The micro-elimination approach – a new way of tackling hepatitis C in the paediatric population

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Submitted: 27 December 2020; **Accepted:** 28 May 2021;
Online publication: 4 June 2021

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/138260

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Abstract

Recent advances in antiviral drug development towards the hepatitis C virus (HCV) have revolutionized the therapy and paved the way towards the elimination of chronic hepatitis C (CHC). Difficulties in achieving time-bound elimination targets of the World Health Organization's Global Strategy on viral hepatitis might be overcome through a novel micro-elimination approach. A new, emerging strategy focuses elimination efforts on high-risk and ignored populations, and therefore allows for quick, efficient targeting of treatment and prevention services. So far, gaps in antenatal and/or paediatric care, and a lack of reimbursement and approval of direct-acting antivirals (DAA) in the paediatric population have been a barrier to accessing treatment, leading to marginalization of children and adolescents. Recently approved DAAs for use in children aged ≥ 3 years seem to be the cornerstone of HCV elimination by reducing the risk of future horizontal and vertical transmission, firstly on a national, and ultimately on a global level.

Key words: HCV, DAA, novel strategies, micro-elimination, HCV cascade of care.

Introduction

According to the World Health Organization's (WHO) Global Strategy, viral hepatitis should be eliminated as a serious public health threat by 2030. An estimated 90% decrease in the number of new chronic hepatitis C (CHC) cases, a 65% decrease in hepatitis C virus (HCV)-associated mortality, and treatment coverage of 80% of all eligible patients are assumed [1]. Many countries will need to substantially intensify their HCV control efforts to meet the aforementioned targets. These ambitious goals might be achieved by the implementation or enhancement of the HCV cascade of care. It consists of HCV prevalence estimation, identification of individuals with CHC and linking them to care, assessment of liver disease, introduction of antiviral treatment, achievement of clinical cure (defined as sustained viral response – SVR), and post-SVR follow-up (screening for cirrhosis, hepatocellular carcinoma [HCC], and other HCV-related liver diseases) [2–4]. Hepatitis C virus cascade of care varies across regions. It reflects the disparities in the burden of hepatitis C and dynamics of public health response, and leads to an identification of gaps in care (e.g. those lost to follow-up LTFU) and foci for improvement [2, 5]. There are many challenges across the care cascade. A significant economic burden results mainly from diagnosis- and medication-related costs. Unfortunately, HCV infection often remains undiagnosed. Although there are highly effective direct-acting antivirals (DAA) available, the rates of treatment initiation continue to be low. According to the WHO, in 2015 only 20% of HCV-infected individuals worldwide were aware of their health status, and treatment was started by less than 10% of them [6]. Such results are unsatisfactory and pose a challenge for the time-bound goals of the mass-screening approach of the Global Strategy.

Micro-elimination – a novel emerging strategy and a target subpopulation

Hepatitis C virus elimination progress varies even across European countries. To overcome all formidable obstacles, a micro-elimination strategy is suggested. Micro-elimination is defined as a pragmatic approach, which allows for the identification of realistic goals of HCV elimination, distribution of resources, and assistance for local specialists in the process of intervention modification, delivery, and enhancement [3, 7]. Compared to the comprehensive, country-level actions undertaken to eliminate HCV, this approach is less costly [8]. Provided that elimination efforts are focused on smaller affected populations, tailored treatment and prevention services can be introduced quickly and effectively [9].

