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HIV-1 outbreak among injecting drug users in Greece, 2011: a preliminary report

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A significant increase (more than 10-fold) in the number of newly diagnosed HIV-1 infections among injecting drug users (IDUs) was observed in Greece during the first seven months of 2011. Molecular epidemiology results revealed that a large proportion (96%) of HIV-1 sequences from IDUs sampled in 2011 fall within phylogenetic clusters suggesting high levels of transmission networking. Cases originated from diverse places outside Greece supporting the potential role of immigrant IDUs in the initiation of this outbreak.

During the first months of 2011, an unprecedented upward shift in the number of newly diagnosed cases of human immunodeficiency virus type 1 (HIV-1) infection among injecting drug users (IDUs) in Greece was noticed. In order to verify the epicentre of the outbreak and to identify unusual patterns of viral transmission, enhanced surveillance and a molecular epidemiology study among IDUs were conducted. This is a brief overview of surveillance data up to 31 July 2011 and of the preliminary results of the molecular epidemiology analysis.

Epidemiological situation in Greece between 2000 and 2010

From 2000 to 2010, between 397 and 653 cases of HIV-1 infection were notified annually in Greece, with the majority of cases in men who have sex with men (MSM) (Figure 1) [1].

The newly reported cases among IDUs ranged from nine to 19 per year during 2000–2010 [2], which corresponded to approximately 1.5-4.5% of the total HIV-1 infections reported on an annual basis. A distinctive characteristic of HIV-1 transmission in Greece, compared with other southern European countries, was the unusually low number of HIV-1 infections among IDUs [2]. The low level of HIV-1 transmission in IDUs in Greece was indeed unexpected given the documented sharing of needles and syringes, and the substantial prevalence of IDU-related hepatitis C infection [1].

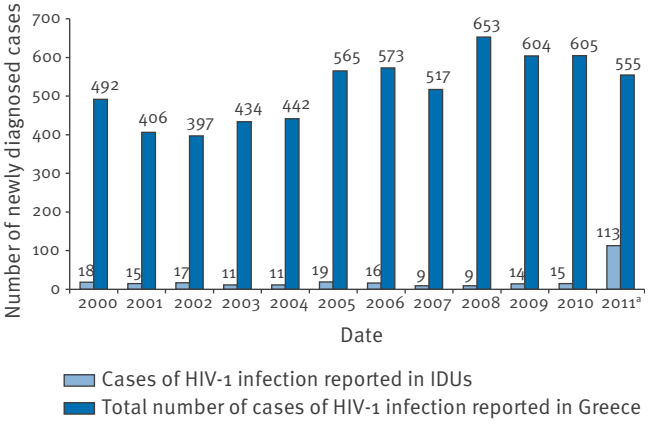
Epidemiological situation in Greece during the first seven months of 2011

From 1 January until 31 July 2011, 555 new cases of HIV-1 infection were notified to the Hellenic Center for Diseases Control and Prevention, in the context of the mandatory HIV-1 / acquired immune deficiency syndrome (AIDS) reporting system (Figure 1).

As in the previous years, most of the cases identified this year were men (n=481; 86.7%) and homosexual contact was the predominant mode of HIV-1 transmission (n=174). Based on the total number of newly

Figure 1

Newly diagnosed cases of HIV-1 infection reported in Greece, 1 January 2000 – 31 July 2011



IDUs: injecting drug users.
[a] 1 January – 31 July 2011.

HIV-1 diagnosed cases reported until the end of July, we anticipate an approximate increase of 55%-60% in the total annual number of reported cases by the end of 2011.

Transmission among IDUs

Of the total number of cases, 113 were registered among IDUs (20.4%), which is the largest number ever reported in this group from the beginning of the epidemic in Greece. This figure represents a more than 10-fold increase in the number of newly diagnosed cases of HIV-1 infection in IDUs. Among them, 87% were men, 74% were aged between 25 and 40-years old and among the cases for whom the place of residence was known, 76% came from the Athens metropolitan area. Sixty-seven of the IDU cases were Greek citizens, 18 were foreigners and for 28 the nationality could not be identified. The analysis of preliminary data suggests that IDUs accounted for 50%-55% of the increase in the total number of HIV-1 infection cases reported during 2011.

Molecular epidemiology analysis in IDUs

To identify the origin and patterns of HIV-1 spread among IDUs, phylogenetic analyses were performed on HIV-1 sequences sampled from newly identified IDUs (n=34) collected from the beginning of 2010 until the end of May 2011. Specifically, 11 plasma specimens collected in 2010 and 23 plasma specimens collected in 2011, submitted for routine HIV RNA and drug resistance testing were analysed. HIV-1 protease (PR) and partial reverse transcriptase (RT) sequences were generated using the HIV-1 TRUGENE Genotyping kit (Bayer, HealthCare) and ViroSeq HIV-1 Genotyping system (Celera Diagnostics). HIV-1 subtypes were determined manually by phylogenetic analysis including a set of reference sequences (http://www.HIV.lanl.gov) and also by using the COMETHIV-1/2 subtyping tool (v. 0.2) (http://comet.retrovirology.lu/). Phylogenetic trees were estimated using the neighbour-joining method under the GTR+gamma model of nucleotide substitution, as implemented in PAUP* [3]. Reliability of clustering was assessed by bootstrap analysis (100 replicates). Further phylogenetic analysis within HIV-1 subtypes, included a large set of HIV-1 sequences from Greece sampled between 1998 and 2009 (more than 2,000 cases) and reference sequences sampled globally [4]. Only grouped sequences from IDUs that received bootstrap support higher than 75% were considered as 'clustered' [5].

According to the subtyping analysis, the prevalence of HIV-1 clades in the newly identified samples from IDUs in 2010 and 2011 was as follows: subtype A: 20/34, subtype B: 9/34, subtype G: 4/34 and CRF02_AG: 1/34 [3] (Table).

These figures were substantially different from the prevalence of HIV-1 subtypes estimated from 2,327 HIV-1 infected individuals sampled during the period from 1998 to 2009, which comprise 24% of the total cases of HIV-1 infection reported in Greece since the beginning of the HIV epidemic (Table) [4,6].

Further analysis of the subtype G sequences classified them as CRF14_BG, which belongs to subtype G in the partial PR and RT region.

Detailed phylogenetic analyses, including a large set of Greek isolates sampled between 1998 and 2011 as well as reference isolates from other countries, revealed that 28 of the 34 sequences from the newly identified cases of HIV-1 infection among IDUs in 2010 and 2011 fell within seven separate phylogenetic clusters. More specifically, six of the 11 of the sequences from 2010 were found in three clusters, and 22 of the 23 the sequences from 2011 were found in four clusters.

Seventeen of the 20 individuals infected with subtype A fell in clusters of IDU local transmission networks. Among those, we identified three phylogenetic clusters consisting of 12, three and two sequences. The cluster of 12, shown as an example in Figure 2A, formed part of a larger cluster of sequences obtained from infected IDUs in Asia. Based on previous analyses of a large population of local viral isolates (n=2,327) [6], this is the first identification of HIV-1 subtype A Asian strains in Greece. This finding supports a recent introduction from migrating population although alternative hypotheses cannot be entirely excluded. The two smaller clusters of subtype A were nested within a large population of IDUs from the Former Soviet Union countries.

For subtype B, six of nine sequences formed two phylogenetic clusters of, both originating from Greece (Figure 2B). One of the clusters contained five isolates, the sixth isolate was part of a cluster of two, one of which was sampled before 2010. For subtypes G and CRF02_AG, all cases were grouped in phylogenetic clusters of four and one sequence, respectively originating from southwest Europe.

