



TECHNICAL REPORT

EU/EEA capacity for the surveillance of hepatitis B and C using molecular methods

ECDC TECHNICAL REPORT

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC) and coordinated by Eeva Broberg.

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Acknowledgements

We acknowledge all survey participants from the following countries:

Belgium - Gaëtan Muyltermans (WIV-ISP, Brussels); Cyprus - Petros Katsioloudes (Nicosia General Hospital, Internal Medicine Clinic, Ministry of Health, Nicosia); England - Samreen Ijaz (Public Health England, London); Estonia - Jevgenia Epstein (Health Board, Tallinn); France - Vaux Sophie/Cécile Brouard/Stéphane Chevaliez/Sylvia Laperche (Santé Publique France/National Reference Center for Hepatitis, Paris); Germany - Ruth Zimmermann (Robert Koch Institute, Berlin); Ireland - Lelia Thornton (HSE Health Protection Surveillance Centre) and Suzie Coughlan/Cillian De Gascun (National Virus Reference Laboratory, Dublin); Italy - Anna Rita Ciccaglione (Istituto Superiore di Sanità, Rome); Malta - Graziella Zahra (Molecular Diagnostics Pathology Department Mater Dei Hospital, Msida); The Netherlands - Birgit van Benthem (National Institute of Public Health and the Environment, Utrecht); Norway - Kathrine Stene-Johansen (Norwegian Institute of Public Health, Oslo); Poland - Małgorzata Stępień, Magdalena Rosińska (National Institute of Public Health – National Institute of Hygiene, Department of Epidemiology, Warsaw); Romania - Gabriel Ionescu (Cantacuzino National Institute of Research, Bucharest); Slovenia - Mario Poljak (Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana); Spain - Ana Avellon (Spanish National Center of Microbiology (Carlos III Institute of Health), Madrid); Sweden: Josefine Ederth (Public Health Agency of Sweden, Stockholm).

The authors would also like to thank Julien Beauté, Phillip Zucs, Denis Coulombier and Mike Catchpole for their valuable comments on the study protocol and the manuscript and acknowledge their contribution in improving the paper.

Suggested citation: European Centre for Disease Prevention and Control. EU/EEA capacity for the surveillance of hepatitis B and C using molecular methods. Stockholm: ECDC; 2018.

Stockholm, January 2018

doi: 10.2900/204257

ISBN 978-92-9498-169-1

TQ-04-18-054-EN-N

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Abbreviations

ECDC	European Centre for Disease Control and Prevention
EDTA	ethylenediaminetetraacetic acid
EU/EEA	European Union/European Economic Area
HBV	hepatitis B virus
HCV	hepatitis C virus
IFN	interferon
PCR	polymerase chain reaction
TESSy	The European Surveillance System

Executive summary

The global burden of disease due to hepatitis B and C virus infection is high, and chronic infection with these viruses can lead to cirrhosis, liver failure and hepatocellular carcinoma. Effective treatments exist for both chronic hepatitis B and C; however, the treatment regimen to be given for hepatitis C depends on the genotype of the virus. Currently, data on hepatitis B virus (HBV) and hepatitis C virus (HCV) genotypes are not widely reported by European Union/European Economic Area (EU/EEA) countries. EU/EEA-wide surveillance of HBV and HCV genotypes would allow for monitoring of circulating genotypes, enhanced identification of populations at risk of infection and mapping of transmission patterns to better target prevention and control interventions, especially for hepatitis C, across European countries. A survey was conducted to assess the laboratory capacity and needs in relation to molecular characterisation of hepatitis B and C virus in EU/EEA countries.

Sixteen (53%) of the 30 EU/EEA countries participated in this survey. Seven countries reported that they conduct sequence-based characterisation of HBV strains to monitor HBV genotype at national level, and eight countries reported that they have similar processes for HCV. Five countries reported that they perform surveillance for HBV genotypes and four countries for HCV genotypes. Similarities in laboratory methods were identified among the countries currently performing such surveillance. Laboratory capacity for HBV/HCV genotyping was reported by eleven of the participating countries. HBV and HCV genotype surveillance has not yet been widely implemented in EU/EEA and this may provide an opportunity for better alignment and comparability in the future implementation of such systems.

