

Hepatitis C Virus Infection in Children and Adolescents

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Abstract

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and associated morbidity and mortality worldwide. Short-course, oral, curative, direct-acting antiviral regimens have now transformed treatment for HCV infection. Since the launch in 2016 of the first global strategy towards elimination of viral hepatitis as a public health threat by 2030, the predominant focus of the global response has been on treatment of adults, who bear the greatest burden of morbidity and mortality of HCV related chronic liver disease. There has been much less attention paid to addressing response to HCV in children and adolescents, in part because of the lack of data to inform specific paediatric management practices and policy. In this review, we summarize current knowledge on epidemiology, natural history, and treatment of chronic HCV infection in adolescents and children, and highlight key differences from infection acquired in adulthood. The estimated global prevalence and burden in children aged 1 to 19 years is 0.15% and 3.5 (3.1-3.9) million, respectively. HCV infection is usually asymptomatic during childhood, and cirrhosis and hepatocellular carcinoma are rare. Sofosbuvir, ledipasvir and ribavirin have now received regulatory approval and guidelines recommend their use in adolescents ages >12 years with HCV infection. Key actions to address the current policy gaps and achieve treatment scale-up comparable to that in adults include: establishment of a testing and treatment access campaign targeted at children and adolescents; fast-track evaluation of pan-genotypic regimens and accelerated approval of paediatric formulations. Research gaps that need to be addressed include age-specific seroprevalence studies of HCV viraemia in priority countries; further validation of non-invasive tests in children; and establishment of paediatric treatment registries and international consortia to promote collaborative research agenda.

Key words: hepatitis C, adolescents, children, elimination, natural history, epidemiology, treatment

Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and associated morbidity and mortality worldwide.^{1,2} Globally, WHO estimates that there were 71 million people living with chronic HCV infection in 2016,² and 399 000 deaths in 2015,^{1,2} mainly from cirrhosis or hepatocellular carcinoma (HCC).^{1,2} In addition, there were approximately 1.75 million new infections.² In 2016, the first Global Health Sector Strategy on Hepatitis 2016–2021 outlined global targets and priority actions for countries to achieve the goal of eliminating viral hepatitis as a public health threat by 2030 – defined as, a reduction in mortality by 65% and in incidence of chronic infections by 90%.³ There has been significant progress in access to curative direct acting antiviral (DAA) treatment due to substantial cost reductions with generic medicines, and by the end of 2016 around three million adults had been treated. But achieving the global targets for mortality reduction will require a substantial scale-up in testing and treatment, as overall WHO estimates that less than 20% of those infected have been diagnosed (representing an 80% testing gap) and only 10% treated (75% treatment gap), and this is even lower in low and middle-income countries. The predominant focus of the global HCV response has been on the adult population, which bears the greatest burden of morbidity and mortality due to chronic liver disease. Much less attention has been paid to testing, treatment and preventive strategies among children and adolescents, in part because until recently none of the DAA regimens had been approved for use in persons less than 18 years, and there were major gaps in evidence to inform paediatric specific management practices and policies. For example, there has been only one recent systematic review of seroprevalence of paediatric HCV infection;⁴ only three moderate sized prospective studies with long-term follow-up⁵⁻⁷ have examined the long term natural history and the risk of complications in children with perinatal HCV acquisition, and to date only three registration trials have been completed on the safety and efficacy of DAA regimens for treatment of HCV infection in adolescents (aged 12 years or more).⁸⁻¹⁰ While more than eight different DAA combinations are available for treatment in adults, only two DAA regimens

(sofosbuvir plus ribavirin and sofosbuvir/ledipasvir) have been approved for HCV treatment in adolescents. Very few countries have included recommendations for systematic testing and treatment of adolescents and children in their national policies. As a result, globally only a tiny fraction of HCV infected children or adolescents have been diagnosed or treated, especially in low and middle-income countries (LMICs).

The objective of this review is to provide a comprehensive synthesis of current knowledge on the epidemiology, natural history, and treatment of HCV infection in children and adolescents and to highlight key differences and similarities from the experience with infection acquired in adulthood. We conclude with key priorities for action, which include addressing critical evidence gaps to inform future policy development in children and strategies to promote scale-up of testing and treatment.

