

Treatment and monitoring of children and adolescents with hepatitis C in Russia: Results from a multi-centre survey on policy and practice

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ABSTRACT

Background: The Russian Federation has the largest paediatric hepatitis C virus (HCV) disease burden in the World Health Organization European region with an estimated 118,000 children living with HCV viraemia. Direct-acting antivirals (DAAs) have been available for adults in Russia since 2015 and approved for treatment of adolescents aged ≥ 12 years since 2019. We evaluated DAA availability and uptake for HCV treatment of children and adolescents and clinical practices on diagnosis and management of paediatric HCV in Russia.

Methods: A survey was distributed to regional ministries of health in 85 administrative regions during September 2020. The survey consisted of 22 items collecting data on: type of facility, aggregate patient characteristics, HCV testing practices for children and pregnant women and HCV management and treatment practices for children.

Results: Survey responses were received from 37 of the 85 regions in Russia (response rate 44%). 2159 children and adolescents with chronic HCV were in follow-up; 1089 (50%) were female. Of 2080 children with available data on age-groups, 134 (6%) were < 3 years, 336 (16%) 3- < 6 years, 718 (35%) 6- < 12 years and 892 (43%) 12- < 18 years. 134 (15%) of 892 adolescents ≥ 12 years received DAAs, 96 (72%) glecaprevir/pibrentasvir, 26 (19%) sofosbuvir, 8 (6%) daclatasvir and 4 (3%) sofosbuvir/ledipasvir.

Conclusions: This study provides a baseline of DAA uptake in early stages of rollout for children and adolescents. The use of DAAs for treatment of adolescents in Russia presents a unique opportunity for HCV micro-elimination in this population.

1. Introduction

Globally, 3.26 million (2.07–3.90) children were estimated to have hepatitis C (HCV) viraemia in 2018.¹ Vertical transmission is the main route of acquisition among children and occurs in up to 5% of children born to infected mothers.^{2,3} HCV can also be transmitted through unsafe medical interventions, especially in some low- and middle-income countries.⁴ Adolescents may acquire infection through injecting drug use^{5,6} and high-risk sexual practices.^{7,8} While the incidence of severe disease or cirrhosis in children is low, progression of liver disease does

occur in childhood,^{9–11} leading to serious liver damage in adulthood,¹² and has been shown to adversely impact quality of life.^{13,14} Early diagnosis in childhood can help timely access to treatment and prevention of long-term morbidity.¹⁵ Historically, treatment coverage in childhood has been low, with limited treatment in children with interferon-based regimens resulting in low rates of viral clearance and significant side effects.^{16,17} In contrast to interferon-based regimens, Direct-acting antivirals (DAAs) have demonstrated high rates of cure and minimal toxicity, and several regimens are now approved for use in paediatric patients as young as 3 years of age.¹⁸

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The Russian Federation has the largest paediatric HCV disease burden in the World Health Organization (WHO) European region with an estimated 118,000 (95% uncertainty interval 80,500–123,000) children living with HCV viraemia.¹ This is largely influenced by a substantial population of people who inject drugs¹⁹ resulting in relatively high prevalence of HCV among women of childbearing age.^{19,20} Analysis of routine reporting data from the Russian State Surveillance Forms shows that although between 2001 and 2016 there was a decline in reported incidence of acute HCV (from 16.7 to 1.2 per 100,000 population), the reported rates of chronic HCV have remained largely stable over time fluctuating between 29.5 and 40.9 per 100,000 population with a slight decline in recent years.²¹ Age disaggregated data indicate that older adolescents (15–19 years) had higher chronic hepatitis C (CHC) prevalence rates (9/100,000 in 2016) than younger adolescents and children (1.7/100,000 in the 7–14 year olds; 3.3/100,000 in 1–6 year olds and 2.5/100,000 in <1 year olds).²¹

Previous studies show high proportion of interferon-based treatment for both HCV mono-infected and HIV/HCV co-infected children and adolescents in Russia.^{22,23} These studies highlight the suboptimal outcomes and poor safety profile of interferon-based treatments and the need to expand access to DAAs in the paediatric population. DAAs have been available for adults in Russia since 2015 and approved for treatment of adolescents ≥ 12 years old since 2019. In 2020, sofosbuvir/ledipasvir as well as two pangenotypic DAA regimens, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, were approved for adolescents in the Russian Federation (Fig. 1). According to a 2019 survey conducted by WHO, 20,000 people in Russia were reported to be receiving hepatitis C treatment.²⁴ These estimates are not stratified by type of treatment (interferon-based or DAAs) or by age.