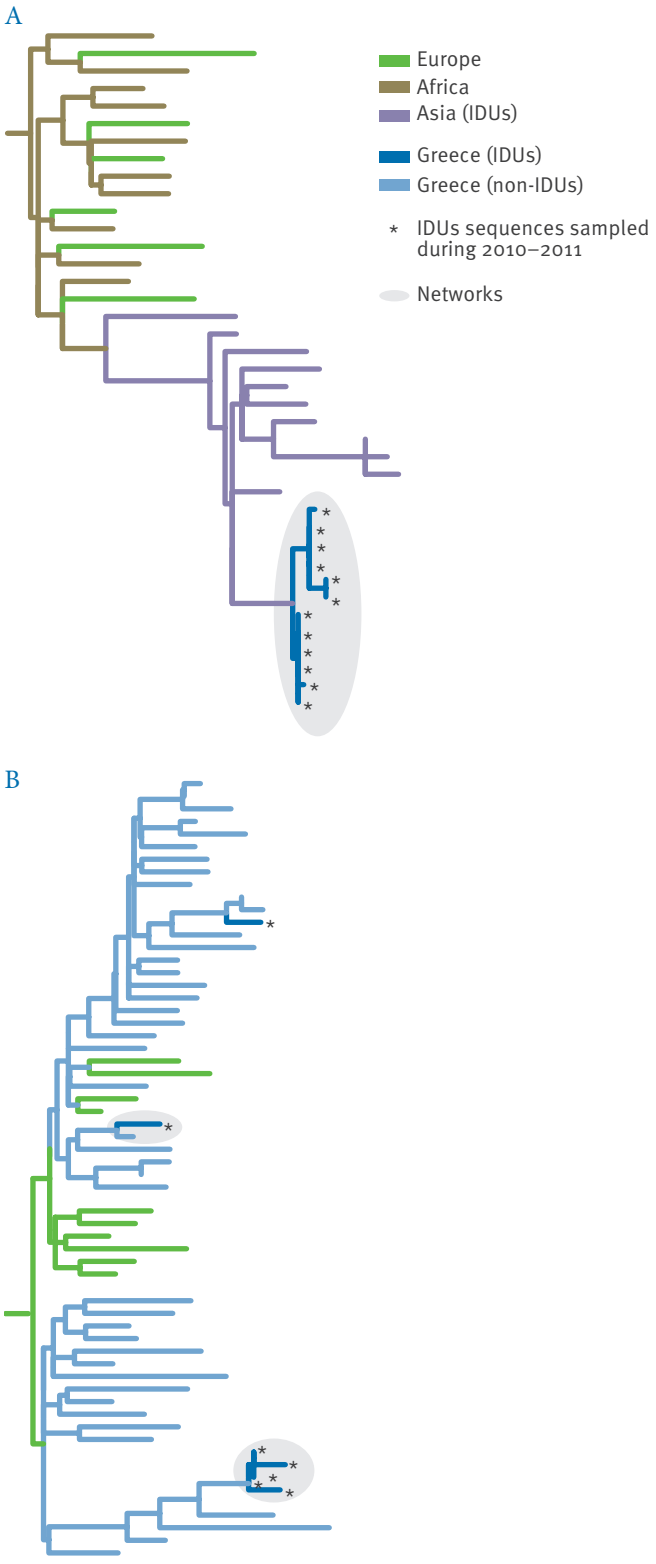
Table

Prevalence of HIV-1 subtypes in the general population and in injecting drug users, Greece, 1998–2009 and 2010–2011

Population	Subtypes (n, %)					
	A	B	G	CRF02_AG	Others	**Total**
Total HIV-1 infected population sampled during 1998-2009	572 (24.6%)	1,396 (60.0%)	20 (0.9%)	44 (1.9%)	296 (12.7%)	**2,327**
Injecting drug users sampled during 2010-2011	20 (58.8%)	9 (26.5%)	4 (11.8%)	1 (2.9%)	0 (0%)	**34**

Figure 2

Phylogenetic trees of HIV-1 isolates sampled in Greece and other countries between 1998 and 2011



A: HIV-1 sequences from IDUs in Greece originating from Asia (subtype A).

B: HIV-1 sequences from IDUs in Greece originating from a local transmission network (subtype B).

Moreover, the branch lengths for all phylogenetic clusters identified in 2011 were very short, suggesting a very recent infection among the study population (Figure 2). Only in one case an additional sequence from 2010 (subtype G) was found within the short-branched phylogenetic clusters from 2011.

Discussion

Until the beginning of 2011, the HIV-1 epidemic in Greece had been concentrated on MSM. Nevertheless, since 2010, the pattern of viral transmission in Greece seems to be changing now affecting also substantially the subgroup of IDUs. Data from the national HIV-1/AIDS registry showed an increase higher than 10-fold in the rate of notified cases of HIV-1 in IDUs, which amounted to approximately one fifth of the total recorded cases for the first seven months of 2011.

Firstly, in accordance with surveillance data, our preliminary molecular epidemiology results indicated short-branched clusters in 2011, which were highly suggestive of a recent epidemic among the IDUs. Secondly, the prevalence of HIV-1 subtypes was different from previous estimates derived from a large population of HIV-1 infected individuals in Greece [4,6]. Thirdly, the new epidemic seems to be spreading through transmission networks of different sizes, suggesting a limited number of sources, or high levels of transmission networking among the IDUs. The largest transmission network consisted of 12 sequences including half of the analysed IDUs samples in 2011. According to the Greek HIV/AIDS molecular surveillance programme, these sequences derived from newly identified cases of HIV-1 infection. Fourthly, viral sources for the different networks were mainly originated from globally circulating viruses (CRF14_BG, subtype A) suggesting a potential role of migrant IDUs for the initiation of the recent outbreak [7,8].

A potential limitation was the small number of HIV-1 sequences from IDUs included in the analysis. Final conclusions about the levels of networking will be made based on additional data as the outbreak evolves.

HIV infection is a serious consequence of drug use and remains an important public health challenge. The high prevalence of HIV-1 infection among the IDUs in the eastern part of Europe is still worrying [9]. Interestingly, a neighbouring country, Bulgaria, experienced a steady increase in HIV reporting rates, from none per million population in 2003 to almost seven per million population in 2008 [10]. Given the estimated large number of IDUs (20,000–27,000) (unpublished data) who inject illicit drugs in Greece and the limited resources in the public sector because of the current financial situation in Greece, public health authorities face the potential of a rapidly growing HIV-1 epidemic in this vulnerable subset of population and, possibly to the wider community, with dramatic medical, social and economical consequences [11-13]. Preventive interventions and epidemiological monitoring along with an appropriate

allocation of available resources are the key components of an effective and sustained response. An integrated and combined prevention initiative including awareness campaigns targeting IDUs and healthcare and social personnel working with IDUs, large-scale distribution of sterile injecting equipment, increased access to opioid substitution therapy, higher uptake of HIV-1 testing and expanded coverage of antiretroviral treatment among IDUs, have shown to be effective in decreasing transmission rates in IDUs. These should be taken into consideration as measures to stop the outbreak [14-19]. Otherwise, the authors believe that the HIV epidemic in Greece is potentially unstoppable.

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Mapping HIV-related behavioural surveillance among injecting drug users in Europe, 2008

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The systematic collection of behavioural information is an important component of second-generation HIV surveillance. The extent of behavioural surveillance among injecting drug users (IDUs) in Europe was examined using data collected through a questionnaire sent to all 31 countries of the European Union and European Free Trade Association as part of a European-wide behavioural surveillance mapping study on HIV and other sexually transmitted infections. The questionnaire was returned by 28 countries during August to September 2008: 16 reported behavioural surveillance studies (two provided no further details). A total of 12 countries used repeated surveys for behavioural surveillance and five used their Treatment Demand Indicator system (three used both approaches). The data collected focused on drug use, injecting practices, testing for HIV and hepatitis C virus and access to healthcare. Eight countries had set national indicators: three indicators were each reported by five countries: the sharing any injecting equipment, uptake of HIV testing and uptake of hepatitis C virus testing. The recall periods used varied. Seven countries reported conducting one-off behavioural surveys (in one country without a repeated survey, these resulted an informal surveillance structure). All countries used convenience sampling, with service-based recruitment being the most common approach. Four countries had used respondent-driven sampling. Three fifths of the countries responding (18/28) reported behavioural surveillance activities among IDUs; however, harmonisation of behavioural surveillance indicators is needed.

Introduction

Injecting drug users (IDUs) are vulnerable to a wide range of viral and bacterial infections through poor injection hygiene [1-3]. These infections, which include HIV, hepatitis C and hepatitis B, result in considerable levels of morbidity and mortality. With an estimated 750,000 to 1 million active IDUs in the European Union (EU) [4], these infections have the potential to place a considerable burden on European healthcare systems, as well as adversely impacting on the well-being of those who inject drugs.

Interventions have been adopted throughout Europe that aim to reduce risk of these infections [5]; these interventions include opiate substitution therapy (OST) and needle and syringe exchange programmes (NSPs), both of which have been shown to effective in preventing infections [6-10]. They aim to reduce infections by changing the behaviours that place individuals at risk of infection, such as through reducing the sharing and reuse of injecting equipment and by decreasing the frequency of drug injection. Monitoring the levels of these behaviours is thus important for assessing the impact of intervention programmes [11]. The systematic collection of information on risk and protective behaviours is therefore an important part of second-generation HIV surveillance systems [12]. Behavioural surveillance focused on IDUs often looks at behaviours related to a range of viral infections of the blood, not just HIV, due to the similarities in the routes of transmission [13].

