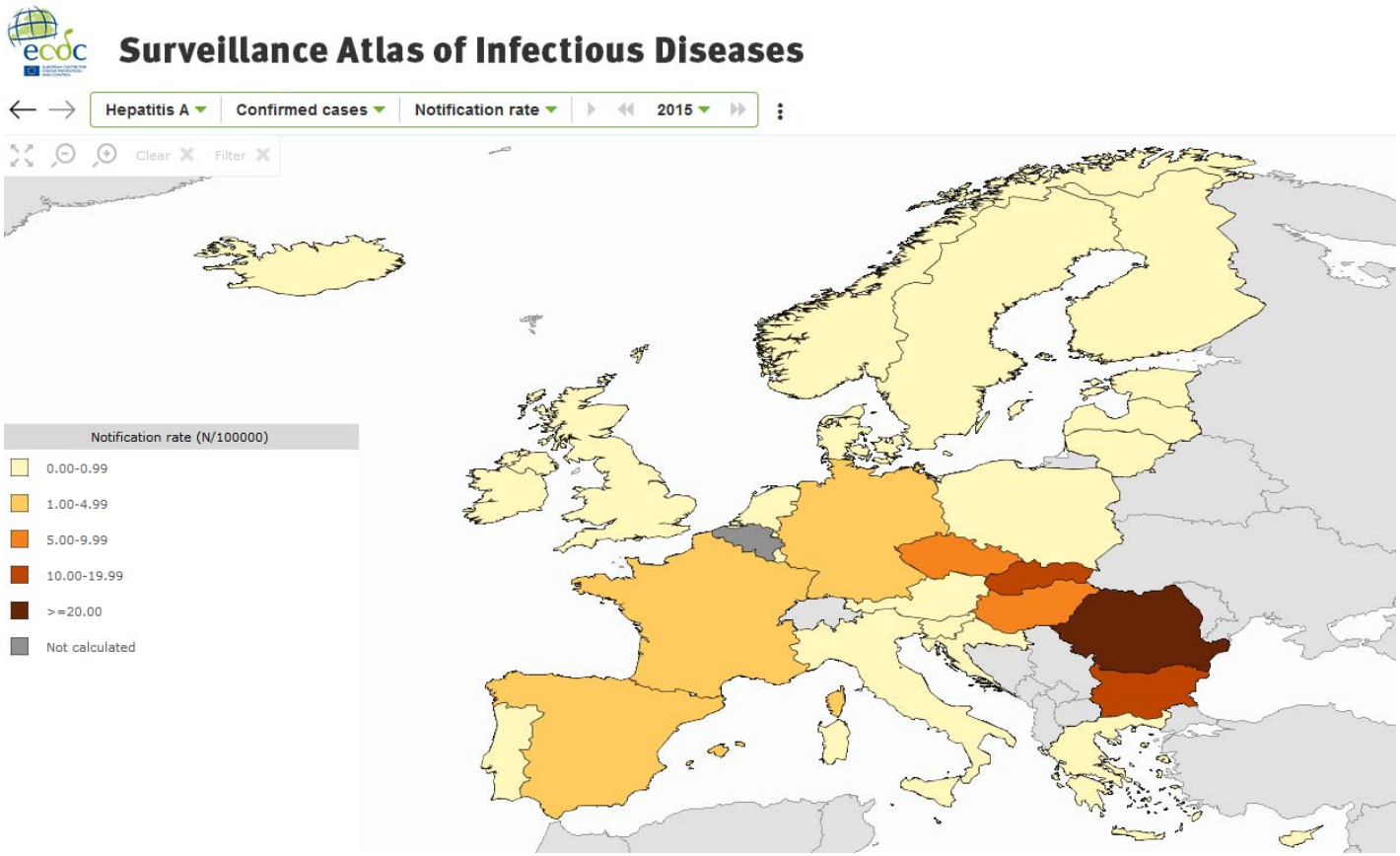
National Reporting of hepatitis A in 2015



- ✓ A large ongoing multi-country outbreak of hepatitis A in Europe (1 500 confirmed cases, 2 660 probable or suspected reported to June 2016 to 2017, Germany, Spain) driven by sexually drug use among MSM

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Nosocomial epidemic in 1998 with judicial repercussions for medical staff and management

Ross et al., NEJM 2000

Brief Report

Transmission of Hepatitis C Virus from a Patient to an Anesthesiology Assistant to Five Patients

R. Stefan Ross, M.D., Sergei Viazov, Ph.D., Tanja Gross, Friedrich Hofmann, M.D., Ph.D., Hans-Martin Seipp, M.D., and Michael Roggendorf, M.D.

PREVENTION and treatment of infections with hepatitis C virus (HCV) remain a major challenge.[1] The main source of HCV infection in developed countries was formerly transfusion of contaminated blood and blood products but is now injection-drug use.[2-4] In general, a potential risk factor can be established for about 90 percent of all cases of HCV infection.[3] One way of contracting HCV may be transmission from infected medical personnel to susceptible patients during medical care. Provider-to-patient transmission of HCV is rare, and in most cases HCV-positive surgeons are the probable source.[5-7] We studied an outbreak of HCV in a municipal hospital. Our findings suggest that an anesthesiology assistant contracted HCV from a chronically infected patient and subsequently transmitted the virus to five other patients.

risk factors for the acquisition of HCV. To search for other potential cases of HCV transmission, we performed a retrospective seroepidemiologic study of all patients who had undergone surgery in the hospital between January and July 1998. Fifty-eight of these patients had died, and 904 were still alive; serum was obtained for antibody testing from 833 of these 904 patients. Hospital personnel were interviewed with special attention to compliance with infection-control practices and were tested for HCV antibodies. The hospital — in particular, the surgical facilities — was inspected by experts in hygiene and occupational health.

