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EDITORIALS

- Treatment as prevention: will it work?** 2
by MJ van de Laar, A Pharris

RAPID COMMUNICATIONS

- HIV infection and AIDS in the European Union and European Economic Area, 2010** 5
by G Likatavicius, MJ van de Laar

- Trends in HIV and hepatitis C virus infections among injecting drug users in Europe, 2005 to 2010** 9
by L Wiessing, G Likatavicius, D Hedrich, B Guarita, MJ van de Laar, J Vicente

- Human immunodeficiency virus in injecting drug users in Europe following a reported increase of cases in Greece and Romania, 2011** 14
by A Pharris, L Wiessing, O Sfetcu, D Hedrich, A Botescu, A Fotiou, GK Nikolopoulos, M Malliori, M Salminen, JE Suk, P Griffiths, MJ van de Laar

- Two cases of mild IgM-negative measles in previously vaccinated adults, the Netherlands, April and July 2011** 19
by A van den Hoek, GJ Sonder, M Scholing, D Gijsselaar, RS van Binnendijk

Treatment as prevention: will it work?

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In the past two years, rapidly emerging new trial results have provided the scientific community and people living with human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) or at risk of infection, with welcome news. Interesting scientific evidence is accumulating for the effectiveness of biomedical interventions to prevent the transmission of HIV. Infected people may become less contagious when the viral load is suppressed by antiretroviral therapy (ART). In 2010, results from the Pre-Exposure Prophylaxis Initiative (iPreX) randomised controlled trial provided the first evidence that antiretroviral pre-exposure prophylaxis can reduce HIV incidence. In their study, Grant et al showed, that that daily oral antiretroviral medication reduced HIV incidence in HIV negative men who have sex with men (MSM) by 44% [1]. In July 2011, two studies from the United States, the TDF2 (tenofovir disoproxil fumarate and emtricitabine (TDF)) study and the Partners Pre-exposure study provided evidence that a daily oral dose of antiretroviral medication can reduce HIV acquisition among uninfected individuals exposed to the virus through heterosexual sex by at least 60% [2-3]. The randomised controlled HIV Prevention Trials Network study (HPTN 052) by Cohen et al demonstrated that earlier treatment (time of enrolment in study compared with CD₄ cell counts within or below 200-250 cells/mm³ or developing an AIDS defining illness) of HIV-infected persons with ART had both a clinical benefit for the infected individual and resulted in a 96% reduction in transmission to the uninfected sexual partner [4].

Early treatment for HIV, prevention of mother-to-child transmission, post-exposure prophylaxis, male circumcision, consistent condom use, behaviour change communication, microbicides, and possibly targeted pre-exposure prophylaxis are the most effective tools to prevent HIV transmission on individual and population levels [2-6]. Mathematical modelling studies indicated that early testing and early treatment of all individuals with HIV could effectively halt HIV transmission at the population level. Ecological studies have confirmed the effectiveness of the test and treat strategy in reducing HIV transmission and it appears to be bolstered further by HPTN 052 trial results [7-11].

New data on HIV in Europe in this issue by Likatavicius and Van de Laar demonstrate that HIV remains a public health problem in the European Union (EU) and European Economic Area (EEA) where more than 27,000 newly diagnosed HIV infections were reported during 2010 [12] (an increase of 4% compared with 2009). HIV diagnoses among men who have sex with men (MSM) have increased by 39% between 2004 and 2010, and represent 38% of the total HIV cases in the EU/EEA. New HIV diagnoses among injecting drug users (IDU) have declined by 44% since 2004, representing only 4% of cases in 2010. However, outbreaks of HIV in this group have been reported in some countries recently [13-14] and the prevalence of HIV and hepatitis C remains high as reported in this issue by Wiessing et al. [15]. The proportion of people diagnosed with a CD₄ cell count less than 350/mL (late diagnosis) [1, 16-17] is unacceptably high in Europe: almost half of the cases where a CD₄ cell count was available at the time of diagnosis. This suggests that individuals present late in the course of infection, cannot benefit from early treatment and are at risk of disease progression.

The potential and feasibility of treatment as prevention needs to be considered in light of the current epidemiological situation of HIV in Europe. For antiretroviral treatment to have a preventive effect, the HIV-positive individual's viral load must be suppressed to a very low level over time. Gardner et al. modelled the achievement of viral suppression by using the pre-requisite steps testing and diagnosis, linking to care, adherence to ART, and viral load suppression as the final outcome. They demonstrate that in order to achieve a sustained population-level reduction in viral load a high proportion of HIV-infected individuals must be i) diagnosed with HIV infection, ii) linked in a timely manner to HIV care, iii) retained in care, iv) placed on effective antiretroviral therapy and v) adherent life-long to this treatment [18]. The steps in this care cascade were reviewed and many individuals seem to drop out of at one of the steps. If all efforts would be maximised to 90% for all steps still only an estimated two-third of the cases would achieve viral suppression.

The care cascade points out key areas for programme and surveillance improvement within Europe. In addition to late testing and diagnosis of HIV, most Member States do not routinely monitor whether people tested positive for HIV are linked to care and, if so, whether they are retained in care. Monitoring access to and retention in care is particularly important for vulnerable populations among those living with HIV, including MSM, IDUs and migrants. Monitoring and surveillance systems should be adapted so that they track engagement in care more effectively and allow monitoring the impact of treatment on the course of the epidemic.

HIV testing, early diagnosis and access to early treatment have always been key strategies for HIV/AIDS prevention. New evidence for biomedical interventions is indeed promising and shows that knowledge of HIV status has now become the cornerstone for HIV prevention. However, the question arises as to whether the implementation of prevention treatment strategies is feasible and affordable as the trial results were obtained under optimised conditions. A recent cost-effectiveness study has highlighted that in addition to HIV testing and treatment substantial reductions in risk behaviour are still needed to contribute to substantial reductions in HIV transmission [19]. Treatment as prevention as an option in Europe is complicated by the fact that the HIV epidemic affects mostly socially vulnerable or marginalised groups who experience multiple barriers to accessing services and adhering to treatment. At the same time, a combination prevention toolkit is available with multiple effective programmatic, behavioural and structural interventions at different levels that can be tailored to local epidemics.

Interventions found to be consistently effective include condom provision, reduction of number of sex partners, partner notification services, needle and syringe exchange programmes, opioid substitution treatment, and behavioural change interventions [20-24]. At present there is little evidence that treatment as prevention works among MSM [25] and in light of the current epidemiological situation more efforts are needed to reverse the trend of sexually transmitted infections and HIV among MSM through combined measures. The evidence for harm reduction and prevention of communicable diseases in the field of drug use is overwhelming. A recently launched ECDC/EMCDDA guidance document brings together evidence and expert opinion and supports EU countries to reduce the burden of drug use as well as the burden of high prevalence of HIV, hepatitis B and C among IDUs [26]. It was launched at a critical moment when an outbreak of HIV among IDUs was reported [13]. In this issue, Pharris et al investigate recent outbreaks in Greece and Romania and assess the risk for HIV transmission among IDUs in Europe [27]. The analysis show a heterogeneous pattern in with a potential risk for outbreaks in a number of countries where immediate action is warranted. It demonstrates the need for having adequate prevention services in place to prevent outbreaks of

HIV and hepatitis C. Outbreaks can be expected when drug using patterns change, the frequency of injection increases in combination with a low coverage of prevention services (including needle exchange programmes and opioids substitution treatment).

In the context of the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2011 political declaration 'targets and elimination commitments' [28] to achieve zero new infections, no AIDS-related deaths and zero discrimination by 2015, we need to review the current HIV prevention strategies in Europe and to re-enforce the respective programmatic approach. With enough people in treatment, the treatment as prevention option will help to reduce HIV transmission however, there is as of yet no evidence that this will reverse HIV trends in Europe. To control the epidemic, primary and secondary prevention of HIV transmission remains crucial. To identify and apply the most effective prevention strategies to reduce the impact of HIV in Europe, there is an urgent need for better programmatic approach, involving a wide range of stakeholders including healthcare providers, civil society, those infected with HIV and prevention workers.

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HIV infection and AIDS in the European Union and European Economic Area, 2010

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In 2010, a total of 27,116 newly diagnosed HIV infections were reported by 28 countries of the European Union and European Economic Area (EU/EEA), with evidence of continuing transmission and no clear signs of decline. The predominant mode of transmission and increasing trend of HIV in the EU/EEA was due to sex between men. An increase in AIDS diagnoses in several countries and a high proportion of late presenters suggest delayed access to treatment and care.