Methods

Search strategy and selection criteria

We undertook a comprehensive narrative literature review using PubMed only to identify key studies on paediatric HCV infection in the following areas: epidemiology (seroprevalence and burden), transmission, natural history, diagnosis with assessment of disease stage, and treatment (including criteria for treatment, treatment options and outcome). A formal, quantitative systematic review was not considered appropriate for this initial comprehensive review. Web Annex A provides details on search strategy and inclusion/exclusion criteria. For each of these topics, we summarised the data in order to highlight the main differences between data and management strategies in adults, and that in children and adolescents. For the purpose of this review, we defined an adult as a person 18 years of age or older; an adolescent as a person from 12 to 17 years; and a child as a person younger than 12 years of age, unless stated otherwise, to conform with the age categories most commonly used in the studies evaluated, although other definitions for adolescents are used by different organisations (e.g. aged 10 to 19 years).

Seroprevalence and burden

The current global estimates of HCV prevalence, burden, morbidity and mortality are largely based on data from the adult population.² WHO estimates that in 2015 there were an estimated 71 million (95% CI 64-103 million or 1% of the global population) persons living with chronic HCV,² with the highest prevalence in the Eastern Mediterranean Region (2.3%) followed by the European Region (1.5%) and African Region (1%).² There is also an estimated human immunodeficiency virus (HIV)–HCV antibody coinfection prevalence and burden of 6.2% (interquartile range [IQR] 3.4–11.9) and 2.3 million (IQR 1.3–4.3 million) cases respectively - approximately half of these are injecting drug users.¹¹

The seroprevalence and burden of paediatric hepatitis C infection is less well established. Historical reports from small hospital-based cohorts indicated rates of infection of up to 20% among adolescents and children who had been treated in hospital for malignancy, renal failure, requiring haemodialysis, and those who had undergone surgical procedures.¹² A recent (as yet unpublished) systematic review of the prevalence of HCV viraemia in adolescents and children aged from one to 19 years based on studies from 102 countries estimated a 0.3% prevalence in high income and 0.6% in low income countries, and an overall burden of 3.5 million (95% CI 3.1-3.9 million) or 0.15% (Figure 1).⁴ Nineteen countries accounted for 80% of worldwide infections. Data were either missing, scanty or based on outdated studies, even from Western Europe and the United States (US), and were overall too limited to generate regional prevalence estimates. As a result, the true prevalence in adolescents and children may be underestimated in some countries.¹³ Data from the US indicate a rising HCV prevalence in adolescents linked to the opioid epidemic and increasing rates of HCV infection in women of reproductive age.¹⁴ HIV-HCV coinfection in children appears now to be rare as HIV vertical transmission rates have declined, worldwide.¹⁵

Routes of transmission

In middle- and high-income countries, injecting drug use, accounts for most infections, particularly in settings where sharing needles and syringes remains common and access to harm reduction is limited. Sexual transmission has been reported mainly in men who have sex with men (MSM)¹¹ including those with HIV-infection and those using pre-exposure prophylaxis,¹⁶ with several outbreaks among MSM in Europe, Australia and the US.¹⁷ In contrast, in LMICs, HCV infection in adults, adolescents and children is most commonly associated with unsafe injection practices and procedures in health-care facilities with inadequate infection control practices, such as renal dialysis units.²

Since the introduction of routine blood-bank screening for HCV infection, vertical transmission is now the principal route of HCV acquisition among children,¹⁸ with a transmission rate of about 5% and 10% from HCV RNA positive mono- and HIV-co-infected mothers, respectively.¹⁹ The rate is increased with a higher maternal HCV viral load, labour duration, use of amniocentesis or foetal scalp monitoring, and prolonged rupture of membranes.¹⁸⁻²⁰ The lack of sero-survey data from antenatal clinics has precluded the generation of reliable estimates of new infections due to vertical transmission in children. In low income settings, iatrogenic transmission and exposure to unsafe medical interventions also play an important contribution to transmission, especially among children with malignancy, renal failure requiring haemodialysis, and undergoing surgical procedures.¹² Horizontal and intrafamilial transmission is generally considered to play a minor role in HCV acquisition.²¹ In high income countries, especially the US, there have been increasing reports of acquisition of hepatitis C (and HIV) in adolescents through injecting drug use,^{22,23} a finding which highlights the need to monitor trends closely in this population and to ensure that barriers to harm reduction services faced by adolescents are addressed.^{22,23} Adolescents are also at risk of infection through high-risk sexual practices especially among MSM and tattooing in unregulated settings.^{17,24}