Reduction in morbidity and mortality by improving access to HCV treatment remains a global priority as a cornerstone of the viral hepatitis elimination agenda. One of the WHO's ambitious targets is provision of HCV treatment to 80% of "eligible" individuals with CHC by 2030.²⁵ As eligibility of treatment has expanded to include all adults and children down to age of 3 years irrespective of liver disease progression this target translates to treatment of 80% of all those with CHC. Analysis presented in WHO's 2020 global progress report showed that HCV treatment coverage levels are insufficient to attain the global goal of eliminating viral hepatitis as a major public health threat by 2030²⁴; however, it utilised estimates of people on HCV treatment between 2014 and 2018, prior to DAAs being approved and becoming available in most countries. Countries are called on to prioritize provision of quality clinical management for those living with chronic viral hepatitis, including timely treatment initiation.²⁵

A survey of paediatric clinics providing HCV care across 15 countries in western and central Europe, prior to DAA approval for treatment of children and adolescents, showed that the majority (64%) of children with HCV in follow-up in 2016 had not received treatment.²⁶ There are gaps in knowledge about uptake of DAAs for the treatment of HCV and there are no age-specific measures available that explore DAA uptake among adolescents and children.

We aimed to evaluate treatment availability and uptake of DAAs for treatment of children and adolescents in Russia. We identified and documented contemporary policies and practices across Russia on clinical and therapeutic management of children with HCV, including pre-treatment monitoring strategies.

2. Methods

As part of the Russian European Alliance for research among women, children and adolescents impacted by HIV, TB and HCV (REACH project), a paper-based survey (see supplementary material) was distributed to regional ministries of health in 85 administrative regions in the Russian Federation during September 2020. Regional ministries were asked to cascade the survey to clinics, hospitals or health facilities providing monitoring and treatment for paediatric HCV. The survey consisted of 22 items divided into 6 sections: facility data, aggregate patient data, HCV testing practices for children and pregnant women, management of HCV in children, treatment of HCV in children and supplementary materials and comments. The survey collected aggregated data on numbers of children (<18 years) with HCV under current care at responding facilities by age group (0–<3; 3–<6; 6–<12; 12–<18 years), sex, HCV genotype (GT), co-infection with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV), and HCV treatment history. Respondents were also asked to provide details of the policies or guidelines used for the identification, monitoring and treatment of paediatric HCV. The data collected was entered centrally into an electronic REDCap database.²⁷ As no individual patient level data was requested, survey data were anonymised, and ethical approval was not required. Respondents did not receive any honorarium for completing the survey.

2.1. Data analysis

Descriptive statistics were used to summarize aggregate patient characteristics across all responding regions. To capture paediatric HCV management policies across most of the regions and diversity of practice we included all regions with three or more paediatric patients per region

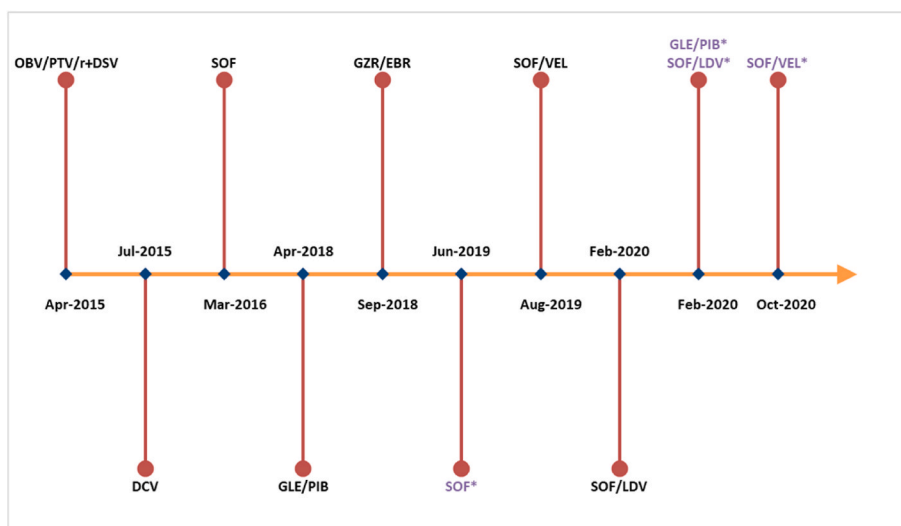


Fig. 1. Sequence of DAA approvals in Russia.

*indicates drug approval for adolescents >12 years

OBV/PTV/R

+

DSV - Ombitasvir/Paritaprevir/Ritonavir/
+Dasabuvir; DCV- Daclatasvir; SOF - Sofosbuvir;
GLE/PIB - Glecaprevir/Pibrentasvir; GZR/EBR - Gra-
zoprevir/Elbasvir; SOF/VEL - Sofosbuvir/Velpatasvir;
SOF/LDV - Sofosbuvir/Ledipasvir.

in the policy analysis; 35 of the 37 responding regions met this inclusion criterion. Where multiple responses on local practices were received for one region, for instance from different facilities, the responses from the site with the largest number of patients in follow-up were evaluated. Analyses were performed using Stata version 16 (StataCorp, College Station, TX).

2.2. Terminology and definitions

In this paper we define treatment uptake as the proportion of children with CHC who had initiated DAA treatment among those in follow-up at the reporting centers, who are screened and eligible for treatment as per national guidelines (uptake = number who initiate DAA treatment/number in follow up and eligible).

Chronic HCV infection was defined as the continued presence of HCV ribonucleic acid (RNA) in the blood six months or more after acquiring infection. Treatment naïve patients were defined as never exposed to treatment. Reflex testing was defined as HCV antibody testing followed automatically by HCV RNA in the lab if HCV antibody test is positive.

2.3. Russian national paediatric HCV management guideline recommendations

At diagnosis, the Russian Society of Paediatric Gastroenterology, Hepatology and Nutrition’s 2020 paediatric HCV management guidelines recommend conducting physical examination, liver function tests (LFTs), abdominal ultrasound, liver fibrosis assessment either through a liver biopsy or noninvasive tests such as transient elastography (FibroScan®) or aspartate aminotransferase to platelet ratio index (APRI) scoring. A computed tomography (CT) scan or magnetic resonance imaging (MRI) is only recommended for those with severe fibrosis or cirrhosis.

For pre-treatment monitoring of children with HCV, the Russian guidelines recommend that physical examination and LFTs be done at least once every six months and HCV RNA, liver ultrasound, urine analysis, and serum protein electrophoresis be done annually (Table 1). Liver fibrosis assessments through either biopsy or noninvasive measures are recommended at least once every three years during the pre-treatment monitoring phase. Alpha-fetoprotein (AFP) testing is recommended for patients with CHC with severe fibrosis or cirrhosis (F 3–4) to facilitate timely diagnosis of hepatocellular carcinoma (HCC).

Table 1

Diagnostic and pre-treatment monitoring practices recommended by the Russian National paediatric HCV guidelines and survey results.

Guideline recommendation	At diagnosis					
	Physical examination	HCV antibody and HCV RNA qualitative	LFTs	Liver ultrasound	Liver fibrosis assessment ^a	CT or MRI ^b
Results from survey	23 (66%)	Age <18 months: 33 (94.3%) Age >18 months: 32 (91.4%)	20 (57%)	17 (49%)	APRI – 10 (29%) Transient elastography – 11 (31%) Biopsy – 1 (3%)	^c
Guideline recommendation	Pre-treatment monitoring					
	Physical examination every 6 months	HCV RNA qualitative every 12 months	LFTs every 6 months	Liver ultrasound every 12 months	Liver fibrosis assessment ^a every 3 years ^e	General urine analysis every 12 months
Results from survey^d	30 (85.7%)	30 (85.7%)	33 (94.3%)	32 (91.4%)	APRI – 13 (37.1%) Transient elastography – 27 (77.1%) Biopsy - 4 (11.4%)	^c

^a Biopsy or non-invasive measures (e.g., elastography, serum biomarkers).

^b Only for those with severe fibrosis/cirrhosis.

^c This test question was not included in the survey.

^d At least at the recommended frequency or more frequently.

^e Results shown for a frequency of at least 12 months.

Although the national guidelines refer to HIV coinfection as a risk factor for increased vertical transmission and reactivation of HBV coinfection during CHC treatment, they do not mandate testing children with HCV for coinfections.

According to the national guidelines, antiviral therapy is recommended for all children with chronic HCV and treatment should be started immediately for those with severe fibrosis (F3 – F4 on the METAVIR scale). The recommended treatment for adolescents ≥12 years is DAA-based regimens and for those aged 3–11 years, interferon and ribavirin (Table 2). Guidelines recommend postponing treatment for younger children who have less pronounced fibrosis until they are eligible to receive interferon-free treatment regimens.

3. Results

Survey responses were received from 37 of the 85 regions in Russia (response rate 44%), representing a total of 268 clinics (Fig. 2).

As of September 2020, 2159 children and adolescents with CHC were in follow-up in the 37 Russian regions participating in the study (Table 3) and 1089 (50%) were female. Data on age groups were available for 2080 children, of whom 134 (6%) were <3 years, 336 (16%) 3-<6 years, 718 (35%) 6-<12 years and 892 (43%) 12-<18 years. Of 2159 children in care, 1312 (61%) were treatment naïve; 153 (7%) were known to have failed previous HCV treatment and 141 (7%) were currently receiving HCV treatment.

Table 2

Russian national paediatric HCV treatment recommendations.

Paediatric HCV Treatment recommendations		
Age	Recommended HCV treatment	Genotypes for which treatment is indicated
<3 years	Interferon-α2b + ribavirin ^a	GT 1, 2 & 3 GT 4, 5 & 6 – not recommended
3–11 years	Peg-IFN-α2b + ribavirin ^a	All GTs
12–18 years	Glecaprevir/Pibrentasvir	All GTs
	Sofosbuvir/velpatasvir	All GTs
	Sofosbuvir + ribavirin	GT 2, 3
	Sofosbuvir/ledipasvir (400/90 mg)	GT 1, 3, 4, 5 & 6

^a Guidelines recommend postponing treatment for younger children until they are eligible to receive interferon-free treatment regimens.

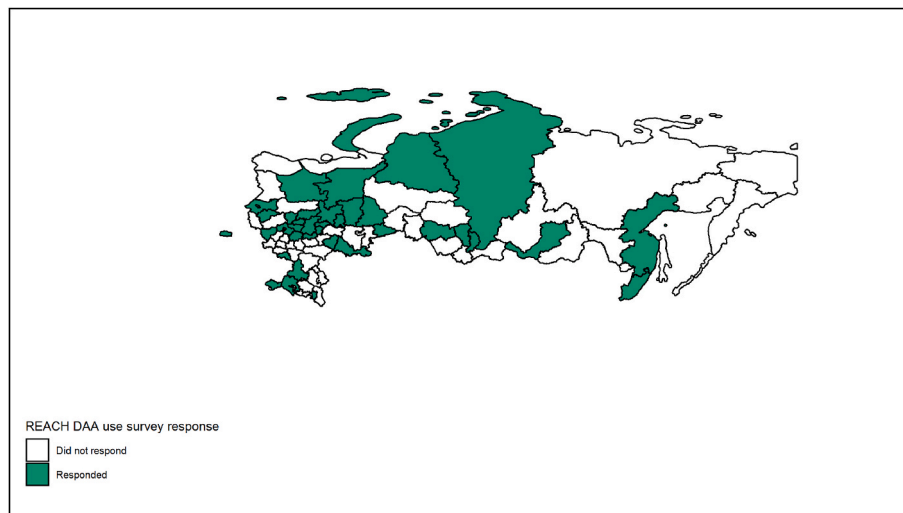


Fig. 2. Map showing regions that responded to the paediatric HCV treatment survey. Children and adolescents with HCV in follow up.

Table 3

Characteristics of children and adolescents with HCV in follow up in 37 regions of Russia.

Number of children (0–17 years)	2159
Age groups (n = 2080)	
0 to <3 years	134 (6%)
3 to <6 years	336 (16%)
6 to <12 years	718 (35%)
12 to <18 years	892 (43%)
Sex (n = 2159)	
Female	1089 (50%)
Mode of transmission (n = 2159)	
vertical transmission	1410 (65%)
Treatment status (n = 2159)	
treatment naïve	1312 (61%)
failed previous HCV treatment	153 (7%)
currently receiving treatment	141 (7%)
missing data	553 (26%)
Coinfection status (n = 2025)	
HCV mono-infection	1864 (92%)
HCV/HIV co-infection	144 (7%)
HCV/HBV co-infection	17 (1%)
HCV/HIV/HBV co-infection	0 (0%)
Genotype (n = 1387)	
GT 1	814 (59%)
GT 2	55 (4%)
GT 3	516 (37%)
GT 4	0 (0%)
GT 5	1 (0%)
GT 6	1 (0%)

Coinfection status was available for 2025 children, the vast majority of whom were mono-infected with HCV (n = 1864, 92%). 144 (7%) had HCV/HIV co-infection and 17 (1%) had HCV/HBV co-infection. No HCV/HBV/HIV coinfections were reported.

Most of the children in follow-up were reported to be vertically infected (n = 1410, 65%). GT was available for 1387 (64%) children, of whom 814 (59%) had GT1, 516 (37%) GT3 and 55 (4%) GT2. Only one child was reported to be infected with GT5 and one with GT6.

3.1. Tests used for diagnosis of children

Table 1 outlines the tests indicated by the Russian national paediatric HCV guidelines at diagnosis and prior to treatment initiation as well as the survey results from the 35 regions included in the policy analysis. The guidelines recommend both HCV antibody and HCV RNA test at diagnosis. For diagnosing infants <18 months of age, both HCV antibody and RNA testing were used in 33/35 (94%) regions and only HCV antibody in one (3%) region. For diagnosing children >18 months of age, both HCV antibody and HCV RNA tests were used in 32 (91%) of the regions and only HCV antibody tests in 2 (6%) regions.

In addition to these tests, HCV core antigen testing was used for diagnosing children <18 months in 10 (29%) regions and for children >18 months in 12 (34%) regions. Reflex testing was used for diagnosing children <18 months in 4 (11%) regions and children >18 months in 5 (15%) regions.

At diagnosis, 23 (66%) regions conducted physical examination, 20 (57%) regions conducted liver function tests and 17 (49%) conducted liver ultrasound. Liver fibrosis assessment was carried out by predominantly non-invasive measures; APRI in 10 (29%) and transient elastography in 11 (31%) regions. Only one region reported conducting liver biopsy at diagnosis.

3.2. Co-infection testing

Of the 33 regions responding to questions on testing for co-infections, 31 (94%) tested for HBV and 27 (82%) for HIV. Thirty of the 31 regions which routinely test for HBV, refer children for Hepatitis B vaccination or revaccination. Compared to HBV testing, fewer regions provide anti-Hepatitis A Virus (HAV) testing (n = 13, 39%). Of these 13 regions, 4 (31%) regions refer for Hepatitis A vaccination if children are HAV antibody negative.

3.3. Pre-treatment monitoring practices

Pre-treatment monitoring practices in the vast majority of regions were in line with guideline recommendations. LFTs were conducted at least every six months in 33 (94.3%) regions, frequency of LFTs were guided by the patient's condition in one region and data were missing for another region (**Table 1**). Annual or more frequent HCV RNA testing was performed in 30 (85.7%) regions. In one region RNA testing was only done at the time of diagnosis and in three regions during or post-treatment only.

Annual liver ultrasound was conducted in 32 (91.4%) regions. APRI scores were calculated annually in 13 (37.1%) regions, with two regions only using APRI scores at the time of diagnosis. Overall, respondents from 27 (77.1%) regions indicated that transient elastography should be conducted at least annually. Even though four regions reported conducting liver biopsies “as per guideline indications” (not annually), some respondents commented that “so far not a single child has undergone this procedure.”

Overall, 29 (83%) regions monitor AFP, either once cirrhosis is diagnosed or routinely (14 annually and six every six months); four never do AFP testing and two did not respond to this question.

3.4. Drugs used for the treatment of children

Overall, DAAs were used for treatment of children <18 years with HCV in 23 of the 35 (66%) responding regions. Respondents from seven regions (20%) stated that DAAs only were used to treat paediatric HCV, 16 regions (46%) used both interferon- or DAA-based treatments, 9 regions (26%) used interferon-based treatments only and 3 (9%) regions did not treat those under 18 years for HCV. In those regions reporting use of DAAs, these were exclusively used for treating adolescents ≥ 12 years old and not for younger children.

3.5. DAA treatment uptake for adolescents

134 (15%) of 892 adolescents ≥ 12 years in follow-up had received treatment with DAAs, 96 (72%) with GLE/PIB, 26 (19%) received sofosbuvir, 8 (6%) daclatasvir and 4 (3%) sofosbuvir/ledipasvir (Table 4). 758 adolescents (85%) had not received DAA treatment.

3.6. Counselling

Among the 33 responding regions, 32 (97%) provided guidance to HCV positive adolescents on prevention of transmission of HCV and other blood-borne viruses and on potential risks of alcohol consumption on liver disease progression.

4. Discussion

This national survey was designed to collate experiences in monitoring and treating children with HCV infection. To the best of our knowledge this is the first study focusing on uptake of DAA treatment for Russian children and adolescents with HCV. Estimated chronic HCV prevalence among children and adolescents in Russia is much higher than that in western Europe and among the highest in the world,^{1,28} making this an important population group to achieve HCV elimination.

Most children with HCV in Russia have previously been reported to acquire HCV vertically through infected mothers, accounting for two-thirds of new infections.^{19,29} Our findings are in line with this, with 65% of children in follow-up infected through mother-to-child transmission. It is possible that some of the other children acquired the infection horizontally through unsafe injections or inadequately screened transfusions; maternal HCV infection may also have been missed in some.³⁰ The distribution of HCV GT in children (GT1 59%, GT3 37%) was similar to that reported in Russian adults²¹ and

Table 4

Direct-acting antiviral (DAA) treatment uptake for adolescents with hepatitis C across Russia.

DAAs	Number of adolescents received DAAs n = 134
Sofosbuvir	26 (19%)
Daclatasvir	8 (6%)
Sofosbuvir/Ledipasvir	4 (3%)
Sofosbuvir/Velpatasvir	0 (0%)
Glecaprevir/Pibrentasvir	96 (72%)

children.²⁹ Around 7% of those in care had HCV/HIV co-infection. HIV coinfecting children and adolescents are considered a priority population for DAA treatment in Russia, with 73% of the HCV/HIV coinfecting adolescents aged ≥ 12 years being treated to date.³¹ HCV/HBV co-infection in 17 children is concerning as co-infection can lead to more severe liver disease and an increased risk for progression to HCC and there are no established guidelines for treatment of HBV-HCV coinfection.³²

In this survey, an estimated 7% of children in care had failed a previous HCV treatment. Previous paediatric HCV studies from Russia have also reported considerable proportions of treatment-experienced children.^{29,33} This is most likely to be interferon-based treatment as DAAs have recently been approved in the country. Unlike with previously used interferon-based treatment, treatment experience does not affect treatment success with current generation of DAAs.³⁴

Since DAAs were registered in Russia for treating adolescents in 2019 and recommended in the subsequent national paediatric HCV treatment guidelines, 15% of adolescents in follow-up have received treatment. DAA uptake may look artificially low if the denominator includes those who are eligible but not offered DAA treatment (as is the case in our estimates). Introduction of new medicines takes time (especially when they are publicly funded) and uptake of DAAs for adolescents should be interpreted in the broader context of paediatric drug regulatory approval timelines. Furthermore, caution should be taken in interpreting uptake, as low uptake does not equate to mean low demand for treatment because this survey did not capture those who were offered and declined treatment. This is the initial phase of DAA rollout when physicians, researchers and policy makers are still working to understand what the most optimal paediatric treatment approaches are. Understanding the different approaches of physicians towards identifying who to treat first is an important part of the DAA rollout process.

Disparities in availability of DAAs across different regions might also affect uptake. Our data show that some responding regions have yet to start treating paediatric patients with DAAs. Reasons for this, including potential barriers, need to be explored to facilitate treatment access for children and adolescents.

Most diagnostic and pre-treatment monitoring practices are aligned with the national recommendations. Although there is a clear move towards non-invasive measures of liver fibrosis, we found that few regions used transient elastography. This might be due to an unavailability of this method in some regions.

In the interferon era, approaches for treatment monitoring of children and adolescents included extensive pre-treatment evaluation, on-treatment laboratory monitoring, frequent physical examinations, and monitoring after treatment to confirm sustained virologic response (SVR). Unlike with the interferon-based treatment, with DAAs minimal pre-treatment screening and on-treatment monitoring are required due to pangenotypic activity of several combinations, robust safety profile and excellent cure rates. International guidelines recommend these simplified approaches for patients who are considered easy to treat e.g. those without cirrhosis.³⁵ Although several studies have examined the effectiveness of simplified monitoring approaches in adults, there are no data in adolescents and children and this is a topic for further research.^{36,37} WHO guidelines do not yet outline any such algorithms for the paediatric population,³⁸ partly because of the limited treatment experience in these younger age groups and partly because the latest WHO guidelines from 2018 still recommend genotype-specific DAA regimens for adolescents. Children are good candidates for minimal monitoring, as very few progress to cirrhosis, and therefore the simplified pre-treatment monitoring approaches used in adults can be extrapolated to children.

Our study had some limitations. As this survey is cross-sectional in nature, we were unable to analyse trends in DAA uptake over time. As we lacked estimated numbers of how many eligible adolescents with HCV in the regions that responded i.e., total target population, we were unable to calculate coverage (defined as the proportion of total target population treated with DAAs at a given point in time or over a period of

time). We were also lacking treatment status information on a quarter of the children and adolescents reported to be in follow-up. Furthermore, there might be heterogeneity in HCV care and management practices within regions.

However, although this survey was not regionally representative, we achieved a fairly high response rate (44%) covering the largest described cohort of children living with HCV to date. Furthermore, this study provides a baseline of DAA uptake in early stages of rollout for children and adolescents. Such evidence is essential for the development of treatment guidelines (within the Russia and globally) and can inform the optimised use of DAAs, improving the quality of life of patients and leading in the long term to the reduction of the burden of HCV.

Modelling studies at the national and sub-national/regional levels in Russia show that HCV prevalence is expected to rise by 2030,^{39,40} emphasizing the importance of accelerating access to safe and effective treatments. The scale-up of testing and treatment with the new drugs is a key strategic intervention set by WHO to achieve the treatment coverage targets for elimination of viral hepatitis as a public health threat by 2030. The inclusion of children and adolescents in strategies to achieve this goal is essential. The use of DAAs for treatment of adolescents in Russia combined with the recent reduction in the incidence of acute and chronic hepatitis C among children under 17 years of age presents a unique opportunity for HCV microelimination in these age groups.

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Author contributions

FM, RL, AT, and GI conceived the project. FM extracted the data, wrote the first draft and made subsequent revisions to the manuscript. FM, RL, AT, and GI designed the survey questionnaire. VC, NP and AF collected the data. All authors reviewed results, provided guidance on methods, critically revised the paper, approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Fariyah Malik, Vladimir Chulanov, Nikolay Pimenov, Anastasia Fomicheva, Rebecca Lundin, Nataliia Levina, Anna Turkova and Giuseppe Indolfi have no conflict of interest to declare. Claire Thorne has received grant funding from ViiV Healthcare and Merck, via the Penta Foundation.

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