Micro-elimination is a novel concept of HCV elimination in a defined group of people (e.g. HIV-infected individuals, people who inject drugs, prisoners, people affected by haemophilia, and children), settings (e.g. hospitals, addiction treatment centres), age cohorts (e.g. baby-boomers), or geographic areas (e.g. city or region). This strategy substantially increases the chances for success because it supports actions undertaken towards national elimination [3, 8, 10]. In line with the micro-elimination concept, specific models of patient-oriented services should be determined throughout the HCV cascade of care, especially for high-risk groups and marginalized populations. Children and adolescents also belong to this group because DAA regimens were not allowed in persons below the age of 18 years until 2017. Furthermore, high costs related to the production of paediatric formulations could have impeded the access to treatment in those groups [3, 11]. Additionally, adolescents are prone to HCV infections. This is reflected by the increase in the number of young individuals who inject drugs, teenage pregnancies, migration, and populations displaced from conflict zones with no access to health care or support [11]. Irrespective of the high socioeconomic and long-term benefits resulting from investing in child and adolescent health, only a few national viral hepatitis policies address these vulnerable populations, including testing, treatment, and preventive strategies.

Epidemiology of chronic hepatitis C in children

The availability of reliable, national data on HCV epidemiology is crucial for accurate assessment of potential subpopulations for micro-elimination and understanding when the target population may drop out of the continuum of care [10]. Compared to adults, the prevalence of HCV infection is lower in children. In 2018, the global prevalence of HCV infection in the group of individuals aged 0–18 years was 0.13% (95% uncertainty interval 0.08–0.16), which corresponds to 3.26 million (2.07–3.90) viraemic paediatric patients [12]. Egypt (with an estimated prevalence 2–9% depending on the region), Sub-Saharan Africa, the Amazon Basin, and Mongolia are the most affected regions. The average prevalence is reported in developing countries at 1.8–5.8%, while the lowest prevalence is reported in the United States and Europe at 0.05–0.36% [11, 13–17].

Hepatitis C virus prevalence in the European paediatric population varies largely between countries due to different past and current risk factors and standards of care. Eastern Europe has the highest HCV prevalence in the paediatric population among Global Burden of Disease regions, estimated at 0.4%, in comparison with Western and Central Europe at 0.04% and 0.09%, respectively [12]. The countries with the highest HCV prevalence are as follows: Ukraine (0.54%), Moldavia (0.44%), Belarus (0.41%), Romania (0.21%), and Bulgaria (0.1%) [12]. The lowest prevalence is reported in the Netherlands and Norway (0.02%), and a slightly higher prevalence of 0.03% is observed in Austria, Belgium, France, Germany, Hungary, and Spain [12].

In Poland, epidemiological data on hepatitis C is available starting from 1997, when this disease was included in routine epidemiological surveillance. Recently, a significant reduction in the number of newly detected HCV infections in the group of children and adolescents has been observed (Table I).

Mother-to-child transmission of hepatitis C virus and probable gaps in the screening strategy

Mother-to-child transmission (MTCT) is the main mode of HCV transmission in the paediatric population. Moreover, it may still substantially increase the burden of hepatitis C [8, 10, 18–24]. The estimated risk of vertical transmission is

Table I. Hepatitis C reported in Poland in 2005–2018. Number of cases (*n*) and rate per 100,000 population by age group and all reported cases (children + adolescents + adults)

Year	Age groups									
	0–4		5–9		10–14		15–19		Total	
	n	Rate	*n*	Rate	*n*	Rate	*n*	Rate	*n*	Rate
2018	9	0.47	5	0.25	3	0.16	10	0.54	3442	8.96
2017	11	0.58	10	0.48	5	0.27	23	1.22	4010	10.44
2016	15	0.80	7	0.34	4	0.22	23	1.18	4261	11.09
2015	14	0.73	8	0.39	10	0.55	32	1.59	4285	11.14
2014	3	0.15	5	0.25	3	0.16	27	1.30	3076	7.99
2013	7	0.35	1	0.05	5	0.27	32	1.47	2705	7.03
2012	9	0.44	5	0.27	2	0.11	58	2.56	2359	6.12
2011	10	0.48	4	0.22	11	0.56	55	2.32	2151	5.58
2010	2	0.10	1	0.11	4	0.20	85	3.44	2111	5.53
2009	6	0.31	2	0.11	11	0.53	95	3.69	1939	5.08
2008	10	0.54	5	0.27	8	0.37	159	5.97	2353	6.17
2007	4	0.22	5	0.26	19	0.84	178	6.48	2753	7.22
2006	7	0.39	4	0.21	37	1.59	178	6.29	2949	7.73
2005	8	0.45	5	0.25	49	1.97	179	6.12	2997	7.85

Note: Data from annual reports of NIZP-PZH and Chief Sanitary Inspectorate "Infectious diseases and poisonings in Poland" retrieved from http://wwwold.pzh.gov.pl/oldpage/epimeld/index_p.html#01.

about 5% in women with detectable HCV-RNA. The risk of transmission is much higher (10.8–25%) in HIV/HCV-coinfected women if HIV coinfection is not adequately controlled [25–27]. The following modes of transmission are the most common in teenagers: injected drug use, high-risk sexual practices – mainly among men who have sex with men, and tattooing in unregulated settings. In developing countries HCV is still transmitted via iatrogenic mode in the youngest population [16, 27, 28]. In Poland, about 4000–8000 children annually are born to mothers infected with HCV [29, 30]. The average risk of vertical transmission is estimated at 8.2% [31, 32]. Hepatitis C virus transmission occurs mainly in the perinatal period and during delivery [22, 33, 34]. Although MTCT is the main mode of HCV transmission in paediatric population, especially in high-income countries, the identification of HCV-exposed children is hampered. Some researchers report that up to 70% of children born to HCV-infected mothers might not have been subject to screening or follow-up adequately. Therefore, they are not included in observation (LTFU) [35].

Although HCV RNA testing is reliable in children aged 2 months, HCV antibody test results in children below the age of 18 months are inaccurate because antibodies may come from the infected mother (maternal antibodies). Therefore, this test cannot be used to confirm HCV infection [36]. It is a common phenomenon that the levels of HCV RNA fluctuate in infants, mainly during the first 2–4 years of life, which could lead to misdiagnosis. Spontaneous clearance of HCV infection is reported in approximately 25–40% of infected children (loss of HCV RNA that was detectable earlier), while the remaining children develop CHC (viral replication is detectable for at least 6 months) [18, 24, 27, 37–40]. The absence of an adequate screening strategy in children may lead to a situation in which children at risk for perinatal transmission may not be diagnosed until hepatitis C symptoms appear or abnormal levels of liver enzymes are detected incidentally. However, detection is challenging because the progress of HCV infection appears to be slower in children than in adults. Thus, most children remain asymptomatic during childhood [27]. Consequently, delayed diagnosis could contribute to delayed referrals and treatment, which may result in irreversible liver disease (e.g. cirrhosis or hepatocellular carcinoma) and a broad spectrum of extrahepatic manifestations [35, 41].

Although histopathological changes in liver tissue are characterized by low inflammatory activity and low stages of fibrosis (unlike in adults), they progress over time. In 2–5% of infected children, they may lead to serious liver damage, including cirrhosis (1.8%) and hepatocellular carcinoma (HCC), although this is rarely encountered, with only a few case reports [13, 14, 19, 27, 39, 42].

Universal screening for hepatitis C in pregnant women is a rapidly evolving area. It could improve the health of mothers and identification of children at risk. However, it is associated with logistic and political considerations. Based on cost-effectiveness analysis, the WHO does not recommend universal/antenatal screening in populations with a prevalence of anti-HCV below 2% [43, 44]. In Poland, the prevalence of anti-HCV antibodies is estimated at 0.86–1.9% (depending on the population tested and the sampling methodology used), while the percentage of people with detectable replication of HCV is about 0.47–0.6% [45–47]. The prevalence of anti-HCV antibodies in pregnant women is estimated at 0.8% [47]. In a pilot study carried out in pregnant women living in the Mazowieckie Province, anti-HCV antibodies were detected in 2.02% of all women tested [31, 32]. Act on Pregnant Woman Care, introduced in 2010 in Poland, recommended routine anti-HCV screening in all pregnant women. It resulted in an increase of the percentage of HCV infections diagnosed in women who did not report any risk factors during an interview (9.9% vs. 46.1% before and after 2010, respectively). Significant involvement of obstetricians contributed to an increase in the percentage of HCV infections detected in pregnant women (21.5% vs. 30.8% before and after 2010, respectively) [48]. A recent report revealed that the peak of HCV infection diagnoses is observed in women aged 25–29 years [49]. This increase results from legal requirements for prenatal standard of care throughout pregnancy, with compulsory HCV testing for pregnant women from 2012 onwards [47]. Maternity care settings are among the dominant reasons for anti-HCV antibody testing in women aged 30–39 years.