Newly diagnosed HIV infections

In the European Union and European Economic Area (EU/EEA), 27,116 new HIV infections were diagnosed in 2010 and reported by 28 countries (no data from Austria or Liechtenstein), a rate of 5.7 per 100,000 population. The overall rate for men was 8.6 per 100,000 population and for women 2.9 per 100,000 population. The highest rates of new infections were reported by Estonia (27.8), Latvia (12.2), Belgium (11.0) and the United Kingdom (10.7). The lowest rates (<1.0 per 100,000 population) were reported by Romania and Slovakia.

Of the reported newly diagnosed HIV infections, 11% were aged 15–24 years. Sex between men is the predominant mode of transmission among people newly diagnosed with HIV in EU/EEA countries, accounting for 38% of the HIV diagnoses (in 2009: 35%), followed by heterosexual contact (24%) when diagnoses from countries with generalised HIV epidemics are excluded. The highest proportion of diagnoses reported as heterosexually acquired from persons originating from countries with generalised epidemics was observed in Belgium (66%), United Kingdom (61%), Sweden (60%), Ireland (56%) and Norway (45%). Of all reported newly diagnosed HIV infections, 4% were reported among IDUs. The transmission mode was unknown for 18% of the diagnoses.

Some 26% of the reported newly diagnosed HIV infections were in females. The male-to-female ratio was highest in Hungary (15.7:1) and Slovakia (8.3:1) and was greater than 5:1 in Slovenia, Czech Republic, Greece, Netherlands and Germany. The predominant mode of

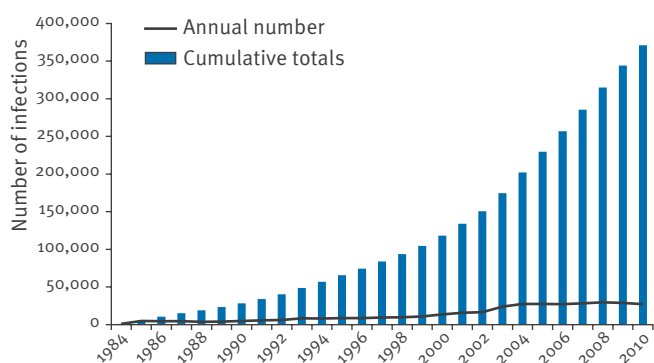
transmission in these countries was sex between men. For countries where the male-to-female ratio was less than 2:1, the main transmission mode was heterosexual contact, as reported in Sweden, Romania and Latvia.

Trends in diagnosed HIV infections

Among the 28 EU/EEA countries that have consistently reported HIV data since 2004, the number of diagnosed HIV infections has been relatively stable, from 6.5 per 100,000 population in 2004 to 5.7 per 100,000 population in 2010. From 2004, more than 27,000 new HIV infections were diagnosed and reported each year, resulting in a cumulative total number of over 370,000 HIV infections reported since the beginning of epidemic (Figure 1). The numbers of newly diagnosed HIV infections per 100,000 population among countries reporting national data have tripled in Bulgaria and Iceland, and increased by more than 50% in the Czech Republic, Finland Hungary and Slovakia. Rates have decreased by more than 20% in Estonia, Luxembourg and Romania.

FIGURE 1

Newly diagnosed HIV infections by year of diagnosis and cumulative totals, 28 European Union and European Economic Area countries^a, 1984–2010



^a No data from Austria and Liechtenstein.

Source: [1].

Since 2004, 26 EU/EEA countries have consistently reported data on transmission mode (Estonia and Poland are excluded). The number of heterosexually acquired HIV infections ranged from 6,200 to 7,000 during 2004 to 2010. The number of diagnosed HIV infections acquired heterosexually and originating from countries with generalised HIV epidemics decreased by 41% during this period. The number of diagnosed HIV infections among men who have sex with men (MSM) increased by 39% and declined among IDUs by 44%. The number of diagnosed HIV infections in people with unknown risk factors increased by 30% (Figure 2).

It should be acknowledged that for a number of countries, there are reporting delays – a time delay between diagnosis of infection and reporting of the diagnosis at national level – which limit the interpretation of trends in recent years. Such delays affect all transmission modes consistently and adjusting for it results in an increase of 4–10% for 2010 (Figure 2).

AIDS diagnoses

In 2010, a total of 4,666 cases of AIDS were diagnosed in 28 EU/EEA countries (no data from Liechtenstein or Sweden), representing a rate of 0.9 per 100,000 population. The highest rates were reported by Latvia (5.5 per 100,000 population), Portugal (3.3 per 100,000 population) and Spain (2.0 per 100,000 population). Among 28 EU/EEA countries reporting AIDS diagnoses consistently between 2004 and 2010, a decline was observed from 9,171 in 2004 to 4,666 in 2010. The

number of AIDS diagnoses decreased in all but seven countries. An increase was reported in Czech Republic (100% increase), Lithuania (57%), Bulgaria (45%), Latvia (39%) and Hungary. Increases were also noted in Cyprus (400%) and Malta (100%) although reported numbers in these countries were low (≤ 10 cases).

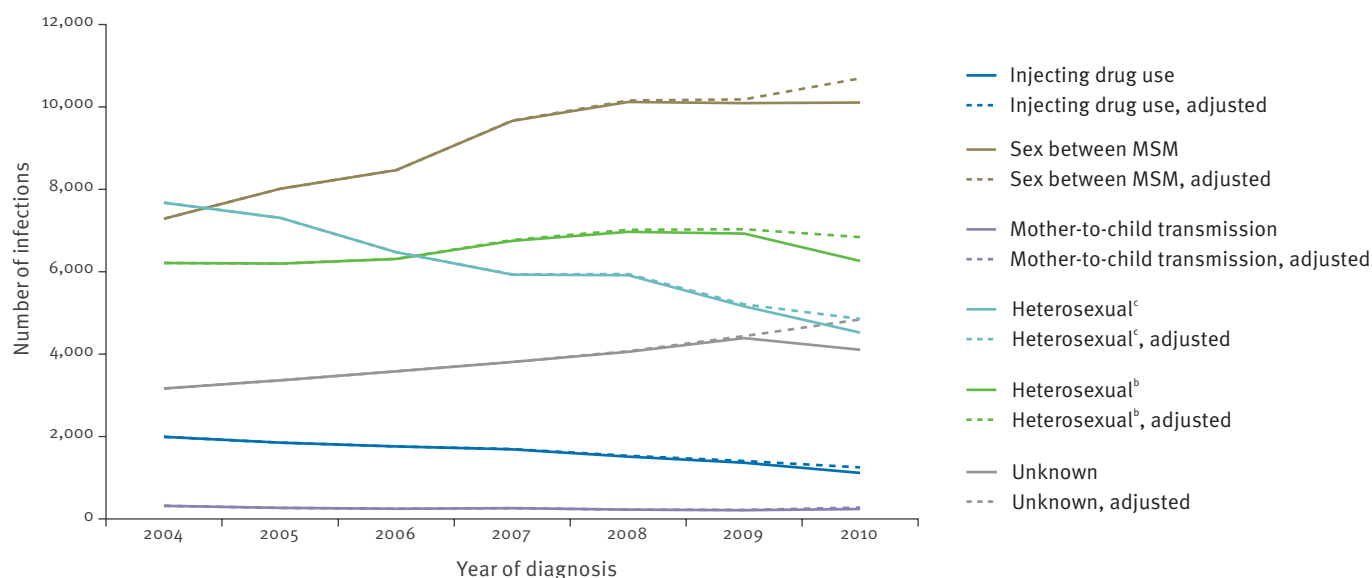
Proportion of late presenters

Late presenters are defined as patients with a CD4 cell count below 350 cells/ μ l at the time of diagnosis of HIV infection. Patients diagnosed with AIDS at the same time as the diagnosis of HIV infection were not included in this analysis. Fifteen countries, where CD4 cell count was available for more than half of the newly diagnosed HIV infections, reported a total of 14,607 diagnoses (74% of all diagnoses) (Table). Among the 14,607 diagnoses, 49% of the patients were reported to have a CD4 cell count $< 350/\mu$ l.

For newly diagnosed HIV infections reported as having been acquired due to heterosexual contact, in 10 countries, more than half of these infections were in people who were late presenters, ranging from 33% in Slovakia to 63% in Netherlands. For MSM, more than half of the late presenters were reported in three countries: the proportion of late presenters ranged from 22% in Slovakia to 63% in Latvia. Among IDUs, more than half of the late presenters were reported from six countries and the proportion of late presenters ranged from 33% in the Czech Republic to 100% in Slovakia.