Virologic and Molecular Studies

The presence of HCV antibodies was determined by enzyme-linked immunosorbent assay (ELISA; Sanofi Diagnostics Pasteur, Freiburg, Germany). Reactivity was confirmed by immunoblot assay (Mikrogen, Munich, Germany). HCV RNA was detected qualitatively and was also quantified with polymerase-chain-reaction (PCR) kits (Roche Diagnostics, Mannheim, Germany). HCV isolates were identified by genotyping, and HCV hypervariable region 1 (nucleotides 1491 to 1572, numbered as reported by Choo et al.[8]) was amplified as described elsewhere.[9,10] Products of the second PCR were purified from the agarose gel (QIAquick, Hilden, Germany) and cloned into a plasmid vector (TOPO TA cloning kit, Invitrogen, Groningen, the Netherlands). Four to six clones from each subject were sequenced in both directions (with the Dye Terminator DNA sequencing kit, Perkin–Elmer, Norwalk, Conn.).

As area controls, the PCR products of HCV isolates that were obtained from chronically infected patients (located within a radius of approximately 200 km from the hospital) were subjected to direct sequencing.[11] To prevent possible cross-contamination of the samples, stringent procedures were used for nucleic acid extraction and amplification,[12] and the analyses were performed several weeks apart. Sequences of HCV hypervariable region 1 that were obtained from the samples have been submitted to GenBank (accession numbers AF227763 through AF227786).

Statistical Analysis

A matrix of nucleotide distances was calculated by Kimura's two-parameter method.[13] The statistical significance of the differ-

Luxemburger Wort

Hepatitis-C-Infektionsfälle im Krankenhaus: die Urteile

Veröffentlicht am Donnerstag, 15. März 2012 um 14:27

Im Verfahren um die Hepatitis-C-Infektionsfälle aus dem Jahr 1998 in der hauptstädtischen Clinique Ste-Elisabeth hat die siebte Strafkammer des Bezirksgerichts Luxemburg den Forderungen der Staatsanwaltschaft weitgehend Rechnung getragen.

Einzig und allein die Klinikleitung wurde am Mittwoch vom Anklagepunkt der unterlassenen Hilfeleistung freigesprochen. Mit den Strafen wegen fahrlässiger Körperverletzung blieb das Richterkollegium um Präsidentin Paule Mersch unter dem von der Staatsanwaltschaft geforderten Strafmaß. Die verschiedenen angeführten Verteidigungsmittel wurden allesamt von den Richtern verworfen.

Gefängnis- und Geldstrafen

Der wegen Hausdiebstahls, fahrlässiger Körperverletzung und dem Konsum von medikamentösen Substanzen hauptbeschuldigte Narkosepfleger (infirmier anesthésiste) wurde zu einer Gefängnisstrafe von zwei Jahren mit zwölf Monaten Haftaufschub und einer Geldbuße von 2 000 Euro verurteilt.

Gegen die beiden angeklagten Narkoseärzte (médecins anesthésistes) wurde der Anklagepunkt der fahrlässigen Körperverletzung zurückbehalten; sie müssen ein Bußgeld von je 2 000 Euro entrichten.

Zwei weitere Ärzte, ein Orthopäde und ein Facharzt für innere Medizin, wurden vom Vorwurf der unterlassenen Hilfeleistung gemäß Art. 410-1 des Strafgesetzbuches freigesprochen. In der gleichen Logik wurden die anderen Mitglieder des Direktionsausschusses der Klinik (conseil de gestion, comité de direction) von diesem Anklagepunkt befreit.

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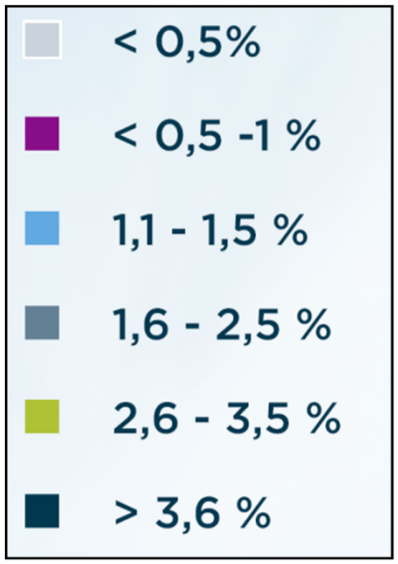
The silent epidemic of HCV



- ✓ 1 % in Luxembourg
- ✓ 4346 cases including 73 to 93% chronic HCV infection from 1990 to 2013
- ✓ Ratio 2:1 male:.female

Saraswat V et al, J Viral Hepat 2015
Gane E et al, J Viral Hepat 2015
Center for Disease Analysis, Dr Homie Razawi

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Merging of 3 databases from Luxembourg

1) Estimate HCV prevalence by merging several large laboratory diagnostic databases

- LNS = National health laboratory, 1st lab to offer HCV diagnostics in 1990s
- CHL/LIH = Large public hospital laboratory which is also reponsible for national HIV surveillance, started diagnosis in late 90s
- Laboratoires Réunis = one of 3 large private laboratories in Luxembourg (data from 2009 onwards)

2) Combine datasets using pseudonomyzed unique personal identifier (matricule national)

3) Estimate overall incidence (age/gender/mortality)

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Methods

- ✓ Approved by ethics committee and data protection

Data files merged using pseudonymized national security number

  - One line per confirmed case including date of birth, sex and age at first diagnosis (either from serology or PCR) & date of death

- ✓ Datasets were pseudonymised before merging into a combined dataset

- ✓ Incidence and mortality calculated using population data from STATEC.lu

- ✓ Survival analysis conducted in Stata 14 (HCV disease burden)