Introduction

Hepatitis B and C pose major global public health problems, with 257 million and 71 million people estimated to be living with chronic hepatitis B and hepatitis C, respectively [1]. Acute infection with either virus may progress to chronic infection, with the concomitant risk of cirrhosis or hepatocellular carcinoma [2,3]. The prevalence of these infections varies geographically, with sub-Saharan Africa and east Asia having the highest prevalence of hepatitis B virus (HBV) infections, and Africa and central and east Asia being the regions most affected by the hepatitis C virus (HCV) [4,5]. In the European Union (EU)/European Economic Area (EEA), the prevalence of HBV and HCV was estimated at 0.9% and 1.1%, respectively, and these countries are therefore considered as low-prevalence countries for both viruses [6].

While there is no vaccine against hepatitis C, an effective vaccine against hepatitis B has been available since 1981, and WHO recommends that all infants be vaccinated against hepatitis B as soon as possible after birth [4,5,7]. There are at least nine HBV genotypes (A-J) as well as a number of subtypes [8,9]. The most frequently occurring HBV genotypes in Europe are A and D, with HBV A2 being the most common subtype [10]. Reports suggest that HBV genotype A is associated with a higher likelihood of progression from acute to chronic infection than the others [11,12]. Seven approved anti-viral agents are available for treatment of HBV infection [8]. Pegylated interferon (IFN) and nucleos(t)ide analogues have been used for the treatment of chronic hepatitis B for more than 10 years and are effective inhibitors of HBV replication [13]. However, treatment with nucleos(t)ide analogues rarely cures HBV infection and patients require long-term therapy [8].

For HCV, seven distinct genotypes and many more subtypes have been reported (14). HCV genotypes 1, 3 and 2, in that order, are the most prevalent genotypes in Europe [15]. There are multiple treatments available for hepatitis C infection, mainly IFN-free based regimens including effective, potent and safe inhibitors against three major viral proteins of HCV [16–18]. The HCV genotype informs the treatment regimen and is linked to disease progression [16,18]. At population level, genotype monitoring allows identification of trends, chains of transmission and at-risk populations [19]. In 2015, two countries submitted HBV genotype data to the European Centre for Disease Prevention and Control and eight submitted HCV genotype data [20,21]. As the submission rate by countries has been low, these data have not been used in annual epidemiological reports at EU/EEA level.

In order to explore whether the current capacity for EU/EEA-wide molecular characterisation for surveillance of HBV and HCV is sufficient to be feasible and what gaps need to be addressed, a survey of EU/EEA Member States was conducted to assess their laboratory capacity and needs in relation to the molecular characterisation of hepatitis B and C.

Methods

In July 2016, the 28 EU Member States, Iceland and Norway were invited to participate in an online survey (created with EUSurvey; <https://ec.europa.eu/eusurvey/>) of hepatitis B and C molecular characterisation for surveillance capacity. As this survey incorporated surveillance system and laboratory elements, the link to the questionnaire was sent to officially nominated national experts for HIV/AIDS; sexually transmitted infections and hepatitis B/C, and microbiology. The national experts were asked to refer the questions on to the most appropriate national virology reference laboratory for their input. Reminders were sent to non-responder countries and data submission was accepted until September 2016.

The survey included questions on the purpose of any current hepatitis B and C sequence data collection, the type and use of clinical samples and on how and to whom surveillance data were reported. It also included questions on the laboratory methods used and on resources required by countries to perform hepatitis B and C sequence analysis and then regularly report hepatitis B and C genotype data. Finally, the survey collected information on potential obstacles to setting up an EU/EEA-wide surveillance system. The questionnaire included 177 questions. Absolute and relative frequency of country responses to survey questions were calculated using R version 3.2.4, R Foundation for Statistical Learning, Vienna, Austria. A map was generated using the ECDC Map Maker (EMMa - <https://emma.ecdc.europa.eu/>).

Results

Sixteen (53%) of 30 EU/EEA countries responded to this survey. Seven (44%) and eight (50%) of these countries reported sequence-based characterisation of HBV/HCV strains at national level for the monitoring of HBV and HCV genotypes, respectively (Figure 1).

Table 1 presents an overview of key elements in HBV and HCV molecular characterisation for surveillance and reporting activity across the EU/EEA. Eleven participating countries (69%, 11/16) stated that HBV genotyping was performed on samples from specific subsets of patients. Nine countries (56%, 9/16) reported that HBV genotyping was conducted for research purposes. Seven (44%, 7/16) countries used HBV genotyping for outbreak

investigations and five (31%, 5/16) used it for surveillance purposes. Clinical, epidemiological and laboratory data were linked in all five countries reporting that they conducted HBV genotype surveillance.

The majority of countries (63%, 10/16) stated that HCV genotyping was conducted on samples from all infected individuals initiating anti-viral therapy. Eleven (69%) of 16 countries reported that HCV genotype data were generated for specific clinical indication for infected individuals, while nine (56%) reported their use for outbreak investigations or research projects, and four (25%) for surveillance purposes. Clinical, epidemiological and laboratory variables were linked among three (75%) of four countries that reported performing HCV genotype surveillance.

Eight (50%) of 16 countries stated that HBV and HCV genotype data are reported at least at the nucleotide level. Twelve countries (75%, 12/16) stated that there were additional laboratories other than surveillance laboratories with HBV and HCV genotyping capacity in their countries. Three (19%) of 16 countries reported that they produced a national report on HBV genotype data and two (13%) of the 16 reported producing a national report on HCV genotype data.

Laboratory capacity

The primary specimens used for HBV molecular testing were reported to be serum (50%, 8/16) and EDTA-plasma specimens (25%, 4/16), while the remaining countries reported using both plasma and serum (25%, 4/16). Similarly, six (38%, 6/16) countries reported using serum and four (25%, 4/16) countries reported using EDTA plasma specimens for HCV molecular testing. Population sequence analysis was the most widely reported method used to generate molecular data for HBV (50%, 8/16) and HCV (50%, 8/16). Next generation sequence analysis is also used by two countries (13%, 2/16) for HBV and three countries (19%, 3/16) for HCV molecular data generation. Among the five countries performing HBV molecular characterisation for surveillance, the majority (80%, 4/5) reported that they sequence polymerase and surface genes for HBV genotyping. Non-structural protein (NS5b) (75%, 3/4) was the most commonly reported gene used for HCV genotyping among countries performing HCV molecular characterisation for surveillance.

Resources and challenges

Of 11 countries currently not conducting HBV genotype surveillance, eight (73%, 8/11) identified a lack of personnel and seven (64%, 7/11) stated that a change of guidelines or policy was required to implement HBV genotyping in the country. Data entry capacity and transfer (36%, 4/11) and database solutions (18%, 2/11) were the main types of technical support identified as lacking for reporting of HBV genotype data.

Among 12 countries not performing HCV genotype surveillance, seven (58%, 7/12) countries stated that both personnel and a change of guidelines or policy were required to implement HCV genotyping in the country. In terms of technical support requirements for reporting HCV genotype data, database solutions (33%, 4/12), data entry capacity and transfer (25%, 3/12), and data reporting (8%, 1/12) were the most commonly highlighted points.

Data ownership issues (81%, 13/16), human resources (75%, 12/16) and legislation issues (56%, 9/16) were the most frequently highlighted obstacles to sharing national HBV/HCV sequence data at international level.

Discussion

This survey presents a snapshot of the current status of the capacity for hepatitis B and C genotype surveillance in EU/EEA countries. Approximately half of the participating countries reported that they monitor HBV and HCV genotypes, mostly either for research purposes in the case of HBV or for specific clinical indications for HCV. While only a small number of countries reported conducting public health surveillance of HBV/HCV genotypes at population level, there were some similarities between their surveillance systems, particularly in relation to the laboratory methods used. Furthermore, most participating countries highlighted that there were laboratories in their countries with HBV/HCV genotyping capacity, which offers some hope for expanding the current hepatitis B and C genotype surveillance system in the EU/EEA. However, the participating countries represent just over half of all EU/EEA countries and therefore these results must be interpreted cautiously.