FIGURE 2

Newly diagnosed HIV infections by transmission mode and origin, with and without adjustment for reporting delay, 26 European Union and European Economic Area countries^a, 2004–2010



MSM: men who have sex with men.

^a No data from Austria and Liechtenstein; data from Estonia and Poland excluded as unknown transmission mode in $> 50\%$ of diagnoses.

^b Excludes persons originating from countries with generalised HIV epidemics.

^c Includes persons originating from countries with generalised HIV epidemics.

Source: [2].

Conclusions

In EU/EEA countries, the highest proportion of the total number of diagnosed HIV infections continues to be reported among MSM, followed by heterosexuals. When analysing the data by reported transmission mode, the only substantial increase in the number of reported infections was in MSM. Heterosexual HIV transmission continues to be reported; although the proportion of infections attributed to heterosexual contact in persons originating from countries with generalised epidemics is decreasing, it is still high in several countries. Among IDUs, despite an apparent decline in the number of diagnosed HIV infections, a substantial number are still reported in the Baltic States, and recent and previous increases were reported in other EU Member States and neighbouring countries [3-5]. Despite the relatively low absolute numbers diagnosed due to injecting drug use, IDUs are disproportionately affected by the HIV epidemic, because of the relatively small size of the population and very rapid spread of HIV, resulting in outbreaks or rapid increases in the number of HIV infections [6]. The European Centre for Disease Prevention and Control (ECDC) has launched guidance on the prevention and control of infectious diseases among IDUs and on HIV testing and counselling in migrant populations and ethnic minorities [7,8].

The number of AIDS cases is decreasing in most EU/EEA countries except in seven Member States from

eastern and central Europe. The rising numbers of AIDS diagnoses and high proportion of HIV-infected patients with low CD4 cell counts suggest a delay in HIV testing, which does not allow individuals to benefit from available treatment regimens and further contributes to HIV transmission.

There are certain limitations, which should be taken into account when interpreting these data. Reported newly diagnosed HIV infections do not represent the incidence of the infection. Newly diagnosed infections can include individuals infected recently as well as those who were infected several years ago. Reporting is influenced by several factors, such as changes in HIV surveillance system, the uptake of HIV testing, patterns of reporting, the long incubation period of the virus and slow progression of the disease. Cumulative totals presented here do not take into account death and migration patterns and therefore do not reflect prevalence. The trends presented here were partly driven by several large countries. For heterosexual transmission, diagnoses originating from countries with generalised epidemic were presented separately. This approach enables us to provide a more accurate reflection of the transmission patterns in Europe and serves as a proxy for HIV transmission occurring outside Europe. However, there is increasing evidence of HIV transmission within migrant communities [9].

TABLE

Reported numbers of newly diagnosed HIV infections^a in people with known CD4 cell counts and those with CD4 cell counts <350 cells/μl, by transmission mode, 15 European Union countries, 2010

Country	Number of newly diagnosed HIV infections in patients with a known CD4 cell count (%) ^b	Number of newly diagnosed HIV infections in patients with CD4 cell count <350 cells/μl (%)	Percentage of newly diagnosed HIV infections in patients with CD4 cell count <350 cells/μl, by transmission mode				
			Heterosexual	Injecting drug use	Sex between MSM	Mother-to-child transmission	Unknown
Belgium	620 (52.4)	240 (38.7)	51.0	75.0	24.1	0.0	46.2
Bulgaria	113 (71.1)	52 (46.0)	54.8	39.1	32.1	NR	NR
Cyprus	22 (53.7)	10 (45.5)	44.4	NR	45.5	NR	0.0
Czech Republic	158 (87.8)	40 (25.3)	46.7	33.3	19.2	NR	4.0
Denmark	227 (83.5)	127 (55.9)	61.1	50.0	50.5	NR	57.1
France	2,270 (57.8)	1,178 (51.9)	59.3	58.9	37.6	100.0	67.6
Italy	2,063 (71.8)	1,101 (53.4)	57.4	63.7	45.1	0.0	54.8
Latvia	157 (58.1)	89 (56.7)	50.5	71.4	62.5	NR	53.8
Luxembourg	31 (70.5)	16 (51.6)	42.9	NR	58.8	NR	NR
Netherlands	843 (85.4)	422 (50.1)	62.5	50.0	43.0	NR	78.9
Romania	125 (88.7)	51 (40.8)	39.7	0.0	28.0	NR	56.7
Slovakia	22 (78.6)	6 (27.3)	33.3	100.0	22.2	NR	NR
Slovenia	33 (94.3)	17 (51.5)	71.4	NR	46.2	NR	NR
Spain	2,438 (84.2)	1,109 (45.5)	55.1	56.8	36.4	NR	49.6
United Kingdom	5,485 (83.2)	2,699 (49.2)	59.5	46.1	38.0	41.9	52.9
Total	14,607 (74.4)	7,157 (49.0)	-	-	-	-	-

NR: no new diagnoses reported; MSM: men who have sex with men.

^a In patients older than 14 years, diagnosed in 2010.

^b Proportion of HIV infections with CD4 cell count reported among the total number of reported HIV infections.

Source: [2].

It is important to develop further HIV surveillance to better reflect the changing epidemiological situation. The inclusion of CD4 cell count at diagnosis provides an opportunity to interpret the data more in depth; however, the reporting of CD4 cell counts as well as other surveillance data needs to be improved.

Surveillance of HIV infection and AIDS in Europe is essential to describe the HIV epidemic in this region and its main characteristics. It is important to monitor the epidemic and guide the public health response in order to reduce HIV transmission. Ensuring that the data are of high quality is of utmost importance to follow up the epidemic response and international commitments [10].

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Trends in HIV and hepatitis C virus infections among injecting drug users in Europe, 2005 to 2010

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Data on newly diagnosed HIV infections and HIV prevalence in 2005 to 2010 suggest falling infection rates in injecting drug users (IDUs) in the European Union (EU). However, recent increases in HIV and hepatitis C virus (HCV) infection rates in IDUs suggest increasing injecting risks in some countries. The coverage of effective prevention measures has increased, but is still low in several countries. Overall the data suggest a continued risk of new outbreaks of HIV infection among IDUs.

Importance of HIV and hepatitis C virus infections in injecting drug users

HIV and hepatitis C virus (HCV) infections are among the most costly consequences of illicit drug use, having a high impact on individuals and on healthcare systems. Injecting drug users (IDUs) have been among the first and largest transmission groups for new HIV infections in many European countries and are still a key transmission group for HCV infections [1,2]. Although in the new millennium rates of newly diagnosed HIV infections that are IDU-related have declined greatly in the European Union (EU) as a whole [3], some countries still report high rates and outbreaks of HIV infection continue to occur [4]. High levels of prevalent infections of HIV and HCV in IDUs, as well as continued high levels of HCV spread, constitute an ongoing threat through blood-borne, sexual and healthcare-associated transmission. In some countries neighbouring those of the EU, HIV infection in IDUs is still rampant and shows few signs of being controlled [3,5,6]. In this report, we present the most recent data available on HIV and HCV transmission among IDUs in the EU. Countries reporting to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) are all EU Member States plus Croatia, Turkey and Norway; countries reporting to the European Centre for Disease Prevention and Control (ECDC) are the EU Member States, plus Iceland, Liechtenstein and Norway – EU/European Economic Area (EEA).

Surveillance and prevalence monitoring of HIV and HCV infections

Case reports on newly diagnosed HIV infections are collected from healthcare services where IDUs and other patients present for diagnostic testing. The data are described by year and as rates (i.e. number of newly diagnosed infections per 100,000 population) [5]. Notification data for HCV infection are not considered here due to data quality problems (1).

Prevalence data for both HIV and HCV infections come mostly from diagnostic testing in healthcare services, as well as from specific prevalence studies. They are provided both at national and/or subnational level by different subsets of countries [7]. They are described by year and as the percentage of people in the sample who are positive, together with sample size, other methodological details and source information [3,7]. The prevalence of HIV or HCV infections in subgroups of IDUs – young IDUs (aged under 25 years) and new IDUs (less than two years since first injection) – are shown separately, as indicators of incidence. Trends in prevalence data are assessed annually using the chi-square test and are used to assess trends over a six-year period (2005–2010): increases or decreases are reported if statistically significant (two-sided test, alpha level of 0.05) [3,7]. Data on the prevalence of HCV infection are interpreted not only to assess trends in this infection, but also as a biological indicator of injection-related HIV infection risk ('injecting risk') in the IDU population [8]. In this report, we focus on regional or national increases, not decreases or stable trends, with a view to detecting regions or countries at potential risk of an outbreak of HIV infection in IDUs [4].