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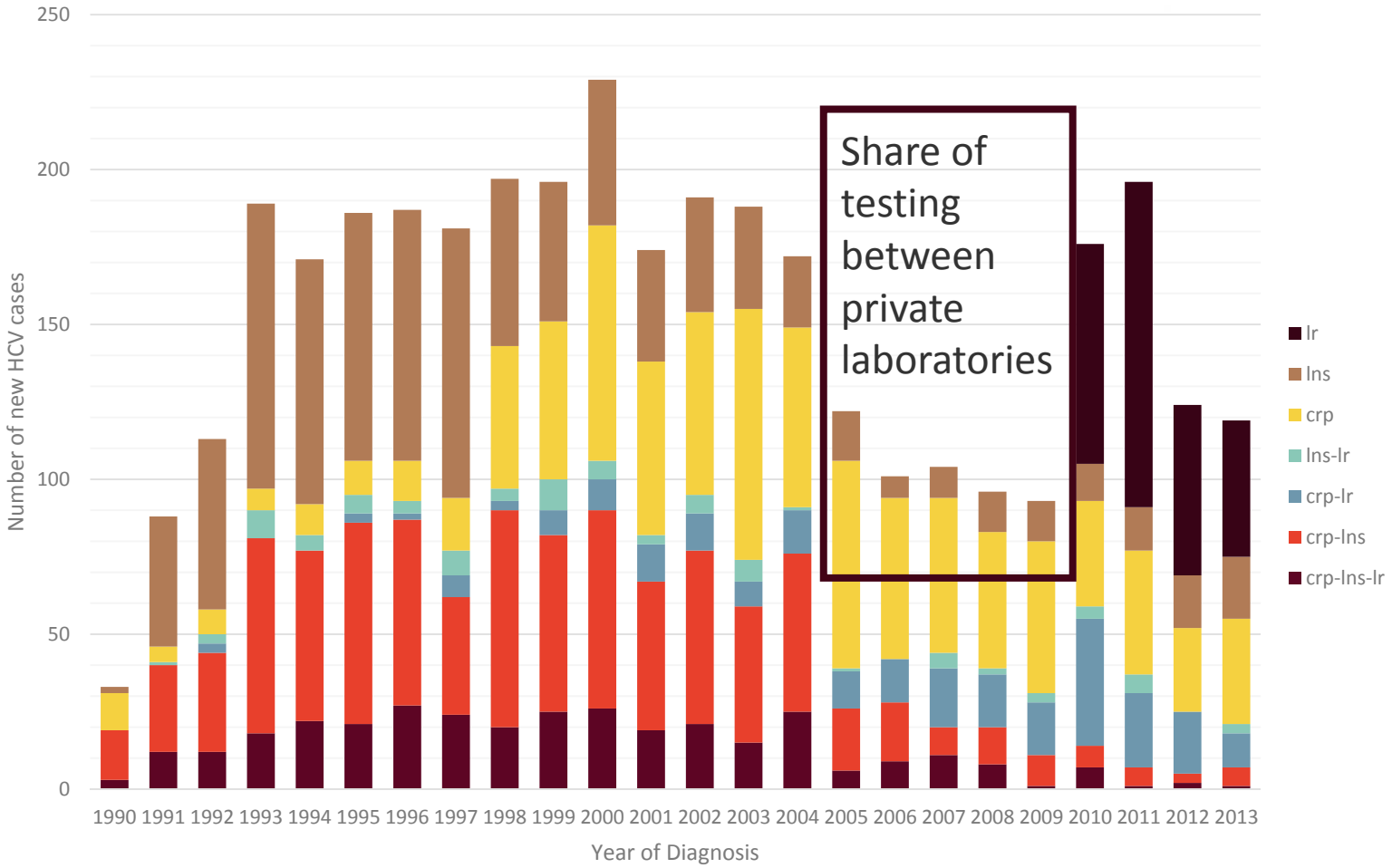
Number of new confirmed HCV cases in 3 laboratories in Luxembourg



- ✓ Overall 3626 laboratory cases identified between 1990 and 2013
- ✓ From 1993 to 2004, an average of ~200 new lab confirmed HCV cases per year

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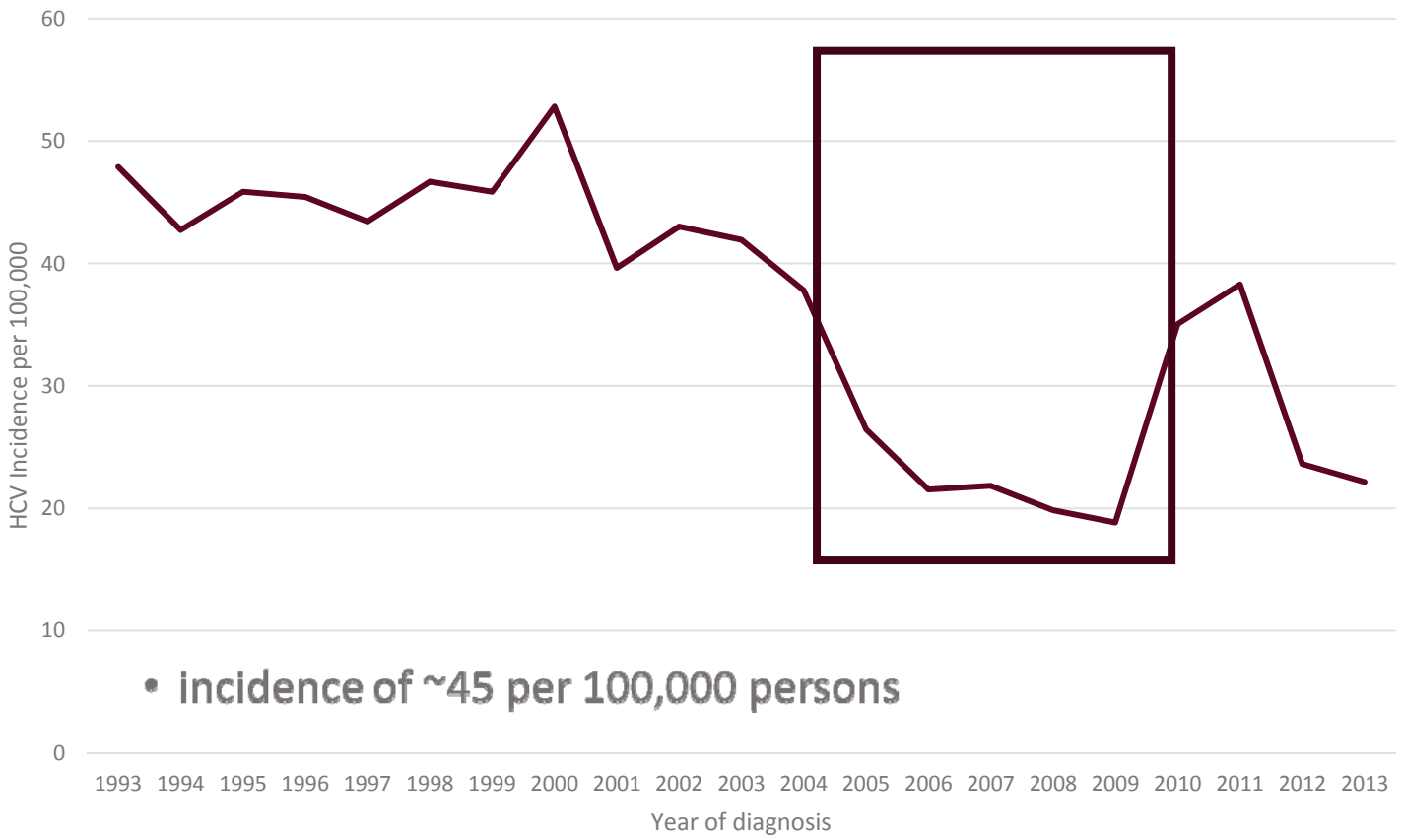
Estimates of HCV incidence in Luxembourg