Inclusion of HBV and HCV genotype data in national reports suggests that such data may assist Member States in controlling hepatitis B and C by monitoring circulating genotypes, better identifying populations at risk of infection and mapping out transmission patterns. The Netherlands, Norway and Sweden reported using HBV genotype data to identify chains of transmission, either for outbreak investigation or routine surveillance [22–24]. Furthermore, HBV genotype data in the Netherlands are used to assess the emergence of vaccine escape mutants and to monitor the entry of non-endemic strains [22]. Recently, genotype and epidemiological data on acute hepatitis B cases in the Netherlands showed that preventive activities could be better targeted, since cases of acute hepatitis B were more clustered among men who have sex with men living in rural areas than heterosexual patients in more urban areas [19]. There were differences in the number of countries that reported HBV and HCV genotype

surveillance data to ECDC for 2015 when compared to the number reporting in the survey and this could be explained by a number of factors. Firstly, half (4/8) of the countries that reported the HCV genotype to TESSy did not participate in the survey. Secondly, individuals who responded to the survey may not have known that a national report contained HBV/HCV genotype data and finally, some countries may only have started HBV genotype surveillance in 2016.

This report highlighted some similarities in the additional resources required by EU/EEA countries for reporting HBV/HCV molecular data to ECDC, as well as in the challenges to sharing national sequence data at an international level. Data ownership issues, human resources and legislation issues are all significant challenges that would need to be addressed at national level before HBV/HCV genotypes could be widely reported in the EU/EEA. Furthermore, as almost half of the EU/EEA is not represented in this survey, it is possible that these challenges are more prevalent than reported here.

The limitations of this study also need to be considered. The response rate was only 53%, and this may have been negatively affected by the length of the questionnaire (177 questions) and the timing of the survey (during the summer period). Moreover, four countries that submitted HCV genotype data to ECDC in 2015 did not participate in this survey. Therefore, the results cannot be interpreted as being fully representative of the HBV/HCV genotyping activities in the EU/EEA countries. In addition, countries with something positive to report in this field may have been more likely to respond, leading to a possible overestimation of the true capacity in the EU/EEA. Furthermore, the accuracy of the replies very much depended on who was tasked with filling in the data and there may be some variability due to incomplete knowledge of the situation by some respondents. In addition, real-time PCR was omitted as an option for the laboratory methods used to generate molecular data for HBV/HCV and so we have no knowledge of how widely this method is used.

In conclusion, this study shows that there is limited laboratory capacity for HBV/HCV genotype surveillance in EU/EEA. More detailed information and discussion at the country level would be required to assess the feasibility of expanding surveillance and increasing the reporting of HBV/HCV genotypes in the EU/EEA. The next steps would include convening a working group of hepatitis B and C surveillance experts to discuss the specifics of the challenges identified and the additional resources required to expand genotype surveillance. If implemented, HBV and HCV genotype surveillance at EU/EEA level could offer better mapping of transmission patterns for circulating genotypes. It would also help with the monitoring of trends in Europe and, over time, with the identification of risk groups that may help guide future treatment protocols and regimens. If expansion of HBV/HCV surveillance at EU/EEA level using molecular methods is considered feasible and believed to add value, further work is required to identify and agree on objectives at EU/EEA level, indicators, the timing of any expansion and other essential elements.

Figure 1. Countries that use sequence-based characterisation of HBV and/or HCV for molecular characterisation for surveillance at national level in the EU/EEA, 2016 (n=16)

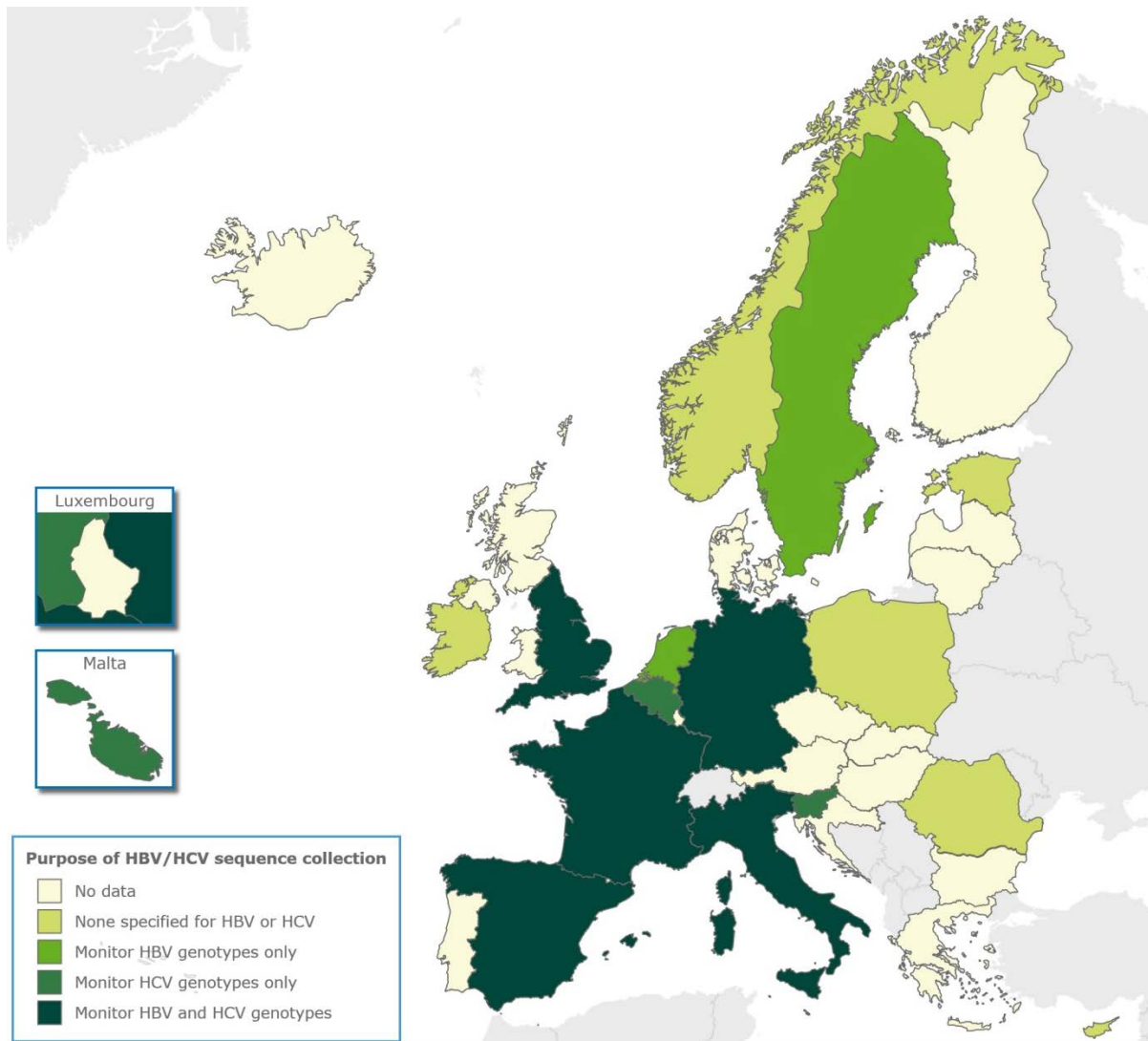


Table 1. Overview of practices applied to HBV and HCV genotypes in the EU/EEA, 2016 (n=16)

Country	Purpose of genotype data collection		Patients selected for genotyping		Linkage between clinical, epidemiological and laboratory data		Level of reporting of genotype data		Laboratories with genotyping capacity	
	HBV	HCV	HBV	HCV	HBV	HCV	HBV	HCV	HBV	HCV
Belgium	Research projects only	Specific clinical indications only	All infected individuals that do not obtain virological response	All initiating anti-viral therapy only	Unknown	No	Unknown	Unknown	Unknown	Unknown
Cyprus	Other	Specific clinical indications only	All infected individuals that do not obtain virological response	All newly diagnosed only	Unknown	Unknown	Nucleotide level	Nucleotide level	Yes	Yes
Estonia	Research projects only	Research projects only	Subset of patients	All newly diagnosed only	Unknown	Unknown	Unknown	Unknown	Yes	Yes
France	Surveillance/research/outbreak investigation	Standard routine/outbreak investigation/research	Subset of patients	All initiating anti-viral therapy and specific subsets	Yes	Yes	Nucleotide level	Nucleotide level	Unknown	Unknown
Germany	Research/outbreak investigation	Specific clinical indications/outbreak investigation/research	Subset of patients - e.g. outbreak cases	All initiating anti-viral therapy only	Yes	Yes*	Nucleotide & amino acid level	Nucleotide level	Yes	Yes
Ireland	Specific clinical indications/outbreak investigation	Surveillance/specific clinical indications/outbreak investigation	Subset of patients - e.g. upon request from a clinician	All initiating anti-viral therapy only	Unknown	Yes	Unknown	Unknown	Yes	Yes
Italy	Surveillance/research	Surveillance/specific clinical indications/research	Subset of patients	All initiating anti-viral therapy/subset of patients/those that do not obtain virological response	Yes	Yes	Nucleotide & amino acid level	Nucleotide & amino acid level	Yes	Yes
Malta	Other	Surveillance/standard routine/specific clinical indications/research/outbreak investigation	All newly diagnosed only	All newly diagnosed/initiating anti-viral therapy/those that do not obtain virological response	Unknown	Yes	Nucleotide level	Nucleotide level	Yes	Yes
Netherlands	Surveillance/standard routine/specific clinical indications/research/outbreak investigation/other	Standard routine/specific clinical indications/outbreak investigation/research/other	All newly diagnosed and specific subsets - e.g. donor population	All newly diagnosed and specific subsets	Yes (acute); No (chronic)	NA	Nucleotide level	Nucleotide level	Yes	Yes
Norway	Specific clinical indications only	Specific clinical indications only	All those initiating anti-viral therapy and specific subsets - e.g. upon request from a clinician	All those initiating anti-viral therapy only	Unknown	Unknown	Nucleotide level	Unknown	Yes	Yes
Poland	Research projects only	Standard routine/outbreak investigation/research	Subset of patients	All those initiating anti-viral therapy only	Unknown	Unknown	Unknown	Unknown	Yes	Yes
Romania	Research projects only	Research projects only	All infected individuals that do not obtain virological response.	All infected individuals that do not obtain virological response	Unknown	Unknown	Unknown	Unknown	Yes	Yes
Slovenia	Specific clinical indications only	Standard routine only	Subset of patients	All those initiating anti-viral therapy only	Unknown	Yes	Unknown	Nucleotide level	Yes	Yes
Spain	Specific clinical indications/outbreak investigation	Specific clinical indications/outbreak investigation	All those initiating anti-viral therapy only	All those initiating anti-viral therapy only	Yes	Yes	Unknown	Unknown	Yes	Yes
Sweden	Surveillance/specific clinical indications/outbreak investigation/other	Specific clinical indications/outbreak investigation/other	Subset of patients	Subset of patients	Yes (acute)	Unknown	Unknown	Unknown	Unknown	Unknown
United Kingdom	Surveillance/standard routine/specific clinical indications/research/outbreak investigation	Surveillance/standard routine/specific clinical indications/research/outbreak investigation	Subset of patients - e.g. upon request from clinicians, research projects, new diagnoses.	Subset of patients	Yes	Unknown	Nucleotide & amino acid level	Nucleotide level	Unknown	Unknown

* Linkage of clinical, epidemiological and laboratory data occurs for outbreak investigation only. For routine surveillance, PCR results only, epidemiological and clinical data are linked.

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