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Treatment and monitoring of children with chronic hepatitis C in the Pre-DAA era: A European survey of 38 paediatric specialists

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Abstract

The burden of paediatric Hepatitis C virus (HCV) infection across Europe is unknown, as are current policies regarding monitoring and treatment. This collaborative study aimed to collect aggregate data to characterise the population of ≤ 18 -year-olds with HCV infection in specialist follow up in a 12-month period (2016) across the PENTAHeP European consortium, and investigate current policies around monitoring and treatment. A cross-sectional, web-based survey was distributed in April 2017 to 50 paediatricians in 19 European countries, covering patients' profile, and monitoring and treatment practices. Responses were received from 38/50 clinicians collectively caring for 663 children with chronic HCV infection of whom three-quarters were aged ≥ 6 years and 90% vertically infected. HCV genotype 1 was the most common (n 380; 57.3%), followed by genotype 3, 4 and 2. Seventeen children (3%) with chronic HCV infection were diagnosed with cirrhosis, and six were reported to have received liver transplantation for HCV-related liver disease. The majority (n 425; 64.1%) of the European children with HCV infection remained treatment-naïve in 2016. Age affected clinicians' attitudes towards treatment; 94% reported being willing to use direct-acting antivirals, if available, in adolescents (aged ≥ 11 years), 78% in children aged 6–10 and 42% in those 3–5 years of age (Pearson correlation coefficient -0.98 ; $P 0.0001$). This survey provides the largest characterisation of the population of children in clinical follow-up for chronic HCV infection in Europe, alongside important contextual information on their management and treatment. Discussion is needed around strategies and criteria for use of direct-acting antivirals in these children.

KEYWORDS

direct-acting antivirals, epidemiology, Europe, treatment, vertical transmission

Abbreviations: ALT, alanine aminotransferase; CEC, Central European countries; DAAs, direct-acting antivirals; EMA, European Medicines Agency; FDA, Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug use; IFN, interferon; PEG, pegylated; RNA, ribonucleic acid; SVR, sustained virological response; TE, transient elastography; WEC, Western European countries.

*Details of the PENTAHeP Study Group are given in the Appendix 1.

1 | INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver-related morbidity and mortality.^{1-4,18} According to latest estimates, 71 million people are living with HCV worldwide^{1,2,5} of whom 3.5 million cases (95% confidence intervals 3.1-3.9 million)⁶ are children younger than 15 years.⁷ Major gaps exist in the current knowledge on the epidemiology of HCV infection in adults and children, including the true burden of infection and disease, and most HCV-infected people are unaware of their status.⁵ In the USA, <15% of HCV-infected children are thought to be diagnosed and a small fraction receives medical care.⁸ It is likely that the ascertainment rate of paediatric cases of HCV in Europe is as low as in USA although this topic has never been formally investigated.

Starting in 2015 with the approval of second-generation direct-acting antivirals (DAAs) active against HCV, the clinical and therapeutic approach to HCV infection in adults has changed substantially. With an efficacy approaching 100%, these new regimens raise the prospect of eliminating HCV on a population level. Indeed, the availability of DAAs was a driving force behind current ambitious World Health Organization targets for viral hepatitis, including the target to reduce new cases of chronic hepatitis B and C by 90% by 2030.

Chronic HCV infection in children is considered a mild disease in general.^{9,10} Liver fibrosis and inflammation in children with chronic HCV infection is time-dependent and slow to progress⁹⁻¹¹ with only around 2% of vertically HCV-infected children developing advanced liver disease during childhood, although it is not possible to predict who will progress rapidly.⁹⁻¹² In general, although few children will experience end-stage liver disease during childhood, they will be at risk of cirrhosis and hepatocellular carcinoma in early adulthood.⁹⁻¹¹ Treatment options for children are currently limited. In 2017, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the use of sofosbuvir/ledipasvir (genotype 1,4) and sofosbuvir in combination with ribavirin (genotype 2,3) for treatment of adolescents (12-18 years of age) with chronic HCV infection. However, for children younger than 12 years there are no approved HCV treatment regimens and there are challenges with respect to availability of DAAs for adolescents across Europe.¹³

In the interferon (IFN)-era, its role in treatment of children with chronic HCV infection was controversial.¹⁴ The mild nature of HCV infection in children together with the low efficacy and the burdensome safety profile of IFN-based treatments have generally explained low use in children.¹⁵ With the availability of DAAs and very favourable safety and efficacy profiles in adults, paediatric treatment of HCV can be reconsidered^{3,16,17}; however, in some countries barriers may remain around the costs of the new therapies and perceived lack of need for treatment in childhood.

The burden of paediatric HCV infection across Europe is unknown, as are current policies around monitoring and treatment of paediatric HCV infection in a rapidly changing treatment context. The main aim of the present collaborative study was to collect

aggregate data to characterise the population of children and adolescents (aged ≤ 18 years) with HCV infection in specialist follow up over a 12-month period (2016) across the PENTA-Hep European consortium, and to investigate current policies around monitoring and treatment.

2 | MATERIALS AND METHODS

2.1 | PENTA-Hep and survey participants

The PENTA-Hep Consortium, established in 2015, is a collaboration of partners (mainly clinical providers) from organizations across Europe, Egypt and the USA involved in research, development and clinical care in paediatric HCV infection. The aim of PENTA-Hep is to generate evidence to inform best practices for the care and treatment of children and adolescents living with HCV infection in the era of DAA. For this study, a survey was conducted within the PENTA-Hep network among European paediatricians selected because they had a special interest in paediatric hepatology and infectious diseases and have followed up children with chronic HCV infection for at least two years before the survey. Fifty paediatricians (31 hepatologists and 19 infectiologists) in 17 countries (Austria, Belgium, France, Germany, Greece, Hungary, Italy, Ireland, Netherlands, Poland, Portugal, Romania, Spain, Switzerland, Sweden, Turkey and UK) received an emailed invitation to complete the web-based survey (implemented using REDCap)¹⁸ in April 2017. Respondents did not receive any honorarium for completing the survey. Ethical approval was not required for this service evaluation study because individual patient data were not collected.

2.2 | Survey content and development

The survey consisted of 20 items divided into two sections: patients' profile; and monitoring and treatment practice (see Table S1). Cross-sectional, aggregate data were collected on number of patients with chronic HCV infection in follow-up at each site in 2016 by age group (0-3; 3-5; 6-10; 11-18 years), sex, HCV genotype, mode of HCV transmission and co-infection with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV), and HCV treatment experience. Monitoring and treatment strategies were explored presenting specific case scenarios.

The survey was piloted with two of the clinicians/respondents to assess clarity and validity. Modifications were made based on feedback and comments.

2.3 | Definitions

Europe was divided into two major areas (Western European countries – WEC – and Central European countries – CEC – Figure 1) as previously reported.¹⁹ Chronic HCV infection was defined as the continued presence of HCV ribonucleic acid (RNA) in the blood six months or more after acquiring infection.³

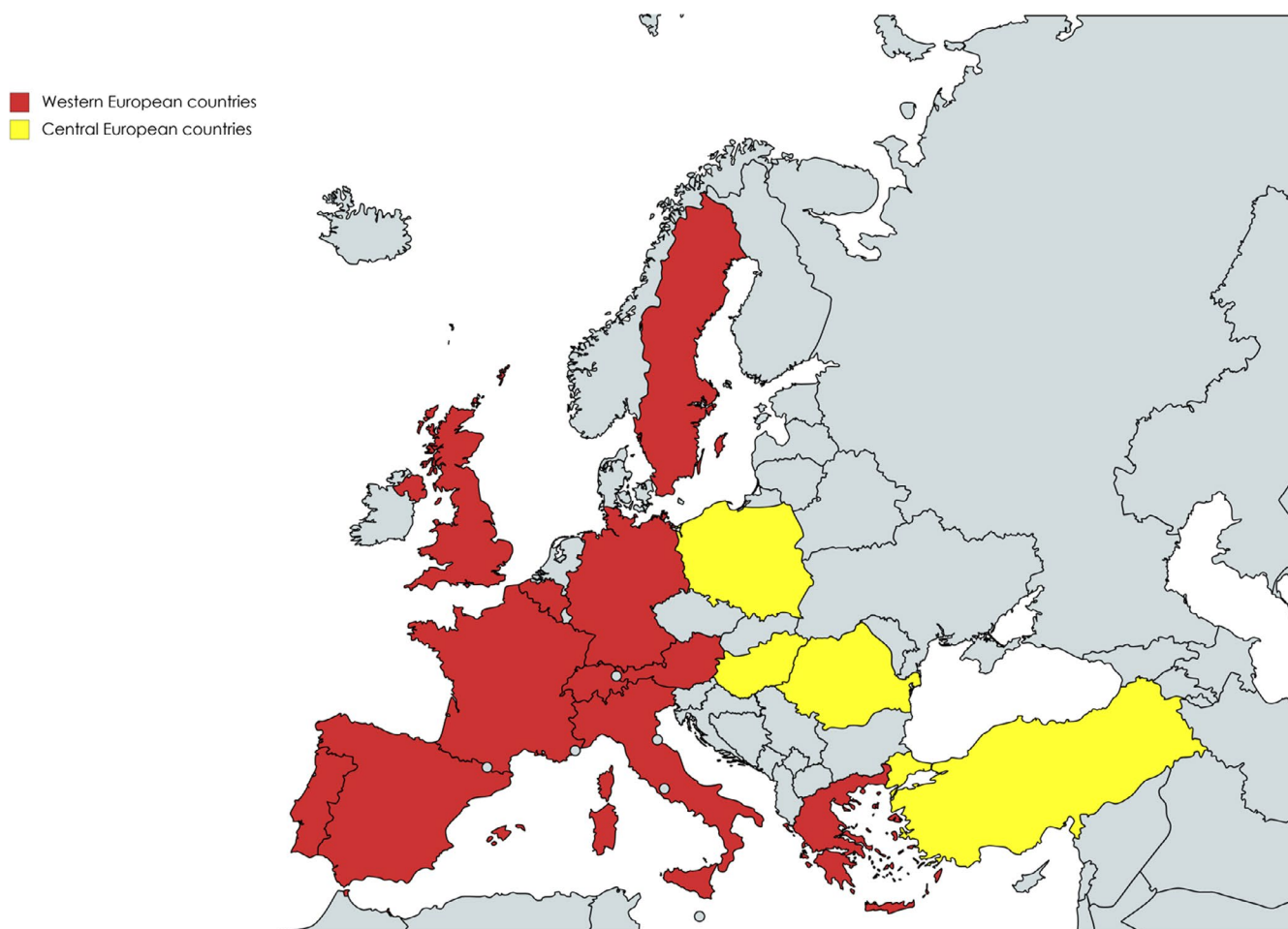


FIGURE 1 Survey responses were obtained from 38 paediatricians from 35 hospitals, from 15 European countries; Europe was divided into two major areas (Western European countries– and Central European countries– CEC) as previously reported.¹⁹

2.4 | Statistical analysis

Standard descriptive statistics were used to describe response frequency. The chi-squared test was used to compare categorical variables; a two-sided $P < 0.05$ was considered to be statistically significant. The correlation between the willingness to use DAAs and the age of the patients was evaluated using the Pearson correlation coefficient. A Pearson's r value $> \pm 0.8$ in conjunction with a P -value of < 0.05 in the significance test was considered to indicate a strong correlation. All analyses were conducted using MedCalc Statistical Software version 17.6 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2017).

3 | RESULTS

Completed survey responses were obtained from 38 (76%) of the 50 paediatricians invited to complete the survey from 35 hospitals. Data were obtained from 15/17 (88.3%) countries (Austria, Belgium, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Turkey and UK; Ireland and

Netherlands were not included due to the lack of reply). These 38 paediatricians were collectively caring for 663 children with chronic HCV infection.

3.1 | Patient characteristics

Characteristics of the children with chronic HCV cared for by the 38 survey respondents according to the European region of origin are shown in Table 1. Three-quarters of the children were aged 6 years or older. Vertical transmission was the main route of transmission of HCV infection, followed by nosocomial or unsafe blood product transfusion routes; there were no reported cases with injecting drug use as the mode of transmission (Table 1). Six-hundred and fifty-nine (99.4%) children were HCV mono-infected and 4 (0.6%) were co-infected with HIV (0.3% [2/587] in WEC and 2.6% [2/76] in CEC; $P = 0.05$). No child was co-infected with HBV. HCV genotype 1 was the most common, followed by genotype 3, 4 and 2 (Table 2). Zero HCV genotype 2 infections were reported in CEC compared with 5.8% in WEC. Genotype 3 infections were reported in 9.2% (7/76) and in 20.4% (120/587) of the children reported in CEC and WEC, respectively. HCV genotype 2 and 3

	Total n (%)	Western European countries (n 587)	Central European countries (n 76)
Age (y)			
0-3	68 (10.3)	47 (8)	21 (27.6)*
4-5	82 (12.4)	68 (11.6)	14 (18.4)
6-10	178 (26.8)	154 (26.2)	24 (31.5)
11-18	335 (50.5)	318 (54.1)	17 (22.3)**
Gender			
Male	319 (48.1)	287 (48.8)	32 (42.1)
Route of HCV transmission			
Vertical	595 (89.8)	531 (90.4)	64 (84.2)
Nosocomial/unsafe blood product transfusions	22 (3.3)	15 (2.5)	7 (9.2)***
Unknown	46 (6.9)	39 (6.6)	5 (6.5)

Note: Central European Countries (CEC) vs Western European Countries (WEC) **, *P 0.0001;

***P 0.008.

TABLE 1 Characteristics of 663 children aged ≤18 y with chronic HCV infection in clinical follow-up in 2016 at 36 European centres

TABLE 2 Genotype distribution according to the European region

	Hepatitis C Virus Genotype							
	n (%)							
	1 (all)	1a	1b	1 unknown	2	3	4	Unknown
Central European countries (n 76)	42 (55.3)	-	23 (30.3)	19 (25)	-	7 (9.2)	5 (6.6)	22 (28.9)
Western European countries (n 587)	338 (57.6)	98 (16.7)	145 (24.7)	95 (16.2)	34 (5.8)	120 (20.4)	64 (10.9)	31 (5.3)
Overall (n 663)	380 (57.3)	98 (14.8)	168 (25.3)	114 (17.2)	34 (5.1)	127 (19.2)	69 (10.4)	53 (8.0)

Note: GT2: Central European Countries (CEC) vs Western European Countries (WEC) P 0.02; GT3: CEC vs WEC P 0.01; GT2 + GT3: CEC vs WEC P 0.001.

infections were more common in WEC when compared to CEC (P 0.001; Table 2).

Seventeen children (3%) with chronic HCV infection were diagnosed with cirrhosis at the responding centres between 2014 and 2016 (2.5% [15/587] in WEC and 2.6% [2/76] in CEC, P 1); 6 (0.9%) were reported to have received or be listed for liver transplantation for HCV-related liver disease.

Almost two-thirds (425, 64.1%) of children were treatment-naïve. Of the 238 who were treatment-experienced, 161 (67.6%) were unsuccessfully treated with pegylated (PEG)-IFN and ribavirin before 2016 and 77 (32.4%) received treatment in 2016. Among these 77 treated in 2016, 35 (45.5%) received PEG-IFN and ribavirin and 42 (54.5%) received DAAs (specific regimens not available). Data on the outcome of treatment for the latter group of patients were not available for the present survey.

3.2 | Monitoring and treatment practices scenarios

Transient elastography (TE) was reported to be used routinely for non-invasive assessment of liver fibrosis by 28/38 (74%) of the respondents. Among the paediatricians surveyed, 29% and 34% reported that they

would perform a liver biopsy in a 6-year-old and in a 14-year-old boy with raised alanine aminotransferase (ALT) level, respectively, while 11% and 13% would do so if ALT level was normal (6-year-old: P 0.08; 14-year-old: P 0.03). Overall, 42% and 47% of respondents reported that they would use liver biopsy as a diagnostic tool in order to decide whether to treat or not in a six and a 14-year-old child, respectively (Table 3).

The survey was completed before 2017 FDA and EMA approval of the use of sofosbuvir and ledipasvir in adolescents aged 12-18 years. Clinicians were asked which age groups they would treat, if DAAs were licensed for paediatric use (a question which is no longer hypothetical for adolescents but remains so for younger age groups); 92% of the respondents reported that they would treat children aged 11-18 years, 74% that they would treat those aged 6-10 years and 39% that they would treat those younger than 6 years (Pearson correlation coefficient -0.99; P 0.0001; Table 4).

4 | DISCUSSION

In this survey of 38 clinicians collectively caring for 663 chronically HCV-infected ≤18-year-old patients across 15 European countries,

TABLE 3 Liver biopsy scenarios: proportion of the 38 respondents that would perform a liver biopsy in children with chronic hepatitis C virus infection by age and situation

	6-y-old patient	14-y-old patient
Persistently normal ALT	4 (11%)	5 (13%)
Persistently raised ALT	11 (29%)	13 (34%)
To decide whether to treat or not	16 (42%)	18 (47%)

Abbreviation: ALT, alanine aminotransferase.

TABLE 4 Attitudes of the 38 paediatricians towards use of direct-acting antivirals in children, if licensed for paediatric use

If DAAs were available for paediatric use now, would you treat children aged:			
	Yes	No	Maybe
3-5 y	15 (39%)	14 (37%)	9 (24%)
6-10 y	28 (74%)	8 (21%)	2 (5%)
11-18 y*	35 (93%)	3 (8%)	0 (0%)

Note: DAAs, direct-acting antivirals; Pearson correlation coefficient -0.99 ; $P 0.0001$; *Survey conducted in 2016, prior to FDA and EMA licensing of sofosbuvir and ledipasvir for adolescents aged 12-18 years.

we found that the majority of children in follow-up for HCV were treatment-naïve based on 2016 data. The only drugs approved by the EMA for use in children at that time were PEG-IFN and ribavirin, a combination with high effectiveness (sustained virological response [SVR] around 90%) in children with HCV genotype 2 or 3 infection, but rather low for genotype 1 and 4 (SVR approximately 50%)^{16,20}; furthermore, adverse effects with PEG-IFN and RBV can be severe, requiring treatment discontinuation or dose modification, and sometimes persisting after the end of treatment.²⁰⁻²³ The low efficacy and the burdensome safety profile of PEG-IFN and RBV was likely a factor contributing to the large number of treatment-naïve HCV-infected children in follow-up at participating centres at the time of the survey. Furthermore, given the overall mild course of HCV-related liver disease progression in childhood and the availability of DAAs for paediatric use on the horizon, it is likely that 'warehousing' of paediatric patients was taking place in which treatment is delayed for well children, until more efficacious and less toxic regimens are licensed.

In addition, our results indicate that other factors such as the age of the patient and the stage of liver disease may be important to the decision to treat. As part of the survey, paediatricians were asked about their willingness to use DAA therapies, well known to be highly effective and safe in adults and, according to the few data available, also in children.²⁴⁻³⁰ Ninety-three per cent of the paediatricians surveyed reported willingness to use DAA if available in adolescents (aged 11 years or older), but fewer (74%) in children aged 6-10 and only 39% in those 3-5 years of age. Beside the efficacy of the treatment, the child's age, therefore, is felt as important in the decision-making process about whether to treat HCV infection in children, as has been observed in HIV co-infected children.³¹ Overall,

anti-HCV treatments are generally considered inappropriate for children younger than three years. Around 20% of the children who acquire HCV infection vertically can present spontaneous clearance in the first 30 months of life^{32,33} and so 3 years are usually considered the threshold age to confirm the chronicity of vertically acquired HCV infection. Fibrosis development in children with chronic HCV infection, although unpredictable, is dependent on different factors; these include the aetiology of the infection (eg, transfusion-transmitted HCV infection),³⁴ the presence of co-morbidities (eg, HIV co-infection)³⁵ and the length and duration of the infection and therefore, especially for those vertically infected, on the age of the child.⁹⁻¹² The association between increasing age of the child and the respondent's willingness to use DAA here is probably dependent on the overall low risk of advanced liver disease in childhood. Around 50% of the paediatricians reported being willing to perform a liver biopsy in children aged 6 or 14 years to decide whether to start treatment or not, confirming the impact of disease severity in the treatment decision. As a further possible factor, we can speculate that the absence of data on the efficacy and safety of DAA in children younger than 6 years could have influenced the response of paediatricians here. It is matter of debate and beyond the scope of this study, whether treatment should be deferred in young children until safe and effective DAA therapies are licensed. The possible benefits of an early treatment and cure not only include prevention of HCV-related disease (hepatic and extrahepatic) but also the opportunity for the child to grow up free of potential stigma and psychological consequences of a chronic transmissible disease; other benefits may include reducing risk of future horizontal and vertical transmission, and reduced burden on families and healthcare providers. The pros of treatment should be balanced against cons including, for DAA, the cost of the therapy.³⁶

The findings from this survey indicate that vertical transmission is the main route of transmission of HCV infection in the contemporary population of children with chronic HCV in clinical care in Europe. Injecting drug use was not reported among the routes of HCV acquisition in the present cohort of European children and adolescents. Recently, an increase in cases of HCV infection among adolescents and young adults was described in the United States.³⁷ Focused studies and interventions are needed for young injecting drug users to engage them and provide access to comprehensive health services that include HCV testing and linkage to care. Knowledge of risk factors for HCV infection is crucial in resource allocation for prevention measures. In the DAA era, this is particularly significant. The systematic screening of women of childbearing age and/or during pregnancy for HCV is a possible route for expanding testing, case identification and treatment. Treatment of women with chronic HCV before pregnancy is one strategy to prevent vertical transmission, although preliminary work is ongoing to investigate use of DAAs in pregnancy (ClinicalTrials.gov identifier NCT02683005). Recent studies from the United States reported transmission of hepatitis C in adolescents through injecting drug use.³⁷ A similar trend could not be confirmed in European children of the present cohort although linkage to care could be delayed and we cannot completely exclude this route of transmission. However, 3% of the children were reported as

having acquired HCV infection nosocomially or through unsafe blood product transfusions. The present survey was designed to provide aggregate data, individual patient data were not collected on age or country of origin (or country where the infection was likely acquired). Since the introduction of universal screening of blood products for HCV was implemented in 1992, blood transfusions are no longer associated with HCV transmission in Western and Central Europe.³⁸

Hepatitis C virus genotype 1 was the most common genotype, followed by genotype 3. Genotypes 2 and 3 were more common in WEC as compared to CEC as already demonstrated in previous studies.¹⁹ The epidemic of HCV infection in Europe is continuously evolving and epidemiological data have changed during the last 15 years. Genotype distribution is associated with the mode of transmission, with subtypes 1a, 3a and 4 being mostly intravenous drug use (IDU) related and genotypes 1b and 2 associated with blood transfusion and unsafe medical procedures.³⁸ The result of the public health drive in the 1990s towards reducing the risk of transfusion-related HCV infection and the improvement of healthcare conditions has resulted in IDU becoming the main risk factor for HCV transmission in adults.³⁸ This shift has switched the HCV genotype distribution among young adults from 1b and 2 to 1a, 3a and 4.³⁸ This study confirms the same genotype distribution of vertically acquired infections in children in Western and Central Europe.

The present survey provides an estimate of the prevalence of HCV-related advanced liver disease in the study population, with cirrhosis reported in 3% and liver transplantation in 1%. This is consistent with previous prospective studies that estimated that around 5% of the children with vertically acquired HCV infection progress to cirrhosis or bridging fibrosis during childhood.^{9,10,34}

This survey also provides insights around common approaches to monitoring of liver disease progression in HCV-infected children. In the IFN-era, liver biopsy was generally indicated in children infected by HCV genotype 1 or 4, where PEG-IFN plus RBV treatment yields no more than 50% success, to justify expectant management if fibrosis was mild.³⁹ Around 50% of the paediatricians reported to be willing to perform a liver biopsy to assist their decision-making for treatment, and more in the scenario of raised ALT. In adults, liver biopsy, the reference method for grading the necroinflammatory activity and staging of fibrosis, has now been replaced by noninvasive methods and TE.^{17,40} Nearly three-quarters of the respondent routinely use TE for noninvasive assessment of liver fibrosis in children. The diagnostic performances of TE for staging fibrosis have been systematically and prospectively evaluated in large cohorts of HCV-infected adults, with the clinical, anthropometric, biochemical and histological features which might affect liver stiffness measurement identified. However, the use of TE in children with chronic viral hepatitis has been poorly evaluated and validated, with only five studies including 140 children to date.⁴¹⁻⁴⁵ The results of TE should therefore be evaluated with extreme caution especially in very young children, and the confounding influences on test results of factors including probe choice, sedation or food intake need to be considered when interpreting results and further evaluated. The high feasibility, acceptability and the noninvasive nature of TE could account for the wide use of TE found in the present study.

This PENTA-Hep survey provides the largest ever characterization of the population of children in clinical follow-up for chronic HCV infection in Western and Central Europe, alongside important contextual information on their management and treatment. Inclusion of respondents from 15 countries supports generalizability of findings in the region. However, as this was a cross-sectional survey, we are unable to assess changes in monitoring and treatment practices over time, or trends in patient characteristics. Since survey responses related only to children with chronic HCV infection who were in active medical follow-up in 2016, we cannot make conclusions about the proportion undiagnosed, or previously successfully treated and discharged. Furthermore, we limited the number of questions on the patients' clinical profile to maximize survey participation and completion. The absence of specific questions on the quality of life and extrahepatic manifestations among other co-morbidities that could have affected the decision of paediatricians to prioritize treatment in children even in the era before DAA are therefore limitations of the present study.

In conclusion, the preliminary insights into the current (2016) epidemiology of hepatitis C in children in Western and Central Europe provided by the survey will inform future research. Most HCV-infected children in active follow-up had acquired the infection vertically and had not been treated with IFN-based therapies. Screening for HCV in women of childbearing age should be evaluated and considered in the DAA era as a possible cost-effective measure bringing the 'double dividend' of curing the woman and preventing vertical transmission. TE is widely used among European paediatricians although its diagnostic performance in children with chronic HCV infection should be carefully evaluated. DAA therapies are a promising opportunity for children with HCV with very positive attitudes to this treatment shown here among paediatricians caring for these children in Europe. As therapies become licensed for paediatric use, there is a need to generate evidence on their use in children and adolescents, including real-world safety, effectiveness and acceptability, in order to inform treatment and follow-up strategies.

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CONFLICT OF INTEREST

The authors declare the absence of any conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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