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HCV genotype shift occurred over the 15 years in PWIDs in the Czech Republic

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ABSTRACT

Objectives: To follow on the epidemiology of HCV, especially genotypes spreading among people who inject drugs (PWID) in Prague and surrounding Central Bohemia, Czech Republic.
Methods: 546 patients who reported past and/or recent injecting of drugs were recruited in the years 2010–2012. They were initially tested for anti-HCV. Real-time PCR was used for quantification and genotyping of hepatitis C virus. Obtained data from the years 2010–2012 were compared with historical controls from periods of 1998–2000 and 2005–2007.
Results: Of 546 initially recruited and tested patients were 393 (72%) anti-HCV seropositive and of them 269 (68.4%) had detectable HCV PCR RNA. The most prevalent subtype was 3a in 97 patients (36.1%), 1a was detected in 85 patients (31.6%) and 1b in 57 patients (21.2%). These three genotypes were responsible for nearly 89% of infections.
Conclusion: Significant increase in both genotypes 1a and 3a over the 15 years was apparent and significant, followed by the decrease in genotype 1b. In the genotype 1b and genotype 3a the significance has risen with the years of data collection. Described genotypic shift reflects the evolution of HCV epidemics and corresponds with the mode of transmission.

KEY WORDS
HCV – HCV genotypes – people who inject drugs – Czech Republic

SOUHRN

Krekulová L., Řehák V., Oktábec Z., Vacek J.: Vývoj v zastoupení genotypů HCV u injekčních uživatelů drog v České republice během 15 let
Cíl: Pokračovat ve sledování vývoje epidemie HCV infekce, zvláště genotypového zastoupení u injekčních uživatelů drog (PWID) v Praze a středních Čechách.
Metody: V letech 2010–2012 bylo zařazeno 546 pacientů, bývalých či současných injekčních uživatelů drog, kteří byli vstupně testováni na přítomnost anti-HCV protilátky, u pozitivních byla pomocí Real-time PCR provedena kvantifikace a genotypizace viru. Získaná data z let 2010–2012 byla následně porovnána s kontrolními skupinami z období let 1998–2000 a 2005–2007.
Výsledky: Z 546 zařazených a testovaných pacientů bylo 393 (72 %) anti-HCV pozitivních; z nich 269 (68,4 %) mělo detekovatelnou HCV PCR RNA. Nejčastější subtyp HCV byl 3a u 97 pacientů (36,1 %), 1a u 85 pacientů (31,6 %) a 1b u 57 pacientů (21,2 %). Tyto tři subtypy byly zodpovědné za téměř 89 % infekcí ve zkoumané skupině.
Závěry: Byl potvrzen statisticky významný nárůst v zastoupení genotypů 1a a 3a se současným poklesem frekvence genotypu 1b. U genotypu 1b a genotypu 3a narůstala statistická významnost změn v závislosti na roce záchytu. Popsaný genotypový posun odráží vývoj epidemie HCV a odpovídá aktuálně převažujícímu způsobu přenosu HCV infekce.

KLÍČOVÁ SLOVA
HCV – genotypy HCV – injekční uživatelé drog (PWID) – Česká republika

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INTRODUCTION

Hepatitis C remains the most prevalent blood borne disease, affecting predominantly people who inject drugs (PWID) in the Czech Republic (CR). In contrast with common population in CR where the historical HCV prevalence used to be very low [1], the transmission in PWIDs in CR [2] is still ongoing in relatively constant fashion. The introduction of broad variety of preventative and awareness programs in early nineties of the last century has apparently had a favorable influence on the control of HIV transmission in PWID group and the number of reported cases of HIV remains low and stable [3]. Such interventions were only partially effective in the case of HCV because of virus higher infectivity and complex nature of HCV transmission [4, 5].
PWIDs are generally a group which is difficult to access and manage [6]. Only part of the users is aware of their infection status, thus low-threshold harm reduction interventions, such as needle-syringe exchange programs (NSP) and opioid substitution treatment (OST), including testing for HCV and treatment of HCV, are primary prerequisities for HCV control [7].
HCV genotype distribution possesses distinct epidemiological patterns in different countries and regions. There is