The role of early diagnosis and access to treatment

Detection of hepatitis C in mothers promotes testing for HCV in their children [50].

Early diagnosis in children enables prompt linkage to care and assessment of liver disease. There are several diagnostic procedures used to assess the grades and stages of liver disease. Previously, liver biopsy was performed as a standard procedure; whereas currently, noninvasive methods are mainly selected. Although they would allow for the stratification of disease severity, further validation is required in the paediatric population.

So far, access to treatment has been impeded by high cost, non-reimbursement, and lack of approval of new DAA regimens in the younger age groups. This generates difficulties in achieving the ambitious WHO targets for HCV elimination [51, 52]. Fortunately, several significant changes were introduced to DAA registration recently in Europe, which revolutionized the therapy of hepatitis C.

In 2017, the Food and Drug Administration and European Medicines Agency (EMA) registered the first DAA-based regimens (fixed-dose combination of ledipasvir/sofosbuvir and the combination of sofosbuvir and ribavirin) for adolescents with CHC aged 12–17 years or weighing > 35 kg.

Since July 2020, a combination of ledipasvir and sofosbuvir has been approved by the EMA to be used in children who are at least 3 years of age. Moreover, in September, a pangenotypic combination regimen (sofosbuvir/velpatasvir) was authorized for use in children aged at least 6 years or weighing at least 17 kg. It is not feasible to predict the critical time of disease progression in early adulthood; thus, early introduction of treatment is considered to be cost-effective [53]. Moreover, treatment of HCV-infected children is of upmost importance because early eradication of HCV is essential for the prevention of high-risk teenager behaviours contributing to the transmission of infection. Oral treatment options characterized by high effectiveness, good safety profile, and simplicity of use are needed to improve treatment coverage in the HCV-infected paediatric population [11]. Irrespective of the high cure rates of DAA (> 95%), access to this treatment for children and adolescents remains a major concern in Poland because it is not reimbursed by the National Health Fund (NHF) [54]. Therefore, it is not included in the national therapeutic programmes for hepatitis C. Such treatment is used as part of enrolment into clinical trials. So far, the marginalized paediatric population finally has an opportunity to be cured. Since July 2019, the non-commercial POLAC project (treatment of polish adolescents with chronic hepatitis C using direct acting antivirals) is offering sofosbuvir/ledipasvir for adolescents (aged over 12 years) with HCV genotype 1 and 4.

Moreover, an ongoing study in Warsaw financed by the Medical Research Agency will offer treatment with a newly approved regimen of sofosbuvir/velpatasvir for children over 6 years of age in 2021 (regardless of the disease severity and HCV genotype).

Broad access to DAA regimens would allow for HCV elimination in the population by decreasing the risk of future horizontal and vertical transmission. Furthermore, HCV-infected children would have a chance to live without the potential stigma and psychological consequences associated with living with a chronic contagious disease [55].

Conclusions

Having considered the absence of an effective vaccine for HCV, treatment with the new DAAs seems to be the cornerstone of HCV elimination (treatment is also a potent method of prevention) [56]. Because there have been revolutionary changes in the pharmacological management of HCV infection in children, with cure rates reaching > 95%, it is of upmost importance to reach this population. Engagement of this group would be essential for success in HCV elimination on the national, and ultimately the global level.

Conflict of interest

The authors declare no conflict of interest.

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