In response to the HIV epidemic, some countries in Europe established studies to monitor HIV and/or related risk behaviours among IDUs [14,15]. The high burden due to infections among IDUs resulted in the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) developing its drug-related infectious disease key indicator [13]. This indicator has collected data on the prevalence of HIV and hepatitis B and C since the late 1990s, and more recently has collated behavioural data.

We examine here the extent of behavioural surveillance among IDUs in the EU Member States and European Free Trade Association (EFTA) countries is examined, focusing on the methods employed and the indicators used. The EU/EFTA countries are Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary,

Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Methods

During August and September 2008, a survey was undertaken of all EU Member States and EFTA countries about behavioural surveillance activities related to HIV and other sexually transmitted infections (STIs).. Each country was sent nine separate questionnaires [16,17]. One explored the overall national system for behavioural surveillance and second-generation HIV surveillance. The remaining eight questionnaires each asked about a specific subpopulation (general population, youth, men who have sex with men (MSM), IDUs, STI clinic attendees, migrants, sex workers and people living with HIV/AIDS). It was emphasised on each questionnaire that the focus was behavioural data collection, as opposed to biological surveillance.

The population-specific questionnaires identified whether a country had undertaken behavioural surveillance activities for that population and if so, asked them to provide information about the methodology used. In particular, more details were requested with respect to the year(s) in which behavioural studies had been performed (since 1985), sample sizes, target populations, geographical coverage, and the recruitment and data collection methods used. Information was requested on: (i) all of the repeated studies undertaken, that is, either cross-sectional behavioural surveys that have been repeated over time, cohort studies and any other repeated collections of behavioural data (referred to as 'behavioural surveillance studies'); and (ii) any one-off behavioural surveys that had been conducted, that is, surveys that have only been undertaken at a single point in time (referred to as 'one-off surveys'). Respondents were asked to indicate the main topics covered in the behavioural surveillance studies from a detailed list grouped as follows: knowledge and attitudes regarding HIV and other STIs, sexual relationships and sexual partners, sexual activity and lifestyle, exposure to risk of infection, HIV and STI testing, drugs and substance use. Information was also requested on any main indicators that the country was currently using for monitoring purposes that were based on the behavioural surveillance data.

The questionnaires were sent by email to people in the countries who were the contact points for HIV surveillance for the European Centre for Disease Prevention and Control (ECDC), with the option of consulting other colleagues with specialist knowledge to complete the questionnaires. In the case of the IDU questionnaire, the contact points were encouraged to liaise with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) national focal point. The key contacts returned the completed questionnaires and these were loaded into a password-protected database. The data for each population were analysed separately by an expert team member (listed at the end of this article).

In February 2009, a draft mapping of behavioural surveillance activities was presented and discussed at the Behavioural Surveillance Expert Meeting that was organised as part of the project. A total of 50 participants, including experts in behavioural surveys in the various populations, national experts and representatives of international organisations – EMCDDA, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) – reviewed the mapping and the suggested sets of indicators. A revised draft of the mapping was sent to the countries for validation and 11 provided additional information on there activities, which was then incorporated into the final mapping.

Results

Of the 31 countries invited to participate, 28 returned a questionnaire on IDUs. Of these 28, 18 reported behavioural surveillance activities among IDUs: 16 indicated that they had one or more behavioural surveillance studies and seven had conducted one-off surveys. Five countries had conducted both types of studies. Thus 10 of the 28 responding countries reported having no behavioural surveillance related activities among IDUs.

Behavioural surveillance studies

Of the 16 countries that had conducted one or more behavioural surveillance studies among IDUs, two did not provide further details. Among the other 14 countries, either repeated surveys or cohorts were used and/or data were collected through the national Treatment Demand Indicator system. Such systems collect data on the drug use and demographic characteristics of all drug users entering into drug treatment programmes [18]. All EU Member States have such a system to collect data from the clinical assessments of those presenting for treatment, but most do not use it to collect information on risk behaviours related to HIV and other infections. Five countries reported using their national Treatment Demand Indicator system for collecting national HIV-related behavioural surveillance data (France, Ireland, Luxemburg, Slovenia and Spain) and in two, it was the only system used (Ireland and Luxembourg).

Of the 29 behavioural surveillance studies, 27 used a repeated survey and two used cohorts (Table 1); 23 studies were still ongoing. They were reported by 12 countries (Belgium, Estonia, Finland, France, Greece, Lithuania, Netherlands, Poland, Slovenia, Spain, Switzerland and United Kingdom). Among the studies, 19 used face-to-face interviewing and eight subject-completed paper questionnaires; for one, the method was stated 'other' and for one, the method was not reported (Table 1). Annual samples sizes ranged from 100 to over 3,000 (mean: 1,107; median: 400). The vast majority of the repeated surveys (21/27) recruited IDUs; however, in three countries (France,

Table 1

HIV-related behavioural surveillance studies among injecting drug users using either a repeated survey (n=27) or a cohort (n=2), EU and EFTA countries, reported in 2008 by 12 countries

Country	Number of studies using either a repeated survey or a cohort	Earliest year data collected in any of the studies	Last year data collected in any of the studies	Future years data collection planned	Frequency of data collection	Target population	Study design[a]	Data collection method[b]	Sample sizes of the studies	Coverage of the studies[c]
Belgium	3	1993	2007	Yes	Annual	IDUs	Network sampling (1), service-based (2)	Face-to-face interview (3)	200 –1,000	Regional
Estonia	2	2003	2007	Yes	Annual (1), biannual (1)	IDUs	Respondent-driven sampling (1), service-based (1)	Face-to-face interview (1), paper questionnaire (1)	700–1,500	Regional
Finland	1	2001	2007	Yes	Annual	IDUs	Service-based	Paper questionnaire	100–300	Regional
France	4	1990	2007	Yes	Annual (2), biannual (2)	Problem drug users	Venue-based sampling (2), cross-sectional (1), service-based (1)	Paper questionnaire (3), face-to-face interview (1)	1,000–3,743	National
Greece	1	2002	2007	Yes	Annual	IDUs	Service-based	Paper questionnaire	1,800	National
Lithuania	6	2000	2007	Yes (for 3)	Variable	IDUs	Cross-sectional (4), cohort (1), respondent-driven sampling (1)	Face-to-face interview (6)	100–400	Local (3), regional (1), national (2)
Netherlands	2	1985	2007	Yes	Annual, now occasional (1), ongoing (1)	IDUs; drug users	Venue-based sampling (1), cohort (1)	Face-to-face interview (2)	400–NR	Local
Poland	1	2002	2005	Yes	Variable	Ever injectors	Other	Face-to-face interview	330	Regional
Slovenia	1	2007	2008	Yes	Annual	IDUs	Cross-sectional	Paper questionnaire	110	National
Spain	2	1993	2004	Yes	Variable	A sample of heroin and cocaine users(1), IDUs (1)	Service-based (1), venue-based sampling (1)	Face-to-face interview (2)	200–3,000	Regional (1), national (1)
Switzerland	1	1993	2006	Yes	Variable	IDUs	Service-based	Other	966	National
United Kingdom	5	1990	2007	Yes (for 2)	Annual (1), variable (1), past studies variable	IDUs	Service-based (3), community-based recruitment (1), other (1)	Paper questionnaire (1), face-to-face interview (3), NR (1)	200–3,200	Local (3), regional (1), national (1)

EFTA: European Free Trade Association; EU: European Union; IDU: injecting drug user; NR: not reported.

Numbers in parentheses indicate the number of studies reported in the country that used the preceding option when more than one study was reported for that country.

[a] Options: venue-based sampling, service-based (e.g. clinic), cross-sectional, community-based recruitment, respondent-driven sampling, network sampling, time–location sampling, cohort or other.

[b] Options: telephone interview, paper questionnaire (subject-completed), face-to-face interview, Internet questionnaire (subject-completed) or other.

[c] Options: national, regional, local or other.

Netherlands and Spain), problem drug users (not just IDUs) were recruited. Of the 27 studies using repeated surveys, 10 had national coverage, 10 covered one region or selected regions, and seven were local. Seven countries had one or more repeated surveys with national coverage (Table 1).