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increasing evidence that the mode of transmission could favor propagation of certain genotypes [8].
Particular genotypes are directly related to clinical outcomes and also determine treatment schedules [9]. The importance of HCV genotypes and subtypes has gained even higher significance with the latest directly acting antivirals (DAA) [10, 11], where the treatment must be tailored precisely according to the subtype, disease stage and resistance scenario. The upcoming pangenotypic medication combinations might resolve this complicated situation.
HCV genotype distribution evolves in specific populations in particular locations over time, as was reported on many occasions [8, 9]. Changes in the routes of transmission are considered as one of the major determinants of HCV genotypic shift. Genotypes 1a and 3a have recently been spread mainly by the risky activities such as injecting drugs or risky tattooing in certain groups.
In our previous work we looked at the genotypes in two papers. In the first publication which was a pilot study, we described 1b as dominating genotype in CR. It was a reflection that 1b used to be a baseline genotype at the beginning of the epidemic [12]. With the ongoing widespread habit of injecting drugs in CR we further noticed the changes in HCV epidemiology and genotypic shift in favor of 1a and 3a genotypes as we described in the second paper [13]. The comparison with the 2010–2012 periods will follow in Table 2. Based on the literature, our previous and current experience we expect continuous changes in HCV epidemiology. In this work we further follow on the development in the distribution of genotypes in the population of CR.
Remedis, where all work has been done, is multidisciplinary outpatient clinic. It provides various services for drug users in one place together with regular medical care and non-medical services, e.g. OST, social programs, etc. Program of Comprehensive Care was established in 1997 with the goal to reach drug users and to offer timely and targeted specific health care services for drug users including the individually tailored HCV therapy. The "under-one-roof concept" was established at that time and subsequently became a current good practice. With this approach Remedis evolved in the largest HCV treatment center in the country, which further enhances the impact of the treatment-as-prevention approach applied within this risk group in this clinic.
CR belonged and still belongs to countries with low HCV prevalence. Unfortunately, data available on HCV prevalence in CR are scarce. The last published serological survey was performed in 2001, where the general anti-HCV seroprevalence was 0.2% [1]. More recent data are based on estimates only, where the viremic prevalence was estimated to be 0,4% and seroprevalence was back calculated as 0,6% in 2012 [14]. We believe that the prevalence in general, especially older population in CR was low and remains so also at present. This is witnessed by the limited number of liver transplants secondary to HCV infection [15], low numbers of HCV captures in general laboratories and transfusion facilities [16].
The only published multicentric study described the average country HCV seroprevalence in PWID within the range of 30%, although there were found broad variations among regions and the highest prevalence was detected in large cities [17]. Substantial drop in the HCV incidence in CR could be achieved in reasonably brief period of time, provided the focused prevention, identification of those infected and fully accessible DAA treatment will be available without restrictive limits.

Objectives

The aim of the work was to monitor the epidemiological situation and the spread of viral hepatitis C in the population

Table 1. Characteristics of patients in 2010–2012 (N/I: not investigated)

	whole period		2010	2011	2012
number of patients	546		180	192	174
males	356	65.2%	115	128	113
females	190	34.8%	65	64	61
mean age	30		29.74	29.91	30.45
number of anti-HCV tests	546		180	192	174
negative	153	28.0%	61	52	40
positive	393	72.0%	119	140	134
anti-HCV positives	393		119	140	134
males	269		87	93	89
females	124		32	47	45
mean age anti-HCV positives	31		31.04	30.37	30.87
number of PCR HCV RNA tests	393		119	140	134
PCR HCV RNA positives	269	68.4%	81	98	90
PCR HCV RNA negatives	123	31.3%	38	41	44
N/I (not investigated)	1	0.3%	0	1	0
PCR HCV RNA positives	269		81	98	90
males	184		62	63	59
females	85		19	35	31

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of PWID in Prague and Central Bohemia, in particular to monitor the representation of individual HCV genotypes in this subgroup and to compare the results with our data published in the past. The genotypes found in the cohort of patients from the years 2010–2012 were compared with the pilot groups investigated in 1998–2000 and 2005–2007.