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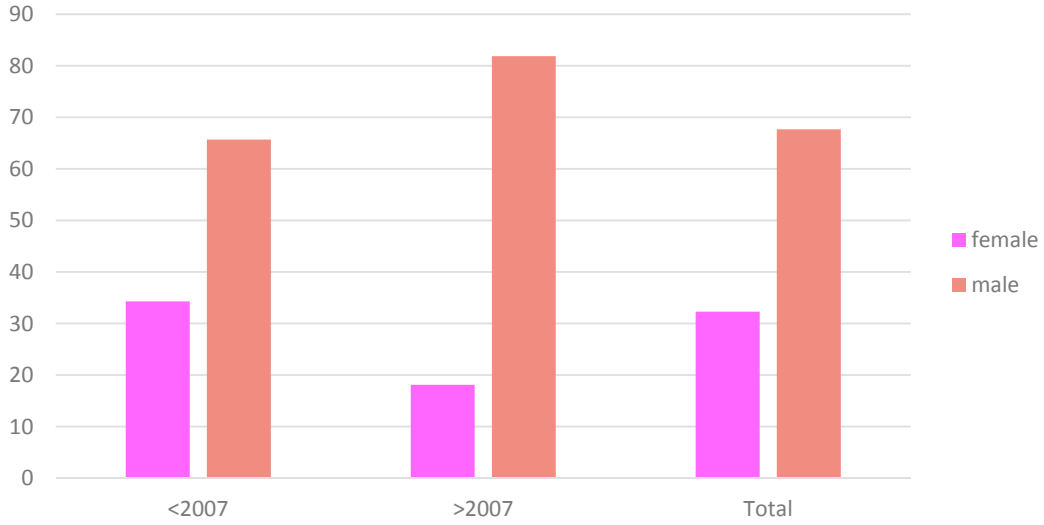
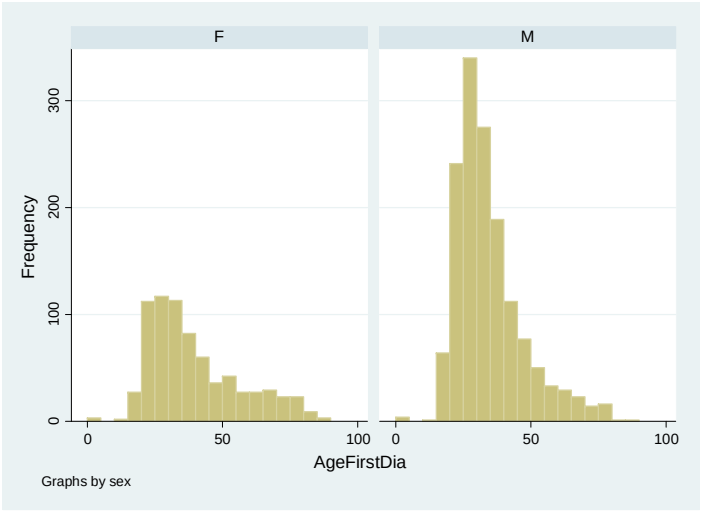
Age at first diagnosis and gender distribution of HCV cases

Gender distribution



LNS



- 33% of HCV cases are female between 1991 and 2016
- The age distribution shows a distinctive IVDU peak for both sexes
- More pronounced in men

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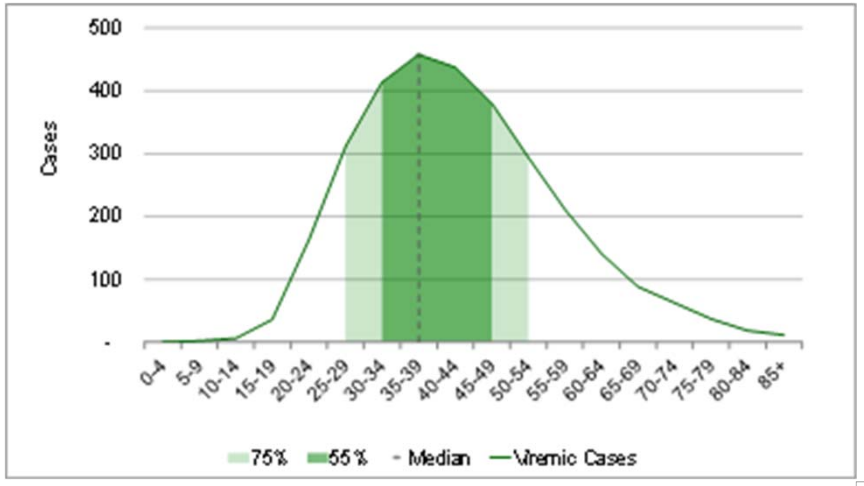
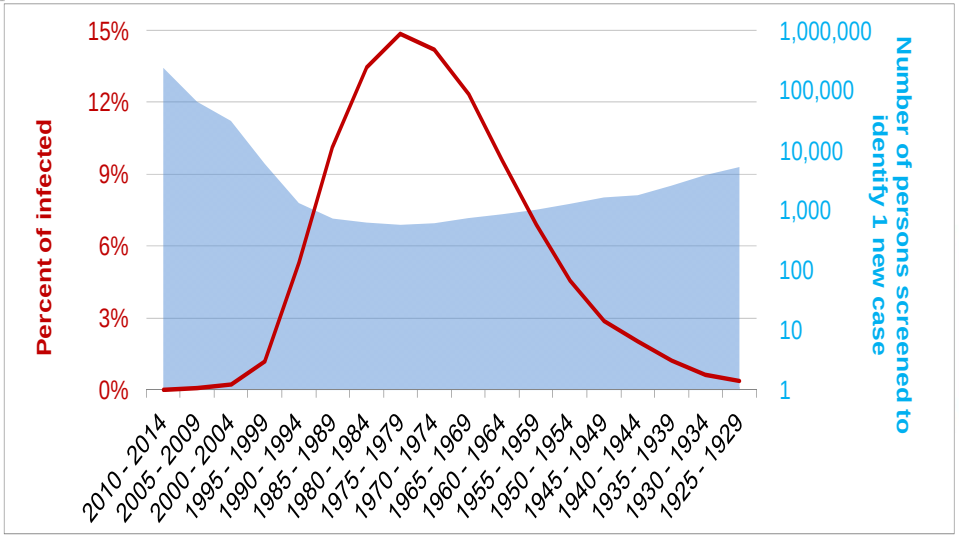
Birth cohort analysis of HCV cases



3084 cases

75% of viremic cases are born between 1960 and 1989 (25-54 years of age)

Screening of 671 individuals to identify one viremic HCV infected case



Percent of infected cases by birth cohort, and the number screened to identify 1 viremic case in 2014

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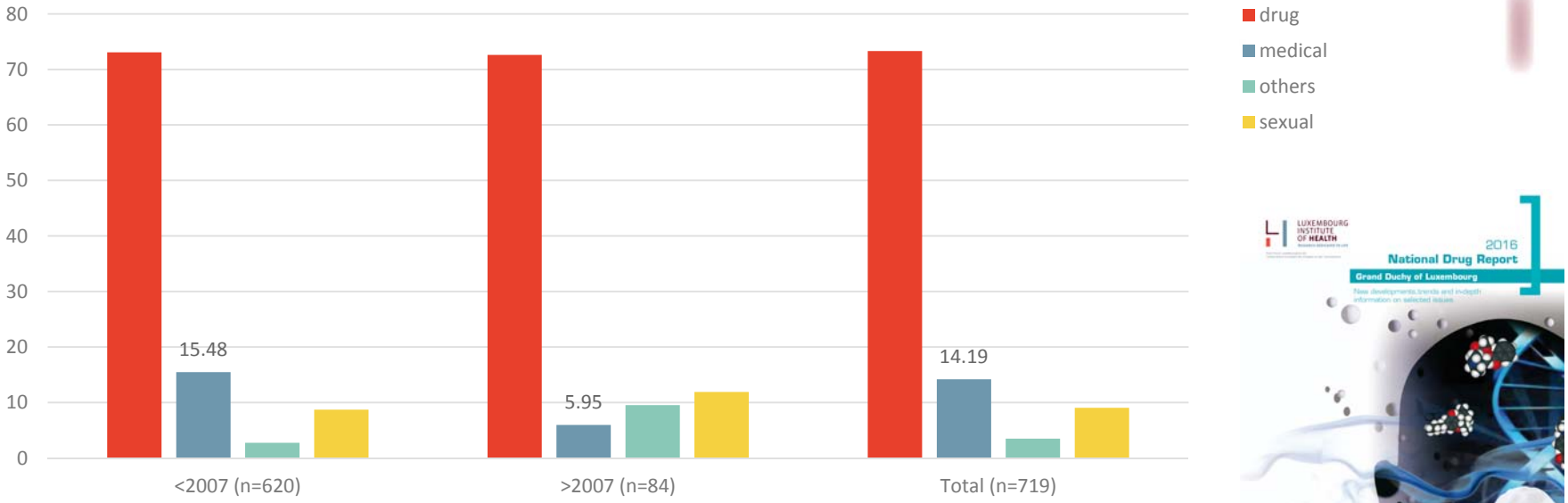
HCV epidemic driven by IVD drug use



Roman F et al, 2009

- ✓ 2 500 PWIDs estimated, 44% of the HCV population
- ✓ National harm reduction offers are highly developed, diversified, decentralized, available in prison, high access to OST (3 000 demanders in 2015), middle coverage for NSP, both available in prison
- ✓ One drug consumption room since 2005 and a new facility will be launched in 2018 in the South of the country.

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Higher prevalence of injecting drug use in Luxembourg than in Belgium

Estimates of the prevalence of injecting drug use (rate per 1 000 population aged 15–64), last study available

		Injecting drug use prevalence (per 1 000 population aged 15–64)			Estimated number of users		
Country	Year	Central	Lower	Upper	Central estimate	Lower bound	Upper bound
Belgium	2015	3.28	2.32	4.61	23828	16841	33517
Croatia	2015	2.21	1.79	2.87	6344	5147	8255
Cyprus	2015	0.42	0.3	0.67	198	141	316
Czech Republic	2015	6.25	6.12	6.38	43900	43000	44800
Estonia	2009	5.89	4.29	10.8	5 362	3 906	9 837
France	2014	2.59	2.1	3.2	105000	85300	130000
Finland	2012	4.6	4.1	6.7	15 611	13 770	22 665
Greece	2015	0.77	0.6	1.02	5397	4225	7129
Hungary	2015	0.98			6707		
Latvia	2012	9.22	7.34	11.68	12 573	10 003	15 914
Luxembourg	2009	5.68	4.5	6.85	1 907	1 524	2 301
Norway	2014	2.47	2.2	2.98	8393	7459	10141
Portugal	2012	2.2	1.94	2.46	14 426	12 732	16 101
Spain	2014	0.24	0.18	0.31	7578	5634	9522
Sweden	2008–11	1.31			8 021		
United Kingdom	2004–11	3	2.87	3.22	122 894	117 370	131 869

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High seroprevalence of HCV among IDUs

Removille *et al. BMC Public Health* 2011, **11**:351
http://www.biomedcentral.com/1471-2458/11/351

Table 2 Seroprevalence (%)

		OTC N/Ntotal	ITC N/Ntotal	PC N/Ntotal	IDUs N/Ntotal	nIDUs % N/Ntotal
HBV (cured or active infection)	Active HBV (HBs ag+)	1.5 2/130	0 0/54	7.0 8/115	3.9 10/254	0 0/45
	Cured HBV (HBs ab+, HBc ab+)	13.1 17/130	14.8 8/54	23.5 27/115	19.3 49/254	6.7 3/45
	Total HBVab *	22.3 29/130	16.7 9/54	34.8 40/115	29.1 74/254	8.9 4/45
HBV vaccination (HBs ab+)		39.2 51/130	57.4 31/54	45.2 52/115	46.1 117/254	37.8 17/45
HBV seropositivity (all types)		61.5 80/130	74.1 40/54	80.0 92/115	75.2 191/254	46.7 21/45
HCV (Elisa +, RIBA +) HCVab		57.3 75/131	75.4 46/61	86.3 107/124	81.3 218/268	19.1 9/47
HAV (IgG+) HAVab		54.7 70/128	57.1 24/42	68.3 41/60	57.1 108/189	65.9 27/41
HIV-1 HIVab		1.5 2/130	0 0/49	7.7 5/65	2.5 5/202	4.8 2/42

*Including 18 cases with HBc antibody only.

- ✓ **81% of HCV seroprevalence in IVDU in 2010 (Removille et al, BMC Public Health 2011), 4% of HBs Ag+, 19% cured HBV, 46% HBV vaccination**
- ✓ **75% of HCV seroprevalence in 300 IVDU attending the drug consumtion room between 2015 and 2017 (60% of viremic patients)**

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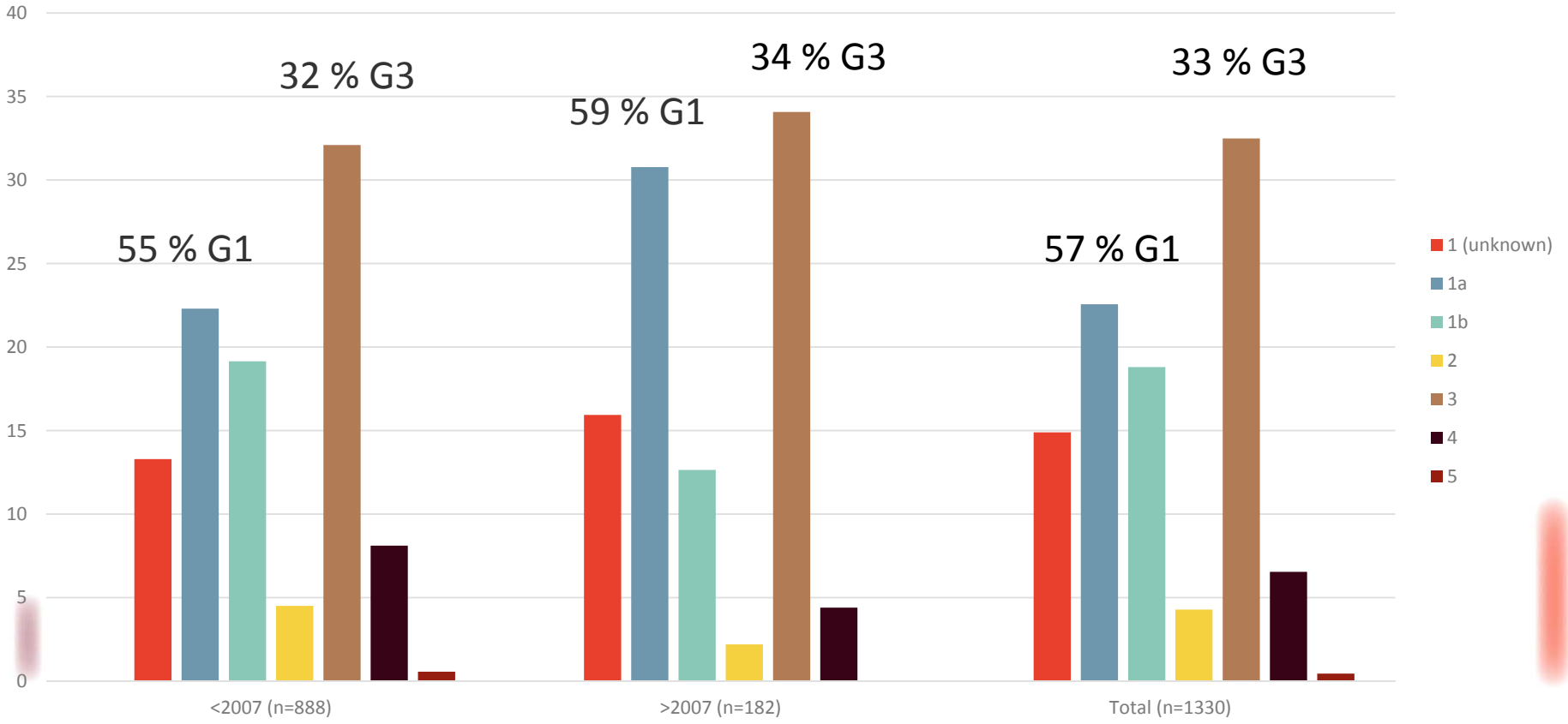
Genotype distribution, high prevalence of genotype 3 at CHL



38% of G3 in 300 IDUs at the drug consumption room between 2015 and 2017

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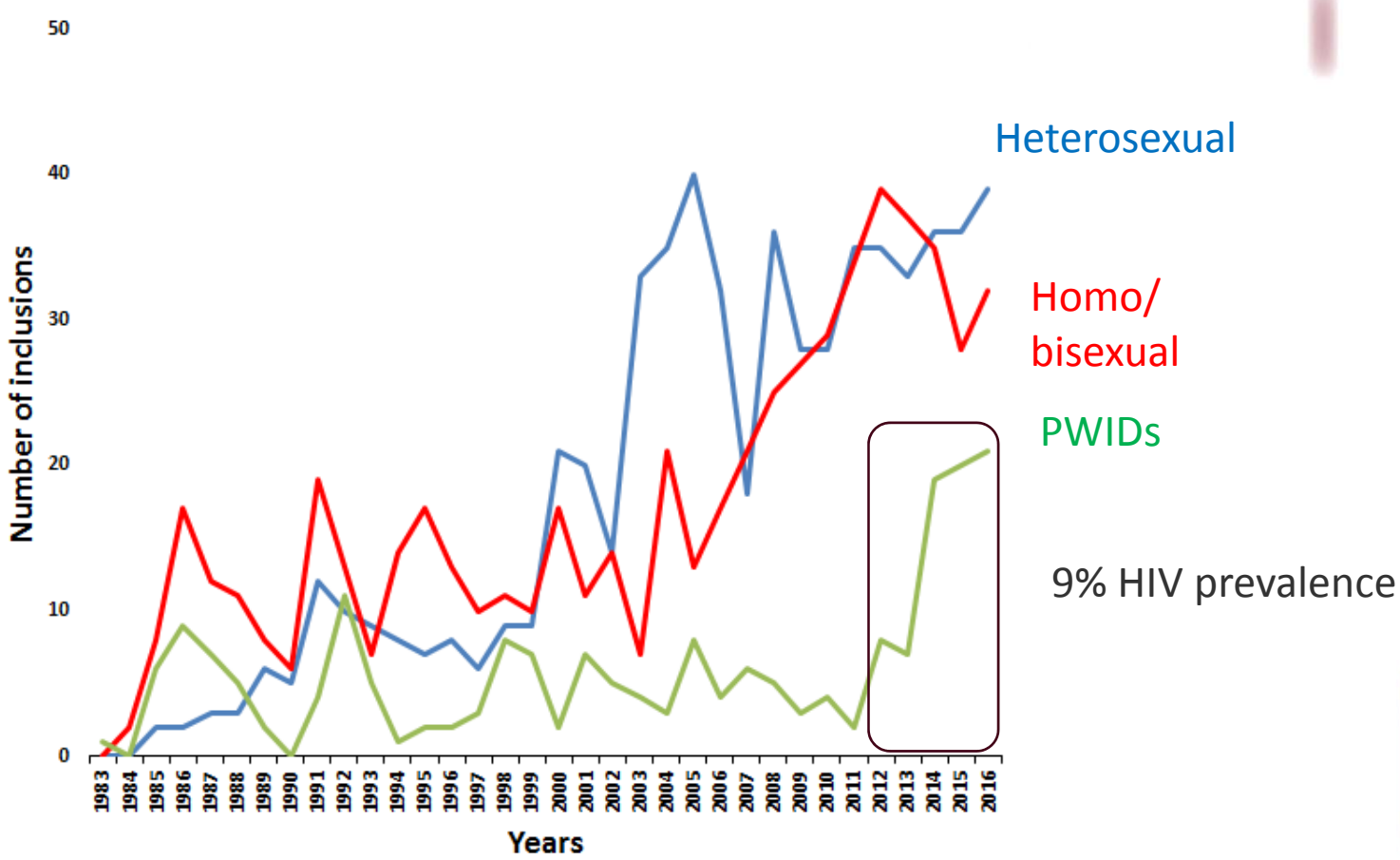
HIV outbreak in PWIDs



- 2013-2016: 67 new PWIDs cases included in the HIV cohort at the National Service of Infectious Diseases
- 8 PWIDs included in 2017 (increased treatment access, reinforcement of awereness and prevention measures).