Natural history of hepatitis C

An understanding of the natural history of HCV infection in adults is based on several large prospective studies.^{25,26} Spontaneous clearance of acute HCV infection generally occurs within six months of infection in around 30% (15–45%) in the absence of treatment.²⁷ Overall, the 20-year cumulative incidence of developing cirrhosis ranges from 15 to 30%,^{25,26} while the risk of HCC is 2–4% per year in persons with cirrhosis.²⁸ Extrahepatic manifestations²⁹ are reported in up to 74% of HCV infected adults, and the most common are diabetes mellitus (15%) and chronic renal disease (10%).¹²

Table A provided in the Appendix summarises key studies on natural history of HCV infection in adolescents and children. In contrast to the several landmark large and long-term cohort studies in adults, there have been only two moderate sized (>100 children) prospective studies with longer-term follow-up (>4 years): one study of 504 Italian children and adolescents followed for a mean of 5.9 ± 3.8 years after recruitment, and 10.6 ± 6.0 years from putative time of infection;⁵ and the European Paediatric HCV Network (EPHN) multicentre prospective study of 266 children born to HCV-infected women followed for a median of 4.2 years (range 3.2 months – 15.9 years).⁶ There are also three large retro/prospective studies with long-term follow-up:- a cohort of 113 HCV-seropositive paediatric cancer patients from the United States followed for a median of 30 years (IQR 28-36) post-cancer diagnosis³⁰; a national cohort of 348 children from Japan followed for 30 years,⁷ and a recently published UK cohort of 1049 persons infected with HCV in childhood, of which 53% were infected through injecting drug use in adolescence, and 24% through receipt of contaminated blood products.

³¹ There are also several other smaller prospective^{32,33} and retrospective cohorts and case studies.³⁴⁻⁴⁴

Following vertical acquisition, between 25 and 40% of infected children spontaneously clear the infection in the first four years of life,^{5,6,33} which is slightly higher than rates reported in adults.

Another 6%-12% of those with chronic HCV infection may clear the virus before adulthood,⁴⁵ whilst the remainder develop chronic infection that persists into adulthood.⁴⁶ Spontaneous clearance rate of

vertically acquired HCV infection is influenced by both host factors (such as the interleukin 28B gene - a rs12979860 single nucleotide polymorphism located on chromosome 19 in the *interferon L4 gene*⁴⁷⁻⁵⁰, and natural killer cells cytolytic function⁵¹) together with viral characteristics such as genotype.³³

Chronic HCV infection is usually asymptomatic during childhood,^{5,6,38,52} and tends to have a more indolent course than that in adults.⁵² In the EPHN study, hepatomegaly was the only clinical finding reported in 10% of 266 enrolled children, but almost 50% had a persistently abnormal alanine aminotransferase (ALT) level during follow-up.⁶ The histological course of chronic HCV infection in adolescents and children is unpredictable with a wide spectrum of findings ranging from normal liver to cirrhosis reported in around 1-2% of chronically infected adolescents and children including decompensation^{5,6,34,35,38,46,52-63} and a few case reports of HCC.⁶⁴ While children as young as three years old and as early as one year after infection have been identified with advanced liver disease and decompensated cirrhosis,^{34,54,55,58} 80% of the subjects enrolled in the two paediatric studies with the longest follow-up had normal liver biopsies over two to three decades of follow-up.^{37,46} However, evidence of disease progression is much higher in those with longer follow-up and duration of infection, and is more likely 10 years after the onset of infection.^{10,59,64} In the recent analysis of the UK cohort, cirrhosis developed in one-third of those infected in childhood, and the median time to diagnosis was 33 years (range 12-53), independent of the age or route of acquisition.³¹ Some studies have shown that the extent of fibrosis correlated closely with the severity of histological necroinflammation^{42,54,56,57,61}, age^{35,55,58,61} and duration of infection,^{57,58,60,62} indicating slower progression in young children compared to those infected late in life. However, these associations have not been confirmed in other studies.^{38,54} Heterogeneity in the characteristics of the studied populations (age, mode of acquisition, duration of infection) and duration of follow-up explain many of the differences.⁵³ More rapid disease progression occurs in adults also due to the presence of additional risk factors and co-morbidities such as alcohol consumption and HIV co-infection. In