PATIENTS AND METHODS

Patients for current work (the last group) were recruited over the years 2010–2012. The basic demographic data and epidemiological and clinical characteristics were obtained from each patient on admission to the study. The study was designed as prospective monocentric study among all PWIDs who were for the first time registered for HCV infection screening (or diagnosis confirmation) without any relation to further individual's cooperation or participation in any subsequent treatment programs. None of the recruited subjects in this study were included in our previous papers.

Study population

All subjects enrolled in the study over the years 2010–2012 were residents of the Czech Republic. All enrolled subjects admitted past or current injecting habit (PWID). They were consecutively referred from cooperating street-work programs or low-threshold facilities or self-referred to Remedis. Informed consent with testing and participation in the study was obtained from all subjects prior to initial interview.

Laboratory methods

The anti-HCV tests and HCV RNA detection, genotype and subtype identification were performed in certified laboratories (ISO 15198) with standard, validated and certified methods. AntiHCV was tested by Monolisa anti-HCV version 2, BioRad, SA. Anti-HCV positive samples (or those suspected from acute HCV) were tested by RT-PCR.

The assessment of HCV RNA in blood samples was done by standardized PCR method (COBAS® AmpliPrep/COBAS® TaqMan HCV Test, Roche Molecular Systems, Inc., Branchburg, NJ, 08876 USA) with limit of detection 15 IU/ml and linearity 43–6,9 × 107 IU/ml and genotyping was performed in samples with detectable viremia (COBAS® HCV GT, Roche Molecular Systems, Inc., Branchburg, NJ, 08876 USA).

In the two previous historical cohorts the direct sequencing of NS5B locus was used as the most reliable method at that time [12, 13].

The statistical data were processed with SPSS Pearson Chi-Square Tests and Z-tests with Bonferroni correction were used for comparison of the three above described periods.

RESULTS

546 new patients, meeting above mentioned criteria were newly registered in Remedis in Prague in the years 2010–2012. Majority of them were males (65%), average age of the whole group was 30 years. The basic demographic data and epidemiological and clinical characteristics are described in the Table 1.

All study participants were tested for HIV with negative result.

393 patients (72%) were anti-HCV seropositive and of them 269 were viremic (HCV RNA positive). Amongst HCV replicating patients, there were 184 males and 85 females. Genotype composition is shown in the Graph 1. The most prevalent subtype was 3a in 97 patients (36.1%), 1a was detected in 85 patients (31.6%) and 1b in 57 patients (21.2%). These three genotypes were responsible for nearly 89% of infections, the rest (4.2%) consisted of mixed genotypes or undistinguishable genotype 1, 1 patient had genotype 2. 7.1% of samples were not typeable for different reasons.

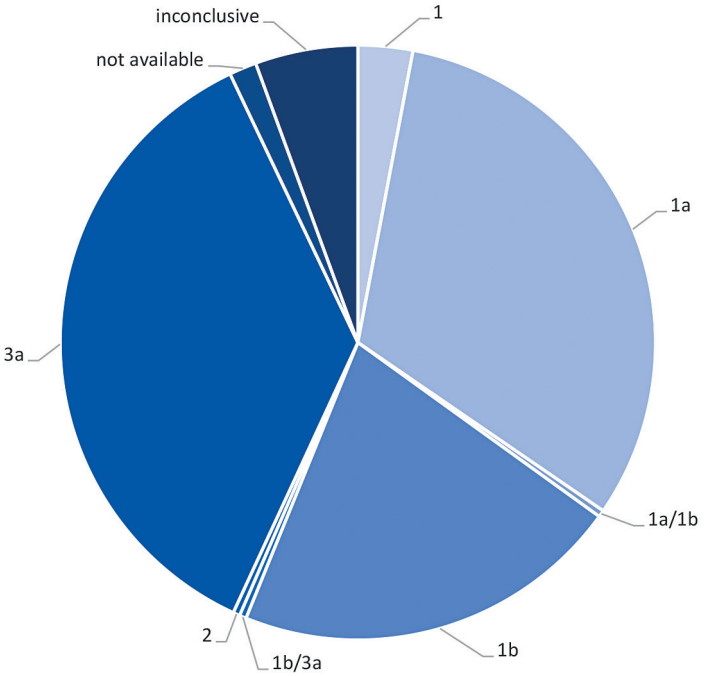
Genotype representation in 2010–2012 is summarized in Table 3 and Graph 1.

For the comparison with the two previous time periods (1998–2000 and 2005–2007) see the Table 2 where the characteristics of patients are shown and Table 3 where the genotype comparison is shown.

The development (genotype shift) of main genotypes over these three periods is depicted in Graph 2.

Increase in both genotypes 1a and 3 over the years was apparent and significant, followed by the decrease in genotype 1b.

We have performed the Pearson Chi-Square Tests and Z-tests with Bonferroni correction for comparison of the three periods. As the results indicate there were statistically significant differences between the groups in the meaning of Pearson Chi-Square Tests ($p < 0.001$). When the Z-tests with Bonferroni correction were applied, the results showed that in the three genotypes tested (1a, 1b and 3a) there were significant statistical differences.



Graph 1. Percentage representation of main genotypes in three periods

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Table 2. Comparison of patients in the three periods (N/I: not investigated)

	1998-2000		2005-2007		2010-2012	
number of patients	53		222		546	
males	29	54.7%	154	69.4%	356	65.2%
females	24	45.3%	68	30.6%	190	34.8%
mean age	22		27		30	
number of anti-HCV tests	53		222		546	
negatives	5	9.4%	7	3.2%	153	28.0%
positives	48	90.6%	215	96.8%	393	72.0%
anti-HCV positives	48		215		393	
number of PCR HCV RNA tests	53		222		393	
positives	53		222		269	
negatives	0		0		123	
N/I (not investigated)	0		0		1	
PCR HCV RNA positives	53		222		269	
males	29		154		184	
females	24		68		85	

In the genotype 1b and genotype 3a the significance of differences of relative prevalence has risen with the years of data collection ($p < 0.001$ in the genotype 1b for period 1998–2000 vs. 2005–2007 comparison and $p = 0.019$ for period 2005–2007 vs. 2010–2012 comparison, in the genotype 3a $p = 0.014$ and $p < 0.001$ respectively). The prevalence of genotype 1a in period 2005–2007 was significantly higher in comparison with the genotype 3a prevalence between all periods ($p = 0.038$).

DISCUSSION AND CONCLUSION

In the three subsequent three-year periods we compared our observations and genotyping data of unique newly registered patients. Although ageing, the HCV infected population in the CR is still relatively young, males remain predominant. The most significant change observed was the steady decrease of initially dominant HCV subtype 1b. Observed directions in genotypic shift testify rather for ongoing HCV epidemic than for stabilized prevalence in the population. The described trends in the evolution of HCV genotypes distribution possess some similarities with other countries. We might assume backwards, that the onset of HCV epidemic among PWID in CR occurred in the times of political isolation and that the initial source was similar like in common population infected from blood transfusions and other medical interventions before 1992. Other subtypes might have been introduced in subsequent years, after the political release from the sources abroad where the 1a and 3a are widely prevalent in high-risk populations. Unlike some countries though, where the incidence of one of the genotypes dominates (either 1a or 3a) [18], in CR we can see the increase in both

Table 3. Comparison of particular genotypes in three periods

genotypes	1998-2000		2005-2007		2010-2012	
1	0	0.0%	0	0.0%	8	3.0%
1a	14	26.4%	90	40.5%	85	31.6%
1a/1b	0	0.0%	0	0.0%	1	0.4%
1b	34	64.2%	78	35.1%	57	21.2%
1b/3a	0	0.0%	0	0.0%	1	0.4%
2	1	1.9%	0	0,00%	1	0.4%
2a	0	0.0%	1	0.5%	0	0.0%
2b	0	0.0%	1	0.5%	0	0.0%
3	3	5.7%	0	0.0%	0	0.0%
3a	0	0.0%	52	23.4%	97	36.1%
not available	0	0.0%	0	0.0%	4	1.5%
inconclusive	1	1.9%	0	0.0%	15	5.6%
Total	53		222		269	

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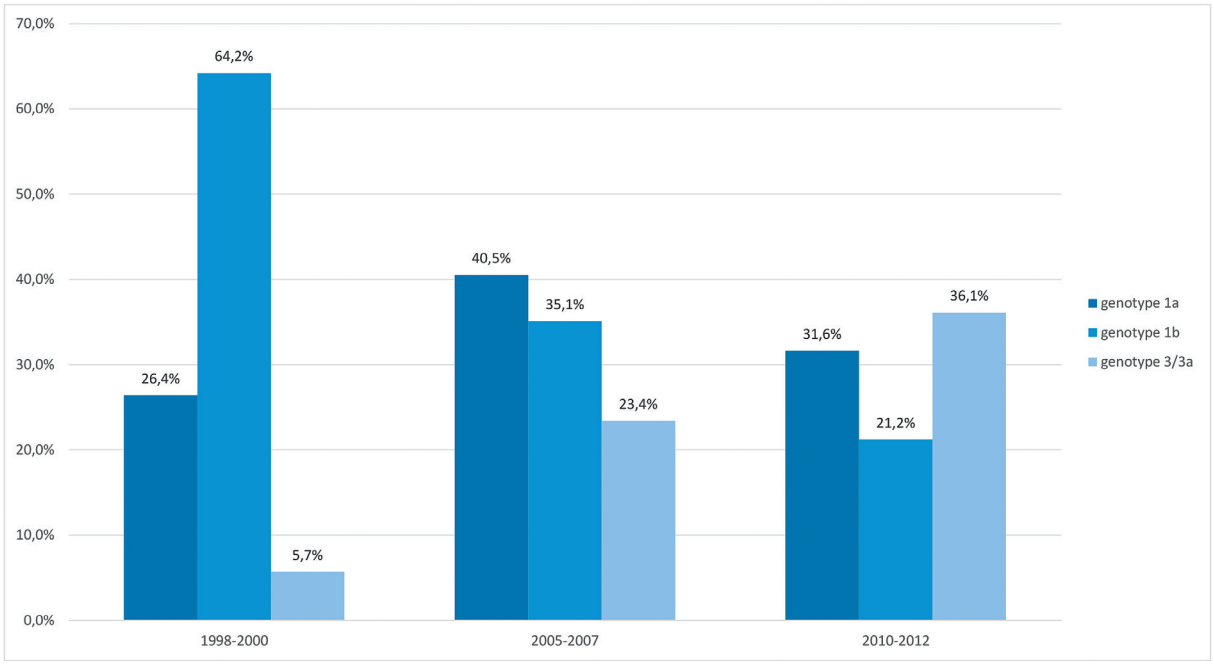

Graph 2. Genotype composition in 2010-2012
Genotype 1–8 patients (3.0%), genotype 1a – 85 patients (31.6%), genotype 1a/1b: 1 patient (0.4%), genotype 1b – 57 patients (21.2%), genotype 1b/3a – 1 patient (0.4%), genotype 2 – 1 patient (0.4%), genotype 3a – 97 patients (36.1%), in 15 patients genotyping was inconclusive (5.6%) and in 4 patients (1.5%) wasn't available.

1a and 3a genotypes. It might be interesting to follow on the further development and result of the "race" of the two competing genotypes. Detailed and updated knowledge of HCV epidemiological characteristics in particular regions can help in precise targeting of eradication campaigns. With the WHO and other authorities goal of HCV elimination in the context of current highly efficacious antiviral treatment [19] the urgent need to precisely document the epidemiological situation and to track all risk groups, excluded communities and another possible reservoirs of HCV possess the greatest challenge.

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