Trends in HIV infection among IDUs

Data on reported newly diagnosed HIV infections related to injecting drug use for 2010 suggest that HIV infection rates are still generally falling in the EU following a peak in 2001–2002, which coincided with

outbreaks in Estonia, Latvia and Lithuania [3,5,9]. The rates seen in 2010 are shown in Figure 1.

Of the five countries reporting the highest rates of newly diagnosed HIV infections among IDUs between 2005 and 2010 (Estonia, Iceland, Latvia, Lithuania and Portugal), Portugal continued a downward trend, but the rates in Estonia, Iceland and Lithuania increased from 2008 levels and in Latvia from that of 2009 (Figure 2). Bulgaria increased from 0.16 (12 new diagnoses) in 2005 to 0.97 (74) in 2009 and 0.74 (56) in 2010. In Sweden, the rate peaked at 0.67 per 100 000 population (61 new diagnoses) in 2007.*

These data suggest that there is a continuing potential for outbreaks of HIV infection among IDUs in some countries.

Trend data from HIV prevalence monitoring in samples of IDUs are available at national or subnational level from 26 European countries in 2005 to 2010. In 18 of the countries, HIV prevalence estimates remained unchanged. In seven (Germany, Spain, Italy, Latvia, Poland, Portugal and Norway), HIV prevalence declined in at least one data source or region. Only one country (Bulgaria) reported increasing HIV prevalence, in the capital city, Sofia, consistent with the increase in newly diagnosed infections. In Italy, although the national trend in HIV prevalence was in decline, an

increase was reported in one region (Veneto, data until 2009). The increases in HIV transmission in Greece and Romania reported in 2011 [4,10-13] were not observed in HIV prevalence or case reporting data before 2011.

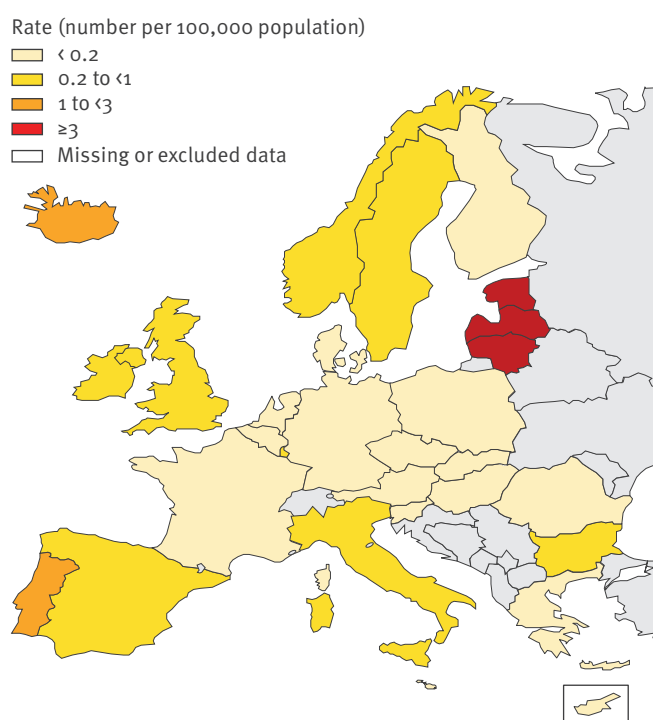
Data from samples of young IDUs (aged under 25 years) indicate ongoing HIV transmission in six countries (Estonia, France, Latvia, Lithuania, Poland and Spain), with prevalence levels above 5% in 2005–2010 (data not shown), and in one country (Bulgaria), where prevalence in young IDUs increased in 2005–2010.

Trends in HCV infection among IDUs

HCV-specific antibody levels among national samples of IDUs in 2009–2010 varied from 14% to 73% (among 12 countries that report national prevalence data). In seven of the 12 countries with national data, the prevalence was over 40%. During 2005 to 2010, a declining prevalence of HCV infection at either national or subnational level in IDUs was reported from six countries and an increase was seen in five (Austria, Bulgaria, Cyprus, Greece and Romania); Italy reported a decline at national level during 2005 to 2009 (more recent data not available), with increases in two of the 21 regions (Table).

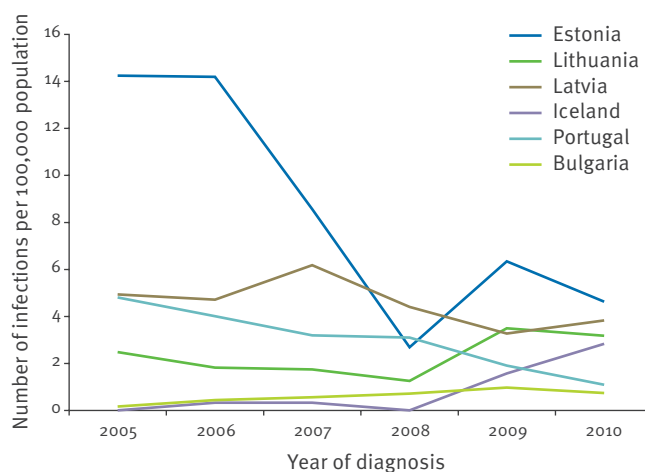
Studies on young IDUs (aged under 25 years) suggest a decline in prevalence at subnational level in Slovakia, which may indicate falling transmission rates (data not shown). However, increases were reported from Austria, Bulgaria, Cyprus and Greece. Increasing HCV prevalence among new IDUs was reported in Greece (nationally and in three regions), whereas declines were reported from Sweden (data for Stockholm only).

FIGURE 1
Newly diagnosed HIV infections attributed to injecting drug use, EU/EEA, 2010



EEA: European Economic Area; EU: European Union.
Source: [5].

FIGURE 2
Five countries with highest rates and one with increasing rate (Bulgaria) of newly diagnosed HIV infections in injecting drug users, EU/EEA, 2005–2010*



EEA: European Economic Area; EU: European Union.
Source: European Centre for Disease Prevention and Control (ECDC).

Coverage of prevention measures

Opioid substitution treatment and needle and syringe programmes are among the most effective measures for preventing infectious diseases among IDUs [14] and are available across the EU. After a massive scale-up of such measures since the mid-1990s, particularly in the western part of EU, opioid substitution treatment currently is estimated to reach about one in two problem opioid users in the EU [3]. However, this overall rate masks important differences between countries, with estimated coverage ranging from 2% to 68% (Figure 3). A regional imbalance with low coverage of opioid substitution treatment in countries in the central and south-eastern part of the EU is apparent.

Similarly, syringe coverage – expressed as the number of sterile syringes distributed from specialist needle and syringe programmes per estimated IDU per year – shows wide variation across Europe (Figure 4). In 2009, very low coverage (less than 100 syringes per estimated IDU) was documented in a majority of the 13 countries for which national estimates of IDU

population size are available (Figure 4); however, estimates for two countries (Luxembourg and Norway) suggest that rates of 200 or more syringes per estimated IDU may be reachable.

Discussion

Overall, a marked decrease in the number of reported newly diagnosed HIV infections due to injecting drug use has been observed in most of the EU/EEA countries; however, high or increasing numbers (in Bulgaria, Estonia, Iceland, Latvia, Lithuania and Portugal) were still reported until 2010, reflecting continued transmission in the region. Recent outbreaks of HIV infection in 2011 in IDUs in Greece and Romania confirm a risk of new increases in countries so far less affected by the HIV epidemic in IDUs [4,10,11].

Very high numbers and rates of newly diagnosed HIV infections continue to be reported from eastern European countries neighbouring those of the EU (e.g. Armenia, Belarus, Georgia and Ukraine) [5,6]. The prevalence of HCV infection remains high overall

TABLE

Countries with data showing an increase in the prevalence of HIV or hepatitis C virus infections in injecting drug users, at national or subnational level, EU, 2005–2010

Country	Coverage	HIV prevalence (%)	HCV prevalence (%)	Additional information
Bulgaria	Sofia	from 0.4 to 2.2	from 53.6 to 62.3	–
	Young IDU ^a	from 0.6 to 3.1	from 52.2 to 65.7	–
Greece	National	–	from 61.7 to 68.8	19 testing sites ^b
	New IDU ^c	–	from 28.4 to 55.5	–
	National	–	from 43.3 to 48.7	18 testing sites ^d
	New IDU ^c	–	from 19.5 to 28.8	–
	Attica New IDUs ^c	–	from 31.4 to 59.4	10 sites ^b
	New IDUs ^c	–	from 25.9 to 45.8	8 sites ^d
	Central Macedonia New IDUs ^c	–	from 0 to 29.4	–
	Thessaly Young IDUs ^a	–	from 20 to 70	–
New IDUs ^c	–	from 0 to 25	2005–2009 ^e	
Italy	Abruzzo	–	from 65.7 to 74.2	2005–2009 ^e
	Valle D'Aosta	–	from 18.1 to 72.4	2005–2009 ^e
	Veneto	from 9.6 to 11.4	–	2005–2009 ^e
Cyprus	National	–	from 29.6 to 51.3	2006–2010
	Young IDUs ^a	–	from 12.8 to 56.3	2006–2010
Austria	Graz	–	from 49 to 73	–
	Young IDUs ^a	–	from 46.8 to 66.7	–
	Vienna	–	from 48.9 to 67.2	–
Romania	Bucharest	–	from 45.8 to 65.6	2005–2007 ^e

EU: European Union; IDU: injecting drug user.

All countries/regions/cities included where data are available and show an increase.

Multiple rows for the same region represent different studies/samples (young/new IDUs are subsamples).

Chi-square test was used for all trends, $p < 0.05$. For more detail of the data up to 2009, see [7] (2010 data are not yet published).

^a Aged under 25 years.

^b Drug treatment centres (maintenance, drug free/detox), low-threshold services, public health laboratories, other hospitals or clinics.

^c Less than two years since first injection.

^d Drug treatment centres, low-threshold services, prisons, other.

^e More recent data are not available.

and suggests a substantial need for treatment, while high and increasing prevalence among young and new IDUs in some countries (Austria, Bulgaria, Cyprus and Greece) points to high incidence and continuing risks of infection among IDUs. Where increasing prevalence of HCV infection coincides with low coverage of effective prevention measures, there may be a potential for increased HIV transmission – as shown in Greece and Romania, where increasing prevalence of HCV infection overall and in new IDUs, appear to have preceded the HIV outbreaks by several years [12]. This suggests that prevalence of HCV infections in new IDUs may be a timely indicator of injecting risk among IDUs [8,18].

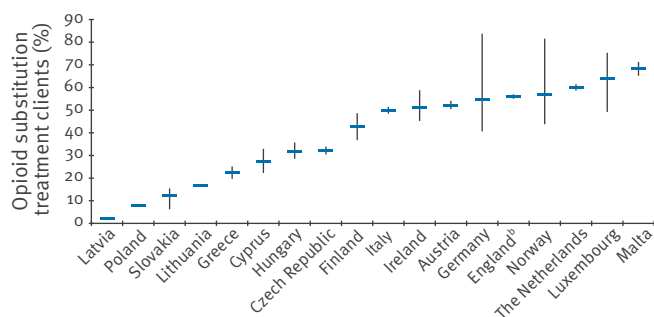
Serious limitations exist regarding the quality and completeness of the data. These include under-ascertainment of injecting drug use as risk factor in case-reporting data, as well as under-reporting and reporting delay, which can show spurious declines in the most recent years. In most EU countries, however, under-reporting is thought to be low, although evidence for this is generally not available and in countries where data are reported by year of diagnosis, reporting delay is not an issue (but under-reporting can still be). Prevalence data are mostly from diagnostic testing and are less sensitive to bias from changes in testing patterns (as they are adjusted for the total number of tests in the denominator) and are not subject to bias from under-reporting or reporting delays. However, they are subject to other biases, such as non-representative sampling or exclusion of known-positives in diagnostic testing samples, they are not available from several countries on a repeated basis (for assessing trends) and are often less timely than case reports, although well-designed and timely prevalence monitoring exists in some countries. In some instances,

caution is warranted, given the limited geographical coverage and/or sample size of the studies. However, when prevalence data confirm the trends observed in case-reporting, they contribute substantially to the robustness of the overall evidence. A recent EMCDDA/ECDC rapid risk assessment provided an overview of the most recent data available and mapped increases in HIV indicators (HIV case reports, prevalence, including in young or new IDUs) and HIV risk indicators (HCV prevalence, including in young or new IDUs) among IDUs in the EU [4,9].

The observed reduction in HIV infections among IDUs in the EU overall in the new millennium is mainly due to large decreases in some of the most affected large countries (in the western part of the EU), which may reflect the combined effects of marked increases in coverage of prevention measures, reductions in risk behaviour among IDUs, declines in the prevalence of injecting drug use (IDU population size) and saturation effects, where incidence naturally declines after explosive spread has reached most high-risk individuals.

In contrast to HIV, HCV infection incidence among IDUs appears to remain generally high, probably due to much higher infectivity of HCV. While recent evidence suggests that sustained provision of combined prevention measures at high coverage levels can reduce the incidence of HCV infection [14,19-21], such coverage seems not to exist to date in most EU Member States where data are available. Outbreaks of HIV infection in some countries with very low coverage of prevention measures (Romania and Greece) have recently drawn attention to the continuing potential for new epidemics among IDUs in the EU [9-11].

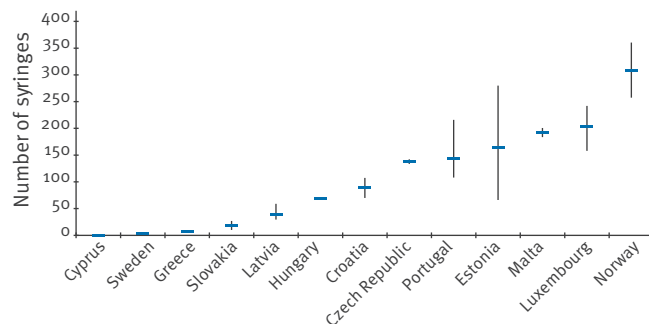
FIGURE 3
Opioid substitution clients as a proportion of the estimated number of problem opioid users, 18 EU/EEA countries^a, 2009–2010



EEA: European Economic Area; EU: European Union.
The horizontal line indicates a point estimate, and the vertical bar indicates an uncertainty interval. For methods, definitions and detailed references see [15].

^a Countries where data are available.
^b Data for the United Kingdom are not available.
Source: [16].

FIGURE 4
Number of syringes distributed through specialised programmes per injecting drug user^a, 12 EU/EEA countries and Croatia^b, 2009



EEA: European Economic Area; EU: European Union.
The horizontal line indicates a point estimate, and the vertical bar indicates an uncertainty interval.

^a Numbers of injecting drug users are estimated. For methods, definitions and detailed references, see [15].
^b Countries where data are available.
Source: [17].

In conclusion, available data from HIV case-reporting and HIV and HCV prevalence studies in IDUs suggest that, although generally the rate of new HIV infections is still in decline, a risk of new outbreaks of HIV infection among IDUs still exists, pointing to the need for implementing effective prevention interventions on an adequate scale.

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* Authors' correction:

At the request of the authors, the following changes were made on 1 December 2011: the paragraph beginning 'Of the six countries reporting the highest rates of newly diagnosed HIV infections ...', was replaced with 'Of the five countries reporting the highest rates of newly diagnosed HIV infections among IDUs between 2005 and 2010 (Estonia, Iceland, Latvia, Lithuania and Portugal), Portugal continued a downward trend, but the rates in Estonia, Iceland and Lithuania increased from 2008 levels and in Latvia from that of 2009 (Figure 2). Bulgaria increased from 0.16 (12 new diagnoses) in 2005 to 0.97 (74) in 2009 and 0.74 (56) in 2010. In Sweden, the rate peaked at 0.67 per 100 000 population (61 new diagnoses) in 2007.'

In addition, the title of Figure 2 was updated to read, 'Five countries with highest rates and one with increasing rate (Bulgaria) of newly diagnosed HIV infections in injecting drug users, EU/EEA, 2005–2010'. The title of the image was updated on 2 December 2011.

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16. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Figure HSR-1. Opioid substitution treatment clients as a percentage of the estimated number of problem opioid users, 2009 or most recent year available. Lisbon:EMCDDA. [Accessed 1 Dec 2011]. Available from: <http://www.emcdda.europa.eu/stats11/hsrfig1>
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Human immunodeficiency virus in injecting drug users in Europe following a reported increase of cases in Greece and Romania, 2011

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Greece and Romania reported an increased number of HIV cases among injecting drug users (IDUs) during 2011. Most European countries reported no changes in the rate of newly diagnosed cases of HIV or HIV prevalence in IDUs; however, six countries did report increases and several additional countries reported increases in injecting risk indicators or low coverage of prevention services. These indicate a potential risk for increased HIV transmission and future outbreaks unless adequate prevention is implemented.

In 2010, the number of newly diagnosed human immunodeficiency virus (HIV) cases among injecting drug users (IDUs) represent only 4% of the total number of reported HIV cases in the European Union (EU) [1]. However, increases in HIV infections among IDUs in Greece were reported in July 2011, through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), followed by a reported increase in Romania in November 2011. Preliminary results of the investigation on the Greek outbreak were released in September [2] and November 2011, respectively [3]. These subsequently led to a request from the European Commission to carry out a rapid risk assessment at EU level.

Epidemiological situation of HIV in Greece in 2011

Since the beginning of 2011, the number of newly diagnosed HIV infections has increased among IDUs in Greece. Between nine and 16 cases were reported annually among IDUs during 2006-2010, representing 2-3% of the total newly diagnosed HIV infections, while during the first 10 months of 2011, cases among IDUs sharply increased to 190, representing approximately 25% of all reported HIV cases [2,3]. Prevalence studies

have also detected a steep increase of HIV among IDUs in 2011, mostly in Athens [3].

Prior to the 2011 outbreak, the coverage of prevention services was low, with waiting times for opioid substitution treatment estimated at 89 months in 2010 and with an estimated distribution of only six sterile syringes per IDU during the entire year of 2009, which is far lower than in most European countries that report data to calculate syringe distribution per IDU [4]. In response to the outbreak, the Greek authorities have sought to rapidly expand opioid substitution treatment services and have started mobile prevention services offering information, voluntary testing, referrals and clean needles and syringes [3].

Epidemiological situation of HIV in Romania in 2011

In November 2011, a strong increase of newly diagnosed HIV infections among IDUs during 2011 was reported to EMCDDA based on the information provided by routine monitoring and case reporting coordinated by the Romanian Ministry of Health. While reporting three to five cases annually from 2007 to 2009, HIV infections among IDUs increased to 12 cases in 2010 and to 62 cases in the first nine months of 2011. Routine monitoring performed at registration for drug treatment services indicated an increase in HIV positive cases among IDUs tested (1.1% (2/182) in 2008, 3.3% (11/329) in 2009 and 4.2% (12/288) in 2010). Cases reported in 2011 were mostly residents of Bucharest and the surrounding area (56/62), predominately males (55/62), and younger than 34 years (55/62). Twenty-nine cases had confirmed CD₄ cell counts at diagnosis higher than 500 cells/mm³ suggesting recently acquired HIV infections. No specific HIV testing campaigns had been initi-

ated and most cases were detected when seeking drug treatment or hospital care for other conditions.

In behavioural surveillance surveys among IDUs, there are reports of changes in drug use patterns from 2009, where 97% of respondents reported heroin as the main drug of injection, to 2010, where 67% reported heroin and 31% reported amphetamine-type stimulants, mostly synthetic cathinones, as the main drug of injection. Stimulant use is associated with more frequent injection and there are reports of increased syringe-sharing [5].

While drug use and injection risk patterns appear to be changing in Romania, access to sterile syringes has decreased. Numbers of sterile syringes distributed reportedly declined from 1.7 million in 2009 to 965,203 in 2010 and to approximately 700,000 up to November 2011. Based on the estimated number of IDUs, syringe provision in Bucharest has thus decreased from 97 syringes per IDU in 2009 to 53 syringes in 2010. While the overall provision of opioid substitution treatment in Romania seems to be limited, the number of clients in such programmes increased from 424 in 2009 to 601 in 2010 [6,7].

Background

HIV infection is one of the most serious potential health consequences associated with IDU, leading to chronic infection, acquired immunodeficiency syndrome (AIDS) and premature death if untreated [1]. In the EU and the European Economic Area (EEA), the estimated HIV prevalence rates among IDUs range from less than 1% to more than 60% [8,9]. Although for the EU/EEA area as a whole the number of new HIV diagnoses reported annually among IDUs has declined by 44% since 2004, outbreaks have been observed within a number of countries in recent years [9-13].

The risk for blood-borne virus infection outbreaks among IDUs depends on multiple factors, including the frequency of needle sharing, the number of needle sharing partners, the social network structures and mixing in the IDU population. Additional determinants include the size of the IDU population, the types of drugs injected, exposure through commercial sex and other risky sexual practices, and awareness of risks and prevention measures available. In a more general perspective, public health and drug policies as well as the legal environment can also determine infection risks [14].

Assessment of the situation of human immunodeficiency virus among injecting drug users in the European Union/ European Economic Area

In response to the notified events in Greece and Romania, the European Centre for Disease Prevention and Control (ECDC) and the EMCDDA conducted a rapid inquiry to HIV surveillance contact points and national drug focal points in the EU/EEA Member States, candidate and potential candidate countries, in November 2011, to investigate possible recent increases in HIV infections detected among IDUs. Information available from routine surveillance and monitoring of HIV and hepatitis C (HCV) as well as prevention coverage among IDUs has been combined with results from the rapid inquiry (Table).

Increases in HIV case reports or prevalence among IDUs were reported by six countries as compared to 2008-2010. Seventeen countries reported no changes, four reported fewer cases or lower prevalence, and two did not have information available to assess a change. Countries reporting an increase in the most recent year from which data were available (2011 or 2010) were Bulgaria, Greece, Italy, Lithuania, Luxembourg, and Romania.

TABLE

Indicators of human immunodeficiency virus and hepatitis C virus transmission, injecting risk and intervention coverage, European Union and European Economic Area, 2008–2011

EU/EEA country	Increase in the number of HIV cases ¹	HIV prevalence increase	Hepatitis C prevalence increase	Other injecting risk increase	Injection drug use prevalence increase	Less than 30% of problem opioid users in opioid substitution treatment ²	Less than 100 syringes per IDU per year from specialised programmes ³	Surveillance changes
Austria	2010	2010	2010 ⁴	5		52%		
Belgium	2010	2010	2010					
Bulgaria	2009	2010 ⁵	2010 ⁷	8				
Croatia	2010				9		89	
Cyprus	2010	2010 ¹⁰	2010 ¹¹		9	27% in 2010	0	
Czech Republic	2010	2010			9	32%	138	
Denmark	2010		2008					
Estonia	2010						164	
Finland	2010	2009	2009			32%		

France	2010							
Germany	2010					55%		
Greece	2011	2011 ¹²	2010 ¹³	¹⁴	9	22% in 2010	6	
Hungary	2010	2010 ¹⁵		^{5,8}	¹⁶	32%	69	
Iceland	2010							
Ireland	2010			8		51%		
Italy	2010	2009 ¹⁷	2009 ¹⁸			50%		
Latvia	2010	2010 ¹⁹	²⁰			2% in 2010	39	
Lichtenstein								
Lithuania	2011	²⁰				17% in 2010		
Luxembourg	2010	2010 ²¹				64%	204	
Malta	2010	2010	2010			68%	193	
Netherlands	2010	²²	2008			60%		
Norway	2010	2010	2010		9	57%	309	
Poland	2010	2010	²³			8% in 2010		
Portugal	2010	2010	2009				144	
Romania	2011	2011 ²⁴	2010 ²⁵	²⁶			53 ²⁷	
Slovakia	2010	2010 ²⁸	2010	8	¹⁶	12% in 2010	19	
Slovenia	2010	2010	2010	8				
Spain	2010	2009						
Sweden	2010	2008 ²⁹	2008				3	
Turkey	2010	³⁰						
United Kingdom	2010	2010	2010	8	³¹	56% in 2009		

ECDC: European Centre for Disease Prevention and Control; EEA: European Economic Area; EMCDDA: European Monitoring Centre for Drugs and Drug Addiction; EU: European Union; HIV: human immunodeficiency virus.

 No alert: no evidence for increased cases/prevalence and/or no evidence of low intervention coverage/no changes in surveillance

 Alert: evidence for increased cases/prevalence and/or low intervention coverage/decreased surveillance

 Information unknown/not reported to EMCDDA/ECDC

¹ HIV case increase taken from 2010 HIV surveillance data. Source: [15]. Bulgaria case report increased in 2008-2009, but returned to 2008 level in 2010. Case increases for Romania and Greece for 2011 were reported from country HIV surveillance and drugs focal points. Focal points from most other EU/EEA countries indicated no detected increase in new cases among IDUs in 2011 as compared to previous years.

² For the purpose of this report a cut-off of 30% coverage was used in order to limit the alert to the lowest range and likely highest HIV risk. Coverage levels below 50-70% of the target population are considered sub-optimal. Source: [7].

³ Syringes given out by specialised needle and syringe programmes, not including pharmacy sales. Source: [4].

⁴ Increases in Graz and Vienna, 2005-2010.

⁵ Based on the EMCDDA 2011 Annual report [9]: both Hungary and Austria reported notable increase of mephedrone injecting.

⁶ The ratio of HIV positive IDUs for the last 10 months (January to December 2011) increased with 8.9% in comparison with the whole 2010. The available data is for the capital city (Sofia) only.

⁷ Increase among all IDUs and among young IDUs, Sofia, 2005-2010.

⁸ Country experienced severe heroin shortage in 2010-2011 and reported on possible increased injecting risks for some groups.

⁹ IDU prevalence estimates (2010 data taken into account only for the Czech Republic and Greece).

¹⁰ Increase among young IDUs 2004-2009 reported in the 2011 EMCDDA Annual report [9] is not continued in 2010.

¹¹ Increase in all IDUs 2005-2010.

¹² Source: [3].

¹³ Increase nationally and in Attica, Central Macedonia and Thessaly, 2005-2010.

¹⁴ Reports of increased injecting of stimulants (home-made) at expert meeting Greece, October 2011 [3].

¹⁵ National trend data until 2009 show no increase, data for 2010 show zero prevalence in six regions.

¹⁶ Trend data available but not recent.

¹⁷ Decline at national level, increase in one out of 21 regions (Veneto), 2004-2009.

¹⁸ Decrease nationally, increasing trend in three out of the 21 regions (Abruzzo, Umbria, Valle d'Aosta), 2004-2009.

¹⁹ Increase in self-reported HIV prevalence 2004-2009 reported in the 2011 EMCDDA Annual report [9] is not continued in 2010.

²⁰ Varying prevalence in 2010 but no trend data available.

²¹ Self-reported data; increase in 2010 reported [16].

²² Zero prevalence in Amsterdam and Rotterdam 2010, but small sample sizes and no trends data.

²³ Varying prevalence in 2009 but no trend data available.

²⁴ Reported in the present paper.

²⁵ Increase 2005-2008 in all IDUs, and in male IDUs only in 2008-2010.

²⁶ Users switched to injecting amphetamine type stimulants (mostly mephedrone and other synthetic cathinones).

²⁷ Sub-national estimate, Bucharest area.

²⁸ Increase in HIV prevalence 2004-2009 reported in the 2011 EMCDDA Annual report [9] is not continued in 2010.

²⁹ Trend data, available only until 2008, suggest some non-significant increase.

³⁰ No trend data available, 2010 data suggest low prevalence.

³¹ Injectors of opiates and/or crack-cocaine

In Bulgaria, HIV case reports for IDUs increased by 8.9% up to October 2011 in comparison with 2010, although 2011 data were only available for Sofia. At national level, an increase in the number of case reports for HIV among IDUs was already documented in 2009 in Bulgaria. In Luxembourg, drug surveillance data showed an increased HIV infection prevalence in current IDUs from 4.3% in 2009 to 8.1% in 2010 (no data available for 2011). However the proportion of all HIV cases who have injection drug use as a transmission route declined from 6.3% in 2010 to 3.6% in 2011, as of November. In Italy, case reporting data for one region has increased, however the average national prevalence of HIV infection among IDUs continues to decline. Lithuania reported more than two times the number of HIV cases in 2009 and 2010 (180 and 153 respectively) as compared to 2008 (95 cases), but also reported increased testing among IDUs in 2010.

In addition to HIV case or prevalence increases, reports from some countries where data are available indicate a potential risk for HIV transmission in the IDU population with changes in drug use patterns, from mostly heroin in 2009 to more stimulant use in (Austria, Greece, Hungary, Romania); increased HCV rates among IDUs (Austria, Bulgaria, Cyprus, Greece, Italy, Romania); low coverage of opioid substitution treatment (Cyprus, Greece, Latvia, Lithuania, Poland, Slovakia) or low coverage of needle and syringe programmes (Croatia, Cyprus, Greece, Hungary, Latvia, Romania, Slovakia and Sweden).

Discussion

Overall, the incidence of HIV among IDUs in EU/EEA has been declining steadily since the early 2000s [15]. However, as a conclusion from the rapid risk assessment we note that two countries reported recent outbreaks of HIV, four countries reported increases in HIV cases or prevalence, and several other countries reported increases in injecting risk indicators (including HCV prevalence) or low coverage of prevention services among IDU. These factors combined indicate a potential risk for HIV transmission and future outbreaks.

There are clear indications of significant increased HIV transmission in Greece and Romania. While the magnitude of the most recent increases in case reports could be partially related to enhanced surveillance, particularly in Greece, the available evidence indicates a real increase in HIV transmission in both countries. In Romania, it is likely that a recent rise in the combined use of opioids and amphetamine-type stimulants resulting in increased injecting frequency could have contributed to HIV transmission. In both countries, there is a temporal association between this increase and reduced provision of prevention services (Romania) or initially low levels of provision of prevention services (Greece). In Romania, these reductions have coincided with the end of a grant from the Global Fund for AIDS, tuberculosis and malaria in June of 2010.

The most robust and recent evidence suggests that the largest reduction of HIV and injection risk behaviour can be achieved by providing comprehensive prevention services, with high coverage of both needle and syringe programmes and opioid substitution treatment in combination [17,18]. In light of the growing prevalence of injection of amphetamine-type stimulants, as is reported in Romania, an additional and important challenge is to identify and implement effective treatment that targets this type of dependence [5, 9].

In order to prevent new outbreaks of HIV among IDUs, it is of utmost importance that countries that have indicated a change in injecting drug use risk factors or HIV and hepatitis C prevalence review their national or local prevention and control programmes in light of the current situation. Countries that experience ongoing increases or outbreaks would need to scale up their services urgently to prevent new cases. In the context of significant increased transmission of HIV among IDUs, rapid interventions in the form of scaling-up of needle and syringe programmes, provision of opioid substitution treatment and of condoms to reduce sexual HIV transmission are warranted.

The extent to which service reductions or changing patterns of risk among IDUs have been related to the current economic crisis in Europe cannot be easily measured and due to complex interactions between many factors, causal links are extremely difficult to establish. However, in past economic downturns, increased HIV incidence and increased injecting drug use have been observed [19,20], and in a recent paper, Kentikelenis et al. have drawn links between the financial crisis in Greece and the increased HIV incidence [21]. In addition to exacerbating vulnerabilities and risk behaviours, economic downturns may also limit the funding available to prevention programmes [22]. The current outbreaks of HIV in IDUs in Greece and Romania show that there is a continuous need to keep prevention of HIV and public health on the agenda also in challenging economic times.

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Two cases of mild IgM-negative measles in previously vaccinated adults, the Netherlands, April and July 2011

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We describe two cases of mild, modified measles in fully vaccinated adults in the Netherlands. The mildness of disease, the lack of an IgM antibody response, the relatively low amounts of virus detected and the fact that no additional cases were reported, suggests that these vaccinated patients were less contagious than unvaccinated patients.

We report here two cases of measles in persons who had received two doses of measles vaccine according to the recommended schedule. They were investigated in the context of two measles clusters that occurred in the Netherlands in April and June–July 2011. The characteristics of these clusters are summarised in the Table.