adolescents and children, comorbid conditions such as haematological diseases with iron overload, obesity, cancer and viral co-infections (HIV and hepatitis B virus) may also accelerate the development of hepatic fibrosis.⁵³⁻⁵⁵ Impact on quality of life and cognitive functioning has been reported.^{65,66} In contrast to adults, HCV-related extrahepatic manifestations have not been systematically studied in children but are less common. There are several small studies and case reports suggesting an association between chronic HCV infection and thyroid disease,⁶⁷ membranoproliferative glomerulonephritis⁶⁸, cryoglobulinemia⁶⁴, myopathy and opsoclonus-myoclonus syndrome.⁶⁹ Impairment of both psychosocial and cognitive functioning have been reported even in asymptomatic HCV infected children compared to non-infected peers.^{65,66}

Prevention

In the absence of a vaccine for hepatitis C to prevent new or re-infection, strategies to prevent HCV transmission among adults are focused on a comprehensive package of harm reduction interventions in PWIDs, 100% safe blood transfusions, and avoidance of unnecessary and unsafe injections or practices to prevent health-care associated transmissions, alongside widespread treatment scale-up which will reduce prevalence of viraemia and thus transmission, especially in high-risk populations such as persons who inject drugs.

In adolescents and children the major targets for prevention of HCV transmission are interruption of vertical transmission¹⁸ and transmission associated with unsafe injections. WHO guidelines advise that information on risk factors for HCV infection should be communicated to pregnant women, and if present, or in high endemic settings, testing for HCV should be considered alongside testing for HIV and HBV.⁷⁰ A systematic review of 18 observational studies showed that no interventions – including Caesarean delivery and avoidance of breastfeeding - significantly reduced the risk of vertical HCV transmission.⁷⁰ However, both the US Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynaecologists recommend that obstetric care providers avoid internal foetal monitoring, prolonged rupture of membranes, and episiotomy in managing

labour in HCV-positive women in order to avoid the contact between maternal HCV-infected blood and the neonate.⁷¹ Effective antiretroviral treatment in pregnant women with HIV-HCV coinfection appears to be associated with a reduced risk of HCV as well as HIV vertical transmission.^{15,20} Pre-emptive treatment and cure of HCV-infected women before they become pregnant is one strategy to prevent vertical transmission, but requires maternal diagnosis prior to becoming pregnant. Although DAA therapy has not yet been approved for use in pregnant or breastfeeding women, the “double dividend” of curing both maternal HCV infection and preventing vertical transmission is compelling. A Phase I pharmacokinetic and safety trial is currently ongoing to evaluate ledipasvir/sofosbuvir use in pregnancy (ClinicalTrials.gov Identifier: NCT02683005). Adolescents, with high-risk sexual or drug use behaviours should be linked with appropriate counselling and harm reduction services.

Diagnosis, staging and monitoring

Diagnosis of HCV infection across all age groups consists of initial screening for evidence of past or current HCV infection with an HCV serological assay (antibody or antibody/antigen) using either rapid diagnostic test (RDT) or laboratory-based immunoassay formats that meet minimum safety, quality and performance standards (with regard to both analytical and clinical sensitivity and specificity), followed by nucleic acid testing for HCV RNA (either quantitative or qualitative) to confirm the presence of HCV viraemia.⁷² With the regulatory approval and recommendation in international guidelines of pan-genotypic DAA regimens,⁷³ WHO guidelines no longer recommend genotyping to guide treatment in adults but may still be required for children, until pan-genotypic combinations are approved for use in children.