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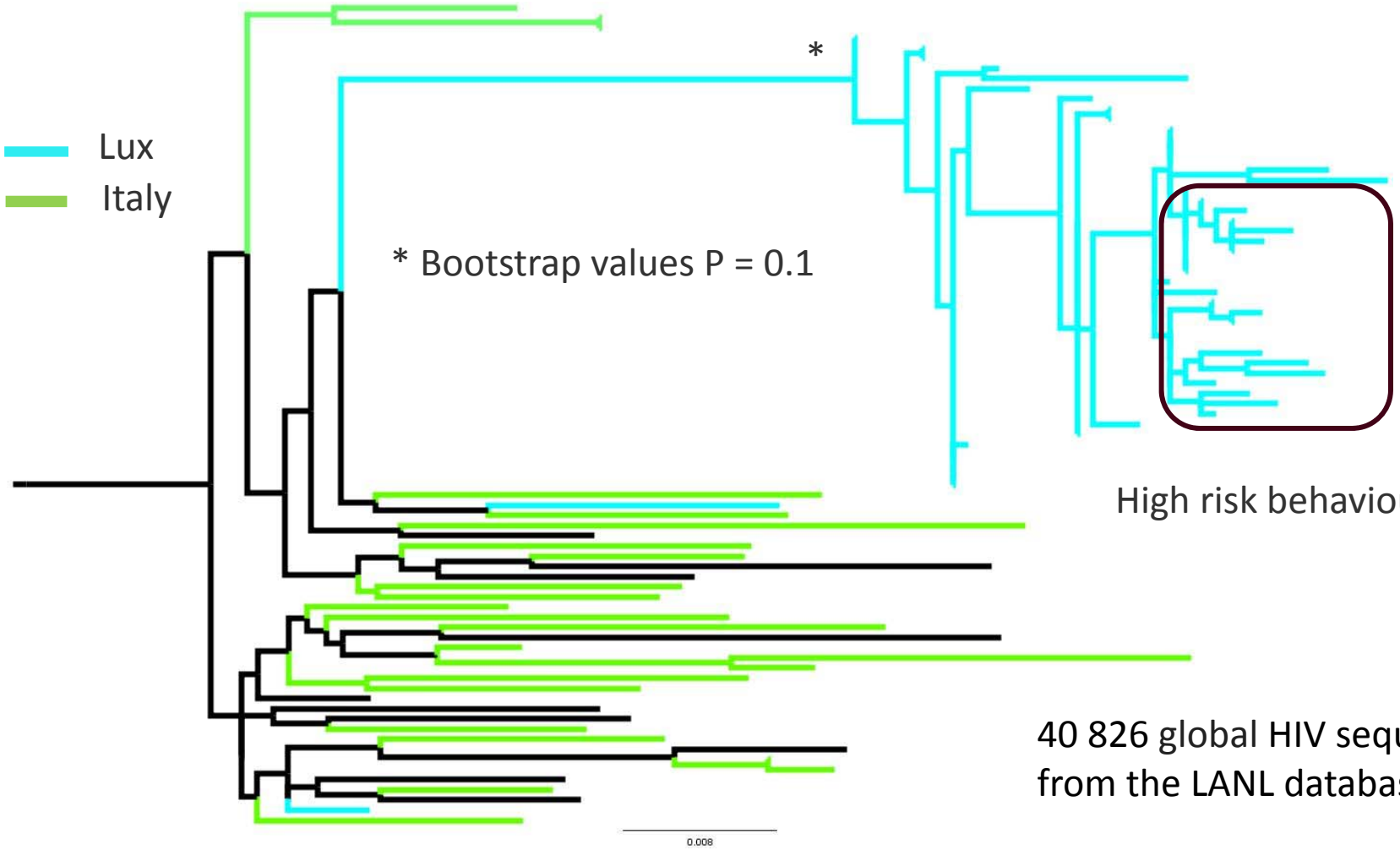
2013-2016: local HIV epidemic, 2 main clusters

33 PWIDs belongs to one HIV-1 subtype B cluster of 45

8 PWIDs belongs to one HIV-1 CRF-14BG cluster of 12



High risk behaviour !

40 826 global HIV sequences from the LANL database

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Cocaine injection vs heroin injection

Characteristic	Total (%)	drug users		p-value
	n=153	COC ± HERO (n=90)	HERO alone (n=63)	
Age				
median (IQR)	41 [34-46]	39 [33-45]	44 [38-52]	0.0015
Age of first consumption				
median (IQR)	17 [14-20]	17 [14-20]	17 [15-21]	0.53
Regular consumption				
Yes	126 (82.9%)	80 (89.9%)	46 (73.02%)	0.0065
No	26 (17.11%)	9 (10.11%)	17 (26.98%)	
poly-use of drugs				
Yes	103 (68.67%)	86 (97.73%)	17 (27.42%)	<0.0001
No	47 (31.33%)	2 (2.27%)	45 (72.58%)	
under OST				
Yes	103 (67.76%)	61 (68.54%)	42 (66.67%)	0.82
No	49 (32.24%)	28 (31.46%)	21 (33.33%)	
Drug sharing				
Yes	92 (63.45%)	63 (71.59%)	29 (50.88%)	0.01
No	56 (36.55%)	25 (28.41%)	28 (49.12%)	
Syringe sharing				
Yes	22 (16.06%)	17 (20.24%)	5 (9.43%)	0.09
No	115 (83.94%)	67 (79.76%)	48 (90.57%)	
Preservative use				
Yes	60 (48.78%)	42 (56%)	18 (37.5%)	0.04
No	63 (51.22%)	33 (44%)	30 (62.5%)	
Prostitiuion				
Yes	19 (12.42%)	14 (15.56%)	5 (7.94%)	0.16
No	134 (87.58%)	76 (84.44%)	58 (92.06%)	
Prison				
Yes	67 (43.79%)	40 (44.44%)	27 (42.86%)	0.84
No	86 (56.21%)	50 (55.55%)	36 (57.14%)	
piercing				
Yes	43 (28.1%)	34 (37.78%)	9 (14.29%)	0.0015
No	110 (71.9%)	56 (62.22%)	54 (85.71%)	
HIV + last test				
Yes	17 (11.18%)	14 (15.56%)	3 (4.84%)	0.05
No	135 (88.82%)	76 (84.44%)	59 (95.16%)	

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Conclusions

- ✓ Laboratory based incidence estimates substantially higher (2x-3x) than clinical notifications but incompleteness since our study did not include all HCV testing labs
- ✓ New mandatory laboratory based notification for all infectious diseases -> improve data collection & incidence estimation for HCV
- ✓ High seroprevalence of HCV among IDUs (> 70%)
- ✓ 38 % of genotype 3 among IDUs
- ✓ Recent HIV outbreak in IDUs due to cocaine injection and high precarisation.

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CHL
Centre Hospitalier de Luxembourg

ABRIGADO

HIV Berodung

croix-rouge luxembourgeoise
Mënschen hëllefen

jugend- an drogenhëllef
Fondation