Seven countries had used two or more repeated surveys or cohorts for behavioural surveillance (Belgium, Estonia, France, Lithuania, Netherlands, Spain and United Kingdom), with different geographical coverage, target populations, and/or settings used within the countries.

Topics covered by the behavioural surveillance studies

The topics covered by data collected in the behavioural surveillance studies focused on drug use, injecting practice, HIV and hepatitis C testing, and access to healthcare. The main topics covered in the studies are summarised in Table 2. The most commonly collected information related to drug use and the sharing of injecting equipment, with 16 countries reporting that data were collected on these through behavioural surveillance studies. A total of 14 countries reported collecting information related to HIV, hepatitis B or hepatitis C testing or status, and information related to healthcare usage by IDUs. Information on IDU knowledge and attitudes was collected by only eight countries.

Table 2

Topics most frequently covered in the injecting drug users behavioural surveillance studies[a], EU and EFTA countries, reported in 2008 by 17 countries

Topic	Number of countries reporting use
Sexual relationships and sexual partners	
Types of partners/relationships (e.g. regular partner, casual partners)	11
Sexual activity and lifestyle	
Recourse to prostitution (as sex worker)	11
Exposure to risk of infection	
Condom use at last intercourse	11
Condom use with different types of partners	12
HIV and other sexually transmitted infections	
HIV testing	14
Result of HIV test (self-reported)	11
Result of HIV test (measured)	12
Hepatitis B status (self-reported)	10
Hepatitis B status (measured)	11
Hepatitis B vaccine (self-report or measured)	13
Hepatitis C testing	13
Hepatitis C status (self-report or measured)	14
Drugs and substance use	
Types of drugs consumed	16
Injecting drug use	16
Non-injecting drug use	16
Sharing of needles and syringes	16
Sharing of other injection material	16
Health and access to care	
Drug substitution treatment (e.g. methadone)	14
Socio-demographic characteristics	
Education	12
Employment	12
Imprisonment	12
Housing conditions	12
Sources of income (work, drug dealing, pension, welfare, prostitution)	11

EFTA: European Free Trade Association; EU: European Union.

[a] Studies using either a repeated survey, cohort or the Treatment Demand Indicator system.

Box 1

Behavioural indicators among injecting drug users, EU and EFTA countries, reported in 2008 by 8 countries

Eight of the 16 countries with behavioural surveillance studies[a] reporting having national indicators.
Countries using each indicator are listed, with the recall period they use (where known).

Sharing needles and/or syringes
- Belgium: not known
- Slovenia: last month and last time
- Switzerland: borrowing and passing on, last month and last six months
- United Kingdom: last month and last six months

Sharing other injecting equipment
- Belgium: not known
- Slovenia: last month and last time

Sharing any injecting equipment
- Finland: last month
- France: borrowing only, last 30 days
- Luxembourg: borrowing only, last 30 days
- Poland: last month, last year, ever
- United Kingdom: last month and last six months

Uptake of voluntary confidential HIV test
- Belgium: last year
- Luxembourg: last five months and ever tested
- Poland: last year and ever tested
- Switzerland: lifetime
- United Kingdom: lifetime

Uptake of voluntary confidential hepatitis C virus test
- Belgium: not known
- Luxembourg: last five months and ever tested
- Poland: last year and ever tested
- Switzerland: lifetime
- United Kingdom: lifetime

Age first injected
- Belgium
- Finland

Condom use
- Finland: last six months (regular or casual partners)
- Luxembourg: last time (by gender)
- Slovenia: last time
- Switzerland: last time, last six months with regular and casual partners

EFTA: European Free Trade Association; EU: European Union.

[a] Studies using either a repeated survey, cohort or the Treatment Demand Indicator system.

Behavioural Indicators

Eight (of 16) countries reported having behavioural indicators related to the monitoring of the impact of programmes to reduce HIV and other infections among IDUs. The seven behavioural indicators that were reported by more than one country, with the country-specific recall periods used, are shown in Box 1. Three indicators were each reported by five countries: voluntary confidential testing for HIV; voluntary confidential testing for hepatitis C; and the sharing of any injecting equipment in the last month or 30 days There were, however, variations in the recall periods for the testing indicators, with 'ever tested' being used by four countries.

One-off behavioural surveys

In total, 20 one-off surveys had been used to collect behavioural data in seven countries (France, Ireland, Latvia, Lithuania, Luxembourg, Sweden and United Kingdom; Table 3). In one country, Latvia, these formed a series of surveys that provided data over time; though these surveys had varied methodologically from year to year, they resulted in an informal surveillance structure. In the other countries with multiple one-off surveys, these were not comparable to each other, as they had, for example, recruited IDUs from different areas or had different inclusion criteria. As with the behavioural surveillance studies that used repeated surveys, these one-off surveys had used a wide range of methods and varied in sample size (from 194 to 2,740; mean: 676; median: 463). They also included surveys of prisoners (one survey) and other drug users (one of problem drug users and one of techno events and clubbing population) as well as IDUs. Of the one-off surveys reported, nine had national coverage, two covered only a region or selected regions, eight were local, and for one, the geographical coverage was not given.

Five countries reported both behavioural surveillance studies and one-off surveys. The approaches used for the behavioural surveillance studies in these countries varied: three collected data through repeated surveys and three through their Treatment Demand Indicator systems (one country, France, had used both approaches).

Sampling approaches

In the absence of a sampling frame for IDUs, all countries had used convenience sampling frameworks to recruit IDUs for one-off surveys or for the repeated surveys used in behavioural surveillance studies (Tables 1 and 3). Most countries used services – typically easy to access (i.e. low-threshold) ones, such as NSPs – as a setting for recruiting and surveying IDUs; however, four countries had used respondent-driven sampling to recruit from communities.

Discussion and conclusion

Mapping behavioural surveillance in 2008 related to HIV and other STIs among IDUs indicated that 16 countries had conducted behavioural surveillance studies for this subpopulation. A further two countries had undertaken one-off behavioural surveys; and in one of these countries, these surveys resulted in an informal surveillance structure. More countries had behavioural surveillance studies for IDUs than for any of the other population groups: 14 countries for MSM; 13 for the general population; 13 for young people (youth); nine for people living with HIV/AIDS; nine for clients of STI clinics; six for sex workers; and three for migrant populations [16,17,19]. A number of these countries have, or have had, more than one behavioural surveillance study among IDUs. Most often the population group with the most studies in a country was also IDUs [16]. While behavioural surveillance related to HIV was more established among IDUs than among other populations, two fifths (n=10) of the 28 countries responding to the survey reported having no behavioural surveillance-related activities among IDUs.

It is important to consider the limitations of our study. The information collected was self-reported and the responses varied greatly in the level of detail provided. The questionnaires were sent to the ECDC national contact person for HIV biological surveillance in each country as there is no specific ECDC contact person for behavioural surveillance. This person may thus have been unaware of the existence of surveys, whether organised or not into a behavioural surveillance system. However, for the questionnaire on behavioural surveillance among IDUs, liaison with the EMCDDA National Focal Point in each EU country and Norway was encouraged. This should have minimised under-reporting of existing studies of IDUs. The draft mapping report [16] was also circulated to countries for validation, so providing an opportunity to both make corrections and review its completeness. The data collected here are likely to be robust; however, three countries did not return the questionnaire on behavioural surveillance among IDUs, and two of those that did return the questionnaire and who reported having behavioural surveillance studies among IDUs provided no details. While the response and completion rates were high (90% and 93%, respectively), it cannot be assumed that the non-responding countries and those not providing information are similar to those who did. Our findings should thus be generalised to the whole of the EU/EFTA area cautiously.

The fact that more countries had ongoing behavioural surveillance among IDUs than in the other groups studied might reflect, in part at least, the impact of the EMCDDA-established key indicator on drug-related infectious diseases. Following its inauguration in 1995, EMCDDA set up a standardised system to collect data for this key indicator [3]. This collates the findings from HIV, hepatitis C and hepatitis B prevalence studies among IDUs and has more recently started to collect behavioural data [3]. In response to HIV in the late 1980s and early 1990s, a number of countries established sero-surveillance studies among IDUs to overcome the potential biases in monitoring HIV prevalence

Table 3

HIV-related one-off behavioural surveys among injecting drug users (n=20), EU and EFTA countries, reported in 2008 by 7 countries

Country	Number of different one-off surveys conducted	Year(s) earliest survey undertaken	Year the most recent survey undertaken	Target populations of surveys	Study design[a]	Data collection method[b]	Sample sizes of the surveys	Coverage of the surveys[c]
France	1	During 2003 to 2005	NA	Techno events and clubbing population	Venue-based sampling	Face-to-face interview	1,496	National
Ireland	2	1999	2000	Prisoners	Venue-based sampling	Face-to-face interview	600–1,200	National
Latvia	8	1997	2008	IDUs (7), IDUs and their main sex partners (1)	Venue-based sampling (5), respondent-driven sampling (1), other (2)	Face-to-face interview	194–614	Local (3), regional (1), national (4)
Lithuania	1	During 2007 and 2008	NA	IDUs and sex partners	Respondent-driven sampling	Face-to-face interview	471	Regional
Luxembourg	1	2006	NA	Problem drug users	Time–location sampling	Face-to-face interview	397	National
Sweden	1	Planned	NA	IDUs	Service-based	Face-to-face interview	NR	Other
United Kingdom	6	During 1994 and 1995	2008	IDUs	Respondent-driven sampling (2), community-based recruitment (1), service-based (1), other (2)	Face-to-face interview	299–1,058	Local

EFTA: European Free Trade Association; EU: European Union; IDU: injecting drug user; NA: not applicable; NR: not reported.

Numbers in parentheses indicate the number of surveys reported in the country that used the preceding option when more than one survey was reported for that country.

[a] Options: venue-based sampling; service-based (e.g. clinic), cross-sectional, community-based recruitment, respondent-driven sampling, network sampling, time–location sampling, cohort or other.

[b] Options: telephone interview, paper questionnaire (subject-completed), face-to-face interview, Internet questionnaire (subject-completed) or other.

[c] Options: national, regional, local or other.

among marginalised populations such as IDUs through diagnostic testing data. These studies, to maximise their public health utility, have also collected behavioural data. Such combined sero-behavioural systems have been established in number of EU Member States over the last 25 years, for example, Spain (in Catalonia) [20], Estonia [21] and United Kingdom (England, Wales and Northern Ireland) [22]. Through its drug-related infectious diseases key indicator, the EMCDDA has encouraged the maintenance and continued development of such studies across the EU.

Undertaking surveys among IDUs presents a number of substantial practical difficulties. In particular, due to the illicit nature of drug injecting and the high levels of marginalisation and associated stigma, accessing populations who inject drugs can be difficult, and there is, of course, no population-based sampling frame. Thus surveys of IDUs typically use accessibility sampling approaches [11,23], either to access individuals in the community or through the services provided to them. This need to use convenience sampling approaches is reflected in the range of methods used to collect behavioural data. These approaches ranged from collecting data from the clients of addiction treatment services using the Treatment Demand Indicator system, through the purposive sampling of individuals in contact with services provided to drug users (such as NSPs, OST, drop-in centres and outreach), to community-based recruitment, including the use of respondent-driven sampling [23]. Sampling through specialist services for drug users (such as services providing NSPs and OST) was the most widely used approach, probably reflecting the extensive provision of a range of such services in many European countries [4].

In most countries with behavioural surveillance studies of IDUs, these were being conducted annually or at regular intervals, indicating that these systems were probably routine surveillance activities. Routine surveillance of risk among IDUs is important, considering the potential for HIV to spread very rapidly through injecting drug use [11]. The samples sizes used in the surveys varied greatly, with the largest samples being about 30 times larger than the smallest. However, in part this variation will reflect the different population sizes of the countries and also what is known about the extent of injecting drug use in each country. It is likely that the range of sampling approaches used reflects what is appropriate, considering the local epidemics of drug use and the responses to these and, of course, the resources available for surveillance in each country. The systems thus took a range of forms, used a variety of recruitment approaches and settings, and varied greatly in size. These variations probably reflect a wide range in the quality, robustness and sustainability of the systems, although these cannot be objectively assessed through a mapping exercise of this kind.

Examination of the topics covered in the behavioural surveillance studies among IDUs indicates that a wide range of topics were addressed. The main ones (reported in at least two thirds of the countries with behavioural surveillance studies) concerned drug use, injecting risks, HIV and hepatitis C testing, hepatitis B vaccination and sexual risks. This list of topics is not surprising considering the ease with which HIV and hepatitis B and C viruses can be transmitted through unsafe injecting practices, but the lack of sexual risk information in a third of the countries is of concern, given that STIs, HIV and hepatitis B virus are readily transmitted through unprotected sexual intercourse.

Almost half of the countries with behavioural surveillance studies had identified key behavioural indicators that they specifically used for monitoring purposes. The most common key indicators focused on voluntary confidential testing for HIV and hepatitis C, and the sharing of injecting equipment. Half of the countries with key indicators had included condom use as indicator. The set of indicators suggested by ECDC after consultation in the 2009 expert meeting [16] are shown in Box 2.

These indicators include those that are most frequently used in the eight countries with key indicators (i.e. testing for HIV, testing for hepatitis C virus and sharing injecting equipment) and they also reflect the

Box 2

Suggested indicators for use with injecting drug users, EU and EFTA countries

Transversal indicators (those common with other population groups)[a]

Main indicators:
- condom use at last sexual intercourse[b]
- HIV testing and test result (reported or measured)[b]

Also where appropriate:
- number of sexual partners in the last 12 months
- involvement in sex work (as client)

Suggested IDU-specific indicators

Main indicators:
- needles and syringe sharing[b,c]
- injecting frequency[b,c]
- number of new needles/syringes obtained[b,c]
- recently received a substitute drug[b,c]

Additional indicators:
- hepatitis C testing (same format as for HIV testing transversal indicator)[a]
- years since first injected[b]
- having been paid for sex[b]

Other possible options include:
- number of sharing partners[b,c]
- ever injected in prison

EFTA: European Free Trade Association; EU: European Union.

[a] Source: [16].

[b] Indicators for which the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is collecting behavioural data.

[c] Recall periods for these indicators need to be agreed, although the mapping exercise indicates that the last month (last 28 or 30 days) is commonly used for these, and would probably be an appropriate period where injecting is a regular event (e.g. from several times a week to daily), but may be too short where injecting is less frequent.

topics covered in most behavioural surveillance studies. While further consultation is needed on the recall periods and the specific definitions for some of these indicators, the studies do provide a framework from which a core set of behavioural indicators for IDUs could be established. The adoption of a core set of indicators, and their incorporation in national behavioural surveillance studies for IDUs, would then allow comparisons of behavioural surveillance data across countries. This currently cannot be done robustly due to the wide range of different indicators being used across the EU and EFTA.

Behavioural surveillance was, in 2008, more frequently reported among IDUs than in other subpopulations (followed closely by MSM, general population and youth) [16]; however, 10 of the 28 of the countries responding reported no behavioural surveillance among IDUs. The approach used here, a mapping survey, may have resulted in under-reporting of surveys, particularly as not all countries replied, and so the findings should be treated cautiously. Even so, the diversity of indicators found indicates a need to harmonise behavioural surveillance indicators among IDUs across European countries, and this should consider international guidance [24] when developing any indicators. To this end, EMCDDA, in consultation with ECDC and international experts, is currently finalising its protocol for collecting data, including behavioural data, on drug-related infectious diseases among IDUs.

The ECDC HIV and STI Behavioural Surveillance Mapping Group

The full report (ECDC Technical Report Mapping of HIV/STI behavioural surveillance in Europe [16]) was commissioned by ECDC, coordinated by Marita van de Laar and produced by the Institute for Social and Preventive Medicine (IUMSP), University of Lausanne, Switzerland, working with an international team of experts listed below. The main role of each person is included in parentheses; each expert focused on one population group.

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A five-year perspective on the situation of haemorrhagic fever with renal syndrome and status of the hantavirus reservoirs in Europe, 2005–2010

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Hantavirus infections are reported from many countries in Europe and with highly variable annual case numbers. In 2010, more than 2,000 human cases were reported in Germany, and numbers above the baseline have also been registered in other European countries. Depending on the virus type human infections are characterised by mild to severe forms of haemorrhagic fever with renal syndrome. The member laboratories of the European Network for diagnostics of Imported Viral Diseases present here an overview of the progression of human cases in the period from 2005 to 2010. Further we provide an update on the available diagnostic methods and endemic regions in their countries, with an emphasis on occurring virus types and reservoirs.

Introduction

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are enveloped RNA viruses that have rodents and insectivores as hosts and are transmitted by aerosols of host excreta or by direct contact to humans. At least five hantaviruses, Puumala (PUUV), Dobrava (DOBV), Saaremaa (SAAV), Tula (TULV) and Seoul virus (SEOV), circulate in Europe. The most prominent and most widely occurring hantavirus in Europe is PUUV, transmitted by the bank vole (*Myodes glareolus*). PUUV causes a mild form of haemorrhagic fever with renal syndrome (HFRS), called nephropathia epidemica (NE). DOBV is transmitted by the yellow-necked field mouse (*Apodemus flavicollis*) and is known to cause more severe HFRS [1,2]. SAAV, which is closely related to DOBV, is carried by the striped field mouse (*A. agrarius*). It should be noted that the hantavirus strains associated with *A. agrarius* in central Europe and Russia have been shown to be phylogenetically distinct from the north-eastern European SAAV strains as well as from strains associated with *A. flavicollis* (DOBV-Af lineage) or the strains associated with the

Table 1

Carrier species, endemic regions and diagnostic tools for hantaviruses, Europe (n=30 ENIVD member countries)

	Carrier species for								
	Puumala virus	Tula virus	Seoul virus	Dobrava virus	Saaremaa virus	Laihia virus	Asikkala virus	Seewis virus	
Austria	*Myodes glareolus*	*Microtus arvalis*							
Belgium	*Myodes glareolus*	*Microtus arvalis*	*Rattus norvegicus*						
Bosnia and Herzegovina	*Myodes glareolus*			*Apodemus flavicollis*					
Bulgaria	*Myodes glareolus*			*Apodemus flavicollis*					
Cyprus									
Czech Republic	*Myodes glareolus*	*Microtus arvalis*		*Apodemus flavicollis*					
Denmark	*Myodes glareolus*								
Estonia	*Myodes glareolus*				*Apodemus agrarius*				
Finland	*Myodes glareolus*	*Microtus arvalis*			*Apodemus agrarius*	*Neomys fodiens*	*Sorex minutus*	*Sorex araneus*	
France	*Myodes glareolus*	*Microtus arvalis*	*Rattus norvegicus*						
Germany	*Myodes glareolus*	*Microtus arvalis* *Microtus agrestis*		*Apodemus flavicollis*	*Apodemus agrarius*			*Sorex araneus*	
Greece				*Apodemus flavicollis*					
Hungary	*Myodes glareolus*	*Microtus arvalis*		*Apodemus flavicollis*	*Apodemus agrarius*				
Italy									
Ireland	*Myodes glareolus*		*Rattus norvegicus*						
Lithuania	*Myodes glareolus*	*Microtus arvalis*		*Apodemus flavicollis*	*Apodemus agrarius*				
Luxembourg	*Myodes glareolus*								
the Netherlands	*Myodes glareolus*	*Microtus arvalis*							
Norway	*Myodes glareolus*								
Poland	*Myodes glareolus*			*Apodemus flavicollis*					
Portugal			*Rattus norvegicus*						
Romania	*Myodes glareolus*			*Apodemus flavicollis*					
Russia	*Myodes glareolus*	*Microtus arvalis*	*Rattus norvegicus*	*Apodemus flavicollis*	*Apodemus agrarius*				
Slovakia	*Myodes glareolus*			*Apodemus flavicollis*	*Apodemus agrarius*				
Slovenia	*Myodes glareolus*	*Microtus arvalis*, *Microtus agrestis*, *Microtus subterraneus*		*Apodemus flavicollis*	*Apodemus agrarius*				
Spain									
Sweden	*Myodes glareolus*								
Switzerland									
Turkey	*Myodes glareolus*			*Apodemus flavicollis*					
United Kingdom									

ELISA: enzyme-linked immunosorbent assay; ENIVD: European Network for diagnostics of Imported Viral Diseases; IFA: immunofluorescence assay; RT-PCR: reverse transcription polymerase chain reaction.

Fields with symbols indicate that the method is in use (x) or not in use (-).

The question marks refer to the presence of an unidentified hantavirus. In Portugal, the Algerian mouse (*Mus spretus*), the house mouse (*Mus musculus*) and the wood mouse (*Apodemus sylvaticus*), species that are so far not known to harbour a hantavirus, were found positive for hantaviral antibodies. No identification of the infecting hantavirus serotype has been achieved until now.

Data as reported by ENIVD members. This list compiles only the obtained information by means of the 2010 questionnaire and not the current state of the literature.

				Deaths (number)	Endemic region	Diagnostic methods			
	?	?	?			IFA	ELISA	RT-PCR	Sequen-cing
	Shrews			Yes (n=1)	95% in the south-east (Styria, Carinthia, Burgenland) 5% in the north-west (Upper Austria)	x	x	x	x
				No	Nationwide; 85% in the south, 15% in the north	x	x	x	x
				Yes (n=1)	Central and north-east	x	x	x	x
				No	South and south-west	x	x	x	x
				No	-	-	-	-	-
				No	DOBV (northern Moravia) PUUV (southern Bohemia)	x	x	x	x
				No	-	x	x	x	x
				No	North, east and couth-east	x	x	x	x
				< 0,1%	Nationwide except northern Lapland	x	x	x	x
				No	North-east, Jura	x	x	x	x
				No	DOBV: north-east PUUV: almost nationwide with hotspots in North Rhine-Westphalia, Lower Saxony, Bavaria and Baden-Württemberg	x	x	x	x
				No	North and north-west	x	x	x	x
				Yes (n=1)	Nationwide	x	x	x	x
				No	None	x	x	x	x
				No	-	x	x	x	x
				-	-	x	x	x	x
				No	Nationwide	x	x	x	x
				No	South-east, bordering Germany	x	x	x	x
				Yes (n=1,in 1998)	Hedmark and Oppland, Agder, Nordland	x	x	x	x
				-	East and south-east	x	x	x	x
	Mus musculus	*Mus spretus*	*Apodemus sylvaticus*	-	Central and south	x	x	x	x
				Yes (n=1 probable)	Cases diagnosed in Arad, Sibiu, Nemt, Iaşi and Vrancea counties	x	x	x	x
				-	-	x	x	x	x
				No	Kosicky and Presovsky (south-east) provinces and DOBV in the central part	x	x	x	x
				Yes (n=4)	Nationwide; most in north-east, south and central	x	x	x	x
				No	None	x	x	x	x
				No	North of the Limes norrlandicus	x	x	x	x
				No	-	x	x	x	x
				Yes	Provinces bordering the Black Sea	x	x	x	x
				No	-	-	-	-	-

Black Sea field mouse (*A. ponticus*) (DOBV-Ap lineage). It is from an epidemiological point of view currently impossible to distinguish between the lineages by routine diagnostics when the viral RNA sequence is not available [3,4]. TULV is transmitted by the common vole (*Microtus arvalis*), the field vole (*M. agrestis*) and the southern vole (*M. levis*, also known as *M. rossiaemeridionalis*). This virus has not definitely been linked to human disease. SEOV, transmitted by the brown and black rat (*Rattus norvegicus* and *R. rattus*), causes mild HFRS in Asia and in many harbour cities worldwide. In Europe, it has so far only been identified once as a human pathogen, in an unpublished case in France that was confirmed by focus reduction neutralisation test [1]. During the past decade several hantaviruses have been discovered that have insectivores as carriers. In Europe these are Laihia, Asikkala and Seewis virus, transmitted, respectively, by the Eurasian water shrew (*Neomys fodiens*), the Eurasian pygmy shrew (*Sorex minutus*) and the common shrew (*Sorex araneus*) (Table 1).

In the past decade (2000-2009) oscillations in the number of hantavirus infections have been reported [5]. The unusually high number of hantavirus infections in Germany in 2010, with 327 cases between January and April in Baden-Württemberg [6], prompted the European Centre for Disease Prevention and Control (ECDC) to request an update on the hantavirus situation in Europe from the European Network for diagnostics of Imported Viral Diseases (ENIVD) and its Collaborative Laboratory Response Network (CLRN). The present article summarises the current knowledge on the occurrence of hantaviruses based on a survey in 30 European countries.

Table 2

Human cases of hantavirus infection in Europe, 2005-2010 (n=30 ENIVD countries)

	2005[a]	2006	2007	2008	2009	2010[c]	**Total[d]**
Austria	16	12	78	33	29	13	**351**
Belgium	372	163	298	336	182	161	**2,845**
Bosnia and Herzegovina	21	26	8	25	19	8	**732**
Bulgaria	5	0	2	4	5	2	**56**
Cyprus	0	0	NA	NA	NA	NA	**0**
Czech Republic	3	2	4	5	7	4	**43**
Denmark	0	0	NA	NA	NA	0	**0**
Estonia	NA	e	7	11	17	4	**39**
Finland	2,526	1,863	1,743	3,259	1,919	326	**31,919**
France	253	24	127	84	62	100	**1,913**
Germany	447	72	1,688	243	181	1,527	**4,956**
Greece	5	4	5	1	4	3	**52**
Hungary	6	NA	16	6	11	7	**342**
Italy	0	0	0	0	0	0	**0**
Ireland	NA	0	0	0	0	0	**0**
Lithuania	NA	0	NA	NA	NA	NA	**9**
Luxembourg	17	11	10	7	3	10	**60**
The Netherlands	3	3	32	32	12	14	**133**
Norway	64	22	76	50	21	8	**1234**
Poland	NA	NA	17	3	6	5	**31**
Portugal	1	4	2	4	0	NA	**37**
Romania	1	1	2	4	9	4	**21**
Russia	7,256	7,157	NA	NA	NA	NA	**173,652**
Slovakia			22	3	11	6	**42**
Slovenia	24	5	14	46	5	8	**294**
Spain	0	0	0	1[b]	0	0	**1**
Sweden	330	213	2,195	569	53	138	**7,198**
Switzerland	0	0	1	0	0	0	**2**
Turkey	NA	NA	NA	NA	23	NA	**23**
United Kingdom							**6**

ENIVD: European Network for diagnostics of Imported Viral Diseases; NA: data not made available.

[a] Previous years: see [7].

[b] Imported case.

[c] Up to 31 August 2010.

[d] Total of diagnosed hantavirus cases since start of surveillance in the specified country.

In general HFRS is characterised by high fever for up to four days and unspecific symptoms at the onset of the disease such as headache, thrombocytopenia and influenza-like symptoms, followed by nausea, abdominal pain and vomiting. After four to 10 days renal manifestations characterised by oliguria and transient renal failure and later polyuria may occur [1,2].

Methods

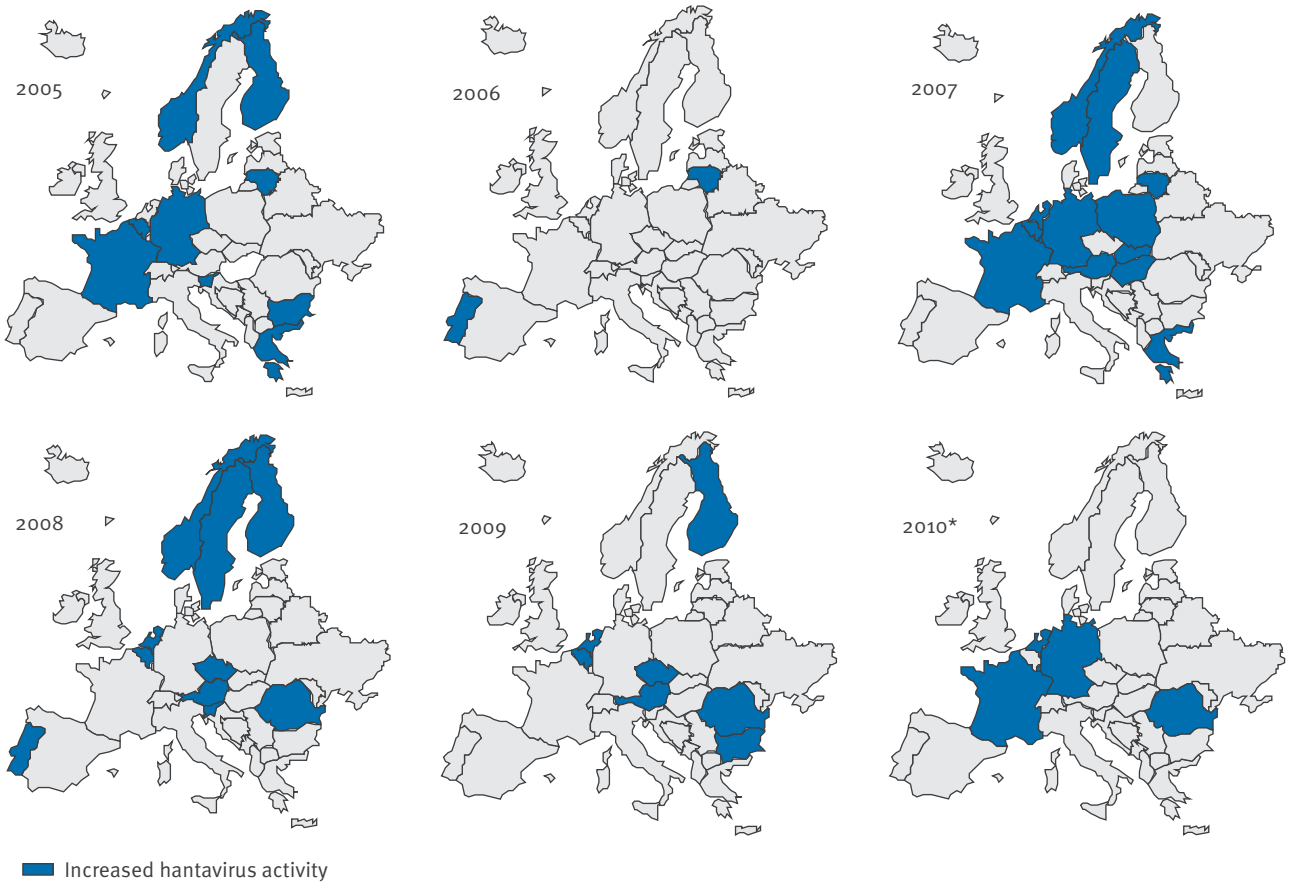
The ENIVD hantavirus working group sent a questionnaire to all ENIVD members (N=30, see Table 1) requesting information on the occurrence of clinically apparent cases of hantavirus infection according to the ENIVD case definition during the period from January 2006 to end of August 2010, fatalities due to hantavirus infection, the hantavirus carrier species present in the country and available diagnostic methods. The questionnaire was similar to the one used in 2006 [7], and was intended to update the information already available up to 2006. In addition, the average numbers of clinically apparent cases reported annually by ENIVD collaborating countries were calculated for the two decades 1990–1999 and 2000–2009 and were used to assess the reported country case numbers in the individual years. A year was regarded as a normal year when the number of cases matched the average case numbers, plus or minus 10% recorded for the respective country during the decade ending in the respective year. Case numbers 10–50% higher than the 10-year average were considered moderate activity, numbers 50-100% higher were considered slightly elevated and numbers at least 100% higher than the average number were considered increased activity.

Results

The annual number of cases diagnosed per country in the years 2006 to 2009 and 2010 up to end of August is summarised in Table 2. The year 2005 is added in order to facilitate the transition between this report and the previous one published in 2008 [7]. 2005 was a year with increased hantavirus activity, with approximately twice as many cases as in the ten previous years in Belgium, Finland, France, Luxembourg, Norway and some regions in Germany, especially North Rhine Westphalia, Lower Saxony and Baden-Württemberg [8]. In the year 2007 Belgium and Norway reported more human infections than the annual average of clinically apparent infections calculated for the decade 2000–2009. In the same year, France, Austria, Germany and Hungary reported between three- and

Figure 1

Countries with increased (over the previous year) hantavirus activity, Europe, 2005–2010 (n=30 ENIVD countries)



ENIVD: European Network for diagnostics of Imported Viral Diseases.
* The epidemic situation for 2010 is depicted up until the 31 August 2010.

five-fold elevated case numbers, and Sweden 10-fold elevated numbers compared with the annual average of the decade. These were the highest numbers of hantavirus infections ever seen in Germany and Sweden. The year 2008 was again an epidemic year in Belgium, with 336 reported cases, and also in Finland, where a record number of 3,259 cases were observed. All other European countries that had data available (Table 2) noted normal hantavirus activity in 2008. In 2009, all European countries had case numbers that corresponded to the annual average of the past decade. In 2010 it became clear already in February that the hantavirus activity in Germany was high, which was confirmed by the number of diagnosed cases up to August 2010 that reached 2.017 [9]. In bordering countries, i.e. Belgium, France, Luxembourg and The Netherlands, the hantavirus activity was normal or moderately elevated in comparison to the annual average of the past decade. In Austria, the Czech Republic, Denmark, Poland and Switzerland the hantavirus activity in 2010 remained low (Table 2 and Figure 1).

From the available information it was possible to calculate the yearly average number of diagnosed cases in Europe. For the 10-year period 1990 to 1999 this annual average was 1,671 cases, calculated for those countries from which reliable data on human infections were available, i.e. Belgium, Finland, France, Hungary, the Netherlands, Norway, Portugal, Slovenia and Sweden, as well as those countries from which apparently not all cases had been reported, i.e. Austria, Bosnia-Herzegovina, the Czech Republic and Greece. However, for the period 2000 to 2009 the annual average was significantly higher, namely 3,138 cases, including available data for further countries. It is at present impossible to state whether there is a real increase in hantavirus cases in Europe or whether the observation is influenced by increased awareness and better use of diagnostic tools. It is noteworthy that in the period 1990 to 1999, the years 1995, 1998 and 1999 were above the calculated arithmetic mean of 1.671 cases (Figure 2), and in the period between 2000 and 2010 the years 2002, 2005, 2007, 2008 and 2010 showed more than average activity, i.e. above the arithmetic mean of 3,138 cases (Figure 3). This is in accordance with already recognised epidemic years in different European countries (Table 2).

Further information we obtained on the carrier species present in the participating countries and the viruses detected in those rodents is summarised in Table 1. It confirmed earlier observations regarding the prominent role of PUUV and DOBV in Europe. Hantaviruses transmitted by insectivores were only found in Finland and Austria in this survey (see Table 1). No link to human disease has been shown so far for these viruses. Given the established role of the rodent-borne viruses PUUV, DOBV and possibly SAAV as human HFRS pathogens in Europe, it seems unlikely that insectivore-borne hantaviruses play a major role as pathogens.

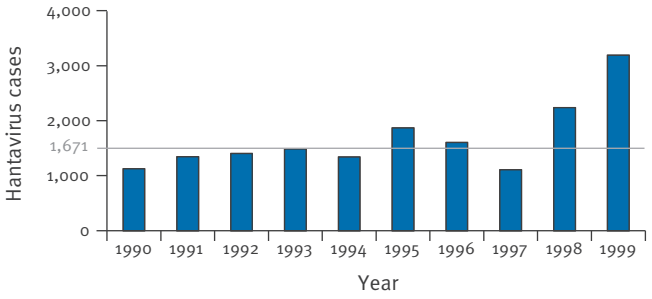
Fatal cases due to hantavirus infection are rare in Europe and mostly linked to DOBV infection. Although some fatal cases have been linked to PUUV infection, the mortality rate due to this virus remains lower than 0.1%.

Discussion

Data on human hantavirus infections have been registered in 30 European countries since 2005. Our knowledge of the disease, virus geno- and serotypes, hosts and diagnostic capacities has increased over the past decade. However, there seem to be large regional differences in the case numbers. The update on endemic regions in the participating countries confirmed the focal aspect of hantavirus infections (see Table 1). In the majority of countries, the endemic regions are forested areas that provide sufficient shelter and food for rodent populations.

Figure 2

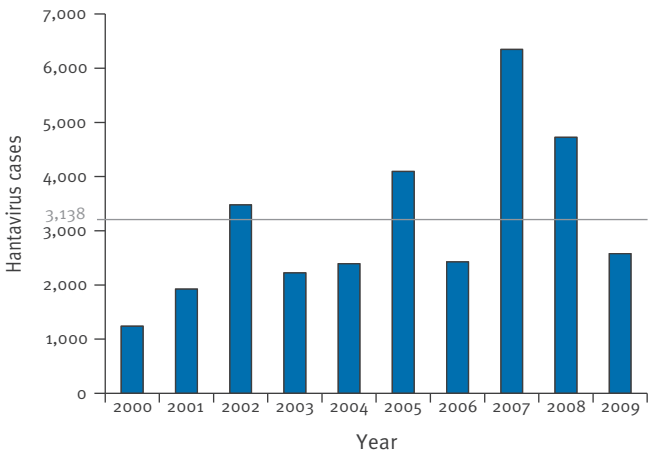
Annual number of human cases of hantavirus infection in Europe, 1990–1999 (n=29 ENIVD countries, excluding Russia)



ENIVD: European Network for diagnostics of Imported Viral Diseases.
Grey line: Average number of diagnosed cases per year: 1,671.

Figure 3

Annual number of human cases of hantavirus infection in Europe, 2000–2009 (n=29 ENIVD countries, excluding Russia)



ENIVD: European Network for diagnostics of Imported Viral Diseases.
Grey line: Average number of diagnosed cases per year: 3,138.

Epidemic peaks may be linked to times of favourable climatic conditions when an abundance of available food triggers a peak in the rodent population [8,10]. A relation between climate, high density of the rodent population and increased virus prevalence in rodent populations was also observed [4]. This puts humans at increased risk of contact with infected rodents and their excreta. According to preliminary findings, it was such a scenario that led to the spectacular increase in cases in Germany in 2010 [6]. Although mast events (increased seed production of various trees) seem to be of importance in triggering hantavirus epidemics, it should be remembered that only hantavirus epidemics in Atlantic and continental western Europe are mast-driven (although this seems not entirely true for Germany as in some years the country experienced very regional outbreaks), while other mechanisms drive these events in northern and eastern Europe [1,2].

The bank vole (*M. glareolus*), the principle vertebrate host for PUUV, is a generalist polyphagous species, i.e. eating seeds and fruits and occasionally invertebrates. It only acquires 50% of its energy intake from hard fruits and this only in the winter months. The yellow-necked field mouse (*A. flavicollis*), the principle vertebrate host for DOBV, is predominantly a seed eater, but the invertebrate portion of its diet can be considerably higher than for the bank vole. The diet of both *M. glareolus* and *A. flavicollis* varies considerably in different regions in Europe: in Atlantic western Europe (Belgium, France) oak and beech seed crops are instrumental [10,11], while in continental Europe (the Białowieża Primeval forest in Poland, for instance) oak (*Quercus petraea*) and hornbeam (*Carpinus betulus*) seed crops regulate population sizes of both species [12,13]. Both the bank vole and the yellow-necked field mouse prefer a forest environment. The third rodent species of interest, the striped field mouse (*A. agrarius*, carrier of SAAV), is typical of a mixed habitat of agricultural fields and forest, and its population dynamics thus relate not only to forest conditions but also to anthropogenic factors [14].

For all three species, winter survival is related to food availability in the preceding summer and autumn, spring numbers are dependent on winter mortality, which according to the rodent catchers is estimated to reach on average 70% of autumn numbers for voles and 85% for mice, and summer/autumn numbers are primarily related to vegetation biomass and temperature.

The hantavirus activity peaks indicated by our data did not in all years correlate with mast cycles. Although mast events are supposed to occur over large areas and even on sub-continental level, hantavirus epidemics in western Europe can probably not be related solely to mast events of one tree species, given the highly different levels of hantavirus activity in neighbouring countries in 2005, 2007, 2008 and 2010 (see Table 2) where mast events occur simultaneously. Unfortunately, detailed information about seed crops of the different endemic tree species, e.g. beech (*Fagus sylvatica*), oak (*Quercus sp.*) and hornbeam (*C. betulus*), that can significantly influence rodent winter survival rates are not always available in most countries.

At present, all European countries dispose of the same range of diagnostic tools (for a recent review, see [15]), i.e. IgG and IgM IFA and ELISA, classical or real-time RT-PCR methods targeting specific hantaviral sero-/genotypes followed by sequence analysis of the amplicons in order to study the molecular epidemiology of the circulating strains. Neutralisation tests are, due to the special requirements of these tests, only available in a few countries and are in general only used for research purposes.

Conclusions

Hantavirus infections continue to be a risk in the European Union. To our knowledge, notification systems have not changed in the past decade. In the past 10 years the annual number of diagnosed cases has significantly increased but it remains unclear whether this is due to higher awareness and better diagnostic tools or to a real increase in acquired infections. Epidemics occur locally and in foci, i.e. in regions where climatic, biotic and abiotic conditions pave the way for the carrier species to become abundant and humans to come in contact with the virus.

Infections caused by PUUV remain the most prevalent in Europe, and in regions where the virus is circulating, the number of infected individuals can reach hundreds or thousands per year, DOBV infections on the other hand are much less frequent, and important outbreaks are scarce. Incidence data on hantavirus infections are unfortunately not available.

The 2010 PUUV outbreak in Germany seems to be an isolated incident and is currently closely monitored by the local authorities. Further longitudinal studies are needed in Europe to better understand the factors that drive the oscillation of human cases on a local, regional and continental scale including a combination of landscape and land use, habitat, climate and geographical parameters.

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