As transplacental maternal antibodies may persist until around 18 months of age, HCV infection in infants and children < 18 months of age can only be confirmed by detection of HCV RNA. In both the 2017 WHO viral hepatitis testing guidelines,⁷² and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosis and management of hepatitis C infection in infants, children, and adolescents,⁷⁴ serological testing in children was recommended

only after 18 months. However, as spontaneous clearance following vertical transmission may continue to occur up to four years of age,^{5,6,33} confirmation of chronic viraemic infection may be postponed until after this age.

WHO has provided guidance on approaches to testing in children and adolescents.⁷² As for adults, WHO recommends testing of high-risk adolescents, but also adults, adolescents and children with a clinical suspicion of chronic viral hepatitis (i.e. symptoms, signs, laboratory markers), and children of infected mothers.⁷²

Staging of liver disease

Although liver biopsy was previously the reference method for grading necroinflammatory activity and staging of fibrosis in adults, this has now been widely replaced by non-invasive methods using both serological markers (aspartate aminotransferase-to-platelet ratio index, fibrosis-4 and FibroTest) and transient elastography (TE) as recommended by key professional and international guidelines.^{73,75-77}

To date, there has been limited evaluation and validation of the use of these non-invasive methods for staging of liver fibrosis in children or adolescents. Five studies have evaluated the role of TE in 140 children with chronic HCV infection,^{41,78-81} although a formal comparison with liver biopsy results was only available in a subset of 58 children, which demonstrated that TE was reliable in distinguishing different stages of liver fibrosis in paediatric patients with HCV infection. Two of these studies, including children with autoimmune hepatitis, non-alcoholic fatty liver disease, liver transplantation and viral hepatitis reported sensitivity and specificity values for detection of fibrosis >F2 of 72% and 76%⁸⁰ and >F3 of 79% and 83%,⁸¹ respectively. Although use of non-invasive methods in routine clinical practice in children is not yet recommended formally in professional society guidelines⁸² their use can be considered pending completion of studies on performance.

Antiviral Treatment and Indications for Treatment

The development of highly effective short duration oral DAA regimens (as short as eight weeks) has transformed the treatment of HCV, resulting in cure rates generally higher than 90%, few serious adverse events and many with pan-genotypic indications.

As of December 2017, ten DAAs have been approved for use in adults as part of multi-drug regimens (daclatasvir, elbasvir grazoprevir, glecaprevir/pibrentasvir, ombitasvir paritaprevir ritonavir, ombitasvir paritaprevir ritonavir dasabuvir, simeprevir, sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir). Four guidelines from either WHO or professional societies now recommend preferred pan-genotypic regimens and alternative DAA regimens for use in all treatment naïve and experienced HCV infected persons, regardless of age, gender, fibrosis stage, risk group or HIV coinfection.^{73,75-77}

The approval by the Food and Drug Administration (FDA) in April 2017 and European Medicines Agency (EMA) in June/July 2017 of the use of a fixed-dose combination sofosbuvir/ledipasvir for genotype 1, 4, 5 and 6 infected adolescents aged 12-17 years-old or ≥ 35 kg, and sofosbuvir/ribavirin for those infected with HCV genotype 2 or 3 was based on two studies (Table B, Appendix).^{8,9} In the first study, 100 GT1 HCV-infected treatment-naïve and -experienced adolescents were treated with sofosbuvir/ledipasvir (400 mg/ 90 mg) as a single tablet once daily for 12 weeks.⁸ The sustained virological response (SVR) was 98% with good tolerability and satisfactory pharmacokinetic profiles. The excellent efficacy (SVR12 99%) and safety profile of this regimen was confirmed in two further Egyptian studies enrolling 184 adolescents with HCV genotype 4 infection.^{83,84} Sofosbuvir and weight-based ribavirin was studied for 12 weeks in 52 adolescents with genotype 2 or 3 infection.⁹ SVR rates were 100% (13/13) in genotype 2 and 97% (38/39) in genotype 3 patients. No serious adverse effects leading to treatment discontinuation or significant abnormalities in laboratory results were reported⁹. Significant improvements in social functioning and school performance domains following attainment of SVR were shown in adolescents receiving DAA.^{85,86} Similar high SVR rates