TABLE

Characteristics of patients in two clusters of measles, Amsterdam, the Netherlands, April–July 2011 (n=6)

Cluster	Case	Year of birth	Disease onset (2011)	Source of infection	Transmission	Measles vaccination history (reason)	IgM serology	IgG serology (mIU/ml)	Realtime PCR ^a	World Health Organization definition (genotype) ^b
1	A	After 1987	3 Apr	France	Unknown	No (critical attitude)	Positive	Not sampled	Throat/urine positive: day 9 (ΔCT 8.4/6.2)	MVs/Amsterdam. NLD/ 15.11/1[D4] ^c
1	B	Between 1976 and 1987	18 Apr	Sports club	Contact of 1A	2x	Negative	6,000/140,000 (day 0/22)	Throat/urine positive: day 0 (ΔCT 11.2/7.9)	MVs/Amsterdam. NLD/ 15.11/2[D4] ^c
2	A	Between 1970 and 1976	26 June	Spain	Unknown	No (age)	Positive	Not sampled	Urine positive: day 11 (ΔCT 7.2)	MVs/Amsterdam. NLD/ 27.11/1[D4] ^d
2	B	Under 12 months-old	4 July	Spain	Contact of 2A (child)	No (age)	Not tested	Not sampled	Oral fluid positive: day 3 (ΔCT 12.5)	MVs/Amsterdam. NLD/ 27.11/2[D4] ^d
2	C	Between 1970 and 1976	9 July	Hospital	Contact of 2A (nurse)	No (age)	Not tested	Not sampled	Throat/urine positive: day 6 (ΔCT 9.1/10.3)	MVs/Amsterdam. NLD/ 28.11/1[D4] ^d
2	D	Between 1976 and 1987	9 July	Hospital	Contact of 2A (physician)	2x	Negative	18,000/36,000 (day 5/38)	Urine negative, throat positive: day 5 (ΔCT 2.5/ -)	MVs/Amsterdam. NLD/ 28.11/1[D4] ^d

^a Measles RNA content of each individual specimen is expressed here quantitatively as a difference operator (ΔCT), which refers to the difference between the cycle threshold (CT) value of the clinical specimen and the CT value of the lowest amount of measles RNA that is detectable in the realtime PCR assay.

^b Genotype analysis is based on the 456 bp N-terminal part of the measles virus nucleoprotein (N) gene.

^c 100% identity with genotype submissions from e.g. France, the United Kingdom and Germany in 2010 (Genbank accession numbers: FR671429, HQ202158, HQ704333, respectively).

^d All four cases in the second cluster had identical D4 sequences, which differed from Cluster 1 by one nucleotide; no exact match was found in Genbank nor in the Measles Nucleotide Surveillance (MeaS) database.

Case 1B

The first case was a patient born between 1976 and 1987 (Table, Case 1B) with a verified history of two vaccinations. The patient developed fever and exanthema on 18 April 2011, with no complaints of coughing, coryza or conjunctivitis and without Koplik spots. The exanthema was typical for measles. Blood samples taken on the same day and tested by Serion Elisa classic Measles Virus IgG/IgM showed an IgM concentration of 7 mIU/ml (negative) and an IgG concentration of >5,000 mIU/ml (positive). PCR tests on urine and saliva were positive for measles virus. We repeated the blood tests on 10 May: the IgM test remained negative (<5 mIU/ml) and the IgG titre remained at >5,000 mIU/ml. A dilution experiment with paired serum samples from Serion Immundiagnostica GmbH showed a more than four-fold increase in IgG titre (from 6,000 to 140,000 mIU/ml). The negative IgM results were confirmed by another reference IgM assay (Enzygnost EIA) which returned values of 0.10 (indeterminate) and 0.15 (indeterminate) for the two consecutive samples. The latter assay was repeated and returned IgM values of 0.09 (negative) and 0.15 (indeterminate).

The source of this infection was an adult contact in a sports club born after introduction of MMR vaccination in 1987 (Table, Case 1A), who had recently suffered from confirmed measles (IgM- and PCR-positive). This source patient was reported to us in the beginning of April 2011. This person did not have a history of vaccination and had travelled during the incubation period in France, where measles outbreaks are ongoing since 2008 [1].

Genotype analysis of the measles RNA detected in urine and saliva of both patients demonstrated the presence of genotype D4 measles virus. This is a highly prevalent genotype found in many European countries in 2010 and 2011, but the epidemiological data corroborates France as the origin of this measles cluster (Table, Cluster 1). In 2011 other genotype D4 measles cases were reported in the Netherlands, some of which had identical D4 sequences, but neither of which could be epidemiologically linked to the two cases of this first cluster (data not shown).

Case 2D

The second case was a physician, born between 1976 and 1987, who also had a verified history of two measles vaccinations (Table, Case 2D). The physician developed a rash typical of measles on 9 July 2011 and did not complain of fever, coryza, coughing or conjunctivitis. A blood test on 14 July was negative for IgM (6 mIU/ml) and positive for IgG (>5,000 mIU/ml). Virus was detected by PCR in a nasopharyngeal sample taken on 19 July. The results of blood tests taken on 16 August were negative for IgM and had an IgG titre of >5000 mIU/ml. A dilution experiment with paired serum samples by Serion Immundiagnostica GmbH showed a less than fourfold increase in IgG titre (from 18,000 to 36,000 mIU/ml), and again IgM results were confirmed

negative by a another reference IgM assay (Enzygnost EIA) which returned IgM values of 0.09 and 0.05 for the two consecutive samples.

The source of Case 2D's infection was a patient, born in between 1970 and 1976 (Case 2A), who did not have a history of measles vaccination and who had travelled to Spain during the incubation period. The patient attended an emergency department where the physician was working on 26 and 27 June 2011, with complaints of fever and rash. The measles diagnosis was confirmed with a positive IgM test and virus detection by PCR in a urine sample (Table, Case 2A).

Besides the physician, the source patient also infected a nurse born between 1970 and 1976, without a history of measles vaccination (Table, Case 2C), and the source patients' 10 month-old child (Table, Case 2B). In all four patients, genotype analysis demonstrated the presence of a similar genotype D4 measles virus RNA as documented in the first cluster, which differed from the first cluster by one nucleotide (Table). This nucleotide change was present in all four cases but did not match any of the currently documented D4 strains in Genbank or the Measles Nucleotide Surveillance (MeaNS) database (<http://www.who-measles.org>). In the time period, when cluster 2 was occurring, three other genotype D4 cases were reported in the Netherlands, but none of these were epidemiologically or molecularly linked to Cluster 2 (data not shown).

In the Netherlands, childhood measles vaccination has been ongoing since 1976. Since 1987, two doses of measles, mumps and rubella (MMR) vaccine have been recommended for children aged 14 months and nine years. The coverage of both doses has been consistently high (>95%) in the last decades [2], but is not even throughout the country. About 1–2% of the population refuse vaccination on religious grounds. The last outbreak of measles in these religious communities was from April 1999 to May 2000 and consisted of at least 3,292 reported cases, including three deaths [3]. No major outbreaks have been observed since, except for a restricted outbreak in an anthroposophic community in 2008 [4]. Since 2009 large outbreaks of measles have been reported in various European countries. The same virus genotype (D4) is responsible for most of these outbreaks [1]. In the Netherlands, no major outbreaks have been seen apart from some small clusters of patients. The majority of the index cases acquired their disease outside the Netherlands.

Conclusions

Our data show that fully vaccinated persons were infected with measles virus, albeit in the absence of IgM seroconversion. Variable results with respect to IgM antibody detection in infected persons who had been fully vaccinated against measles have been presented before [5-7]. Our two cases developed rash and some fever, but no other specific symptoms. Due to resurgence of measles in Europe, we anticipated an increase

in measles importations in the Netherlands, which is why suspected cases were more often investigated. Moreover, laboratory diagnostics were extended to include RT-PCR on nasopharyngeal or urine specimens to detect the presence of measles virus, and serological confirmation on paired serum samples.

We conclude that mild measles in previously vaccinated persons due to waning immunity can occur and the IgM test result can remain negative. Case 1B developed a more than four-fold increase in IgG titre, which, as shown here, strongly depends on early blood sampling. The high IgG titres in case 2D also indicate a strong secondary antibody response.

We preferred measles virus RNA detection by RT-PCR in urine and oropharyngeal samples because this was found to be the most conclusive diagnostic method and also allows epidemiological linkage between the cases using genotyping. On the basis of both molecular data and travel history, the source of these small clusters of measles was found to be unvaccinated adults who had most likely imported measles virus from outside the Netherlands. It should be noted that we do not know the extent of virus transmission other than for the clinical cases presented here. However, surveillance of contacts of the two mild cases did not identify additional cases, which is consistent with findings in other recently published case studies [5]. Given the mild disease in these patients, the lack of a systemic IgM antibody response, and reduced shedding of measles virus estimated by realtime PCR, these vaccinated patients may also have been less contagious than unvaccinated patients. When taking the time of sampling into account, this is best illustrated for the vaccinated case in Cluster 2 (see Table). However, further studies are clearly needed to generalise such a conclusion.

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