and good tolerability have been reported in preliminary analyses from studies of other DAA regimen (sofosbuvir-daclatasvir,⁸⁷⁻⁹⁰ ombitasvir-paritaprevir-ritonavir ± dasabuvir ± ribavirin¹⁰ and glecaprevir/pibrentasvir⁹¹) that include both cirrhotic and non-cirrhotic adolescents. Of note, use of ribavirin in neither the sofosbuvir-ribavirin and ombitasvir-paritaprevir-ritonavir ± dasabuvir ± ribavirin¹⁰ trials were associated with significant laboratory adverse events.^{9 10} Table 1 summarises ongoing clinical trials for adolescents (12-17 years) and children 6 to 12 years using other DAA regimens, in particular sofosbuvir/velpatasvir.

Currently the only approved treatment for children younger than 12 years is 24 to 48 weekly injections of PEG IFN α -2a or -2b with twice-daily ribavirin, according to HCV genotype.⁸² Overall, there have been eleven clinical trials (1 randomized and 10 open-label) on the use of pegylated interferon (PEG IFN) in adolescents and children less than 12 years.⁹²⁻¹⁰² In genotype 1, the SVR of PEG IFN and ribavirin was suboptimal compared to DAA, with an SVR of only 52% in those with HCV genotype 1 and 4, but 89% in genotypes 2 and 3.^{82,103} PEG IFN and ribavirin are associated with significant side effects during treatment, and potentially irreversible after-therapy side effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and growth impairment.⁹²⁻¹⁰² In clinical practice, IFN treatment has been mainly limited to the few children with persistently elevated serum aminotransferases, progressive liver disease (i.e. fibrosis on liver histology) or HIV coinfection,¹⁰⁴ while for most children, follow up without treatment until adulthood has been preferred.⁷⁴

There are now recently completed studies of 200/45 mg fixed dose combination of sofosbuvir/ledipasvir in treatment-naïve or experienced children ages 6 to 11 years infected with HCV genotypes 1, 3 and 4^{83,105} and of sofosbuvir plus ribavirin in treatment-naïve or experienced children ages 3 to 11 years for genotypes 2 and 3¹⁰⁶. In the sofosbuvir/ledipasvir registration trial¹⁰⁵ SVR12 was 99% (89/90); two patients with genotype 3 were treated with 24 weeks of sofosbuvir/ledipasvir and ribavirin, and all achieved SVR.¹⁰⁵ Treatment was well-tolerated, adverse events were mild to moderate, and none led to any treatment discontinuations.¹⁰⁵ There were no ribavirin-related adverse

events in the two children enrolled in this trial.¹⁰⁵ Recently, in a pilot prospective study, 20 Egyptian children, aged from 6- to 12- years, were treated with sofosbuvir/ledipasvir (200/45 mg) once daily for 12 weeks. SVR12 rate was 95% (19/20; 95% CI: 76.4%-99.1%).¹⁰⁷ Data on the pharmacokinetics of 200mg once daily sofosbuvir plus ribavirin in 12 children aged 6 to 11 years old, showed comparable plasma exposures of sofosbuvir to adults.¹⁰⁸ In the sofosbuvir plus ribavirin registration trial the SVR12 rate among patients 6 to <12 years old was 100% (41/41), and among the 3 to <6 years old was 92% (12/13).¹⁰⁶

It is anticipated that other key DAA studies will be completed in children aged 6 to 11 years during 2018 with anticipated regulatory approval in 2019.¹⁰⁹ The anticipated dates of completion of the trials of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin (NCT02486406), glecaprevir/pibrentasvir (NCT03067129) and sofosbuvir/velpatasvir (NCT 03022981) trials are September and December 2019, respectively. There is a relatively small number of adolescents and children diagnosed with chronic HCV infection available for recruitment into clinical studies in high income countries, and a need for more pro-active case finding and enrolment also from LMICs to accelerate completion. Table 1 summarises ongoing clinical trials for adolescents (12-17 years) and children (3 to 11 years) using other DAA regimens.

Criteria for treatment in children have been recently revised by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN),⁸² the American Association for the Study of Liver Disease – Infectious Disease Society of America (AASLD-IDSAs)⁷⁶ and WHO⁷³ (Table 2). The current recommendation is to defer treatment until oral DAA regimens are approved for use across age groups given the overall low efficacy, prolonged treatment duration and significant side effects of IFN-based treatments; the generally low morbidity of chronic HCV in children less than 12 years; and the anticipated approval of more DAAs within the next 12 to 18 months.^{73,76,82} It is anticipated that in due course recommendations for use of pan-genotypic DAA regimens can be harmonised between adults, adolescents and children simplifying procurement in LMICs and reducing

fragmentation of what is already a low volume market in children. Once DAAs are approved in children 3 to 12 years, treatment with DAAs may then be considered for all children to eradicate the infection as early as possible, irrespective of liver disease stage and rate of disease progression. This offers the opportunity for children to grow up free of potential stigma and psychological consequences of a chronic transmissible infection.

Testing and service delivery

The expansion of DAA treatment to adolescents and children requires a concomitant expansion of testing and diagnosis in these populations. To increase case finding in adolescents and children, the 2017 WHO viral hepatitis testing guidelines recommend routine testing of all children born to HCV-infected mothers (requiring in turn more systematic screening of pregnant women and those of child-bearing age), as well as those adolescents and children with a clinical suspicion of chronic viral hepatitis, based on clinical symptoms, signs, abnormal serum aminotransferases or ultrasound.⁷² This approach will require additional advocacy as in some countries access to treatment still remains restricted to those with the most advanced disease. Other considerations for implementation include ensuring access to adolescent-friendly testing and treatment services, and recognition that the age of consent for testing varies across countries, which can pose barriers to adolescents' access to services.

Conclusions, research agenda and future strategies

The main focus of the global hepatitis response to date has been on treatment and prevention in the adult population who bear the greatest burden of morbidity and mortality. However, to achieve the goal of the global strategy for elimination of HCV infection as a public health threat³ inclusion of all affected populations, including children and adolescents is required. If adolescents and children are to benefit from the attention and momentum around global, regional and national strategies towards elimination of HCV infection, there is a need to both address critical evidence gaps in prevention,

treatment and management to inform policy and management guidelines, and overcome challenges in implementation and scale-up.

Key actions to address the current policy gaps and achieve treatment scale-up comparable to that in adults include the inclusion of children and adolescents in national hepatitis strategies and policies; the establishment of a testing and treatment access campaign targeted at children and adolescents; and fast-track evaluation of pan-genotypic regimens and accelerated approval of paediatric formulations. An opportunity for accelerated evaluation and approval of paediatric formulations for DAA regimens is provided by the increasing reliance that stringent regulatory authorities (i.e. US FDA and EMA) now place on extrapolation from adult efficacy trials paired with safety and dose finding Phase I/II clinical studies of 30–40 children.¹¹⁰

Key evidence gaps and research needs were also identified: **Treatment:** (i) Evaluation of effectiveness and safety of pan-genotypic DAA regimens, including sofosbuvir and velpatasvir and sofosbuvir and daclatasvir in adolescents and children, supported by key pharmacokinetic and drug interaction studies to guide development of paediatric formulations in younger children. (ii) Establishment of registries of treated and cured children and adolescents with long-term follow-up to confirm non-progression of liver disease. **Prevention:** (i) Evaluation of the safety and effectiveness of DAAs in pregnancy to reduce vertical transmission, and cure of the infected mother. Continued research on the development of effective HCV vaccine. **Seroprevalence and burden:** Age stratified sero-surveys of HCV antibody prevalence and HCV viraemia in different populations of children and adolescents (high risk and general population) with estimates of burden, morbidity and treatment need by region. There is a need for inclusion of children and adolescents into routine national data collection and global reporting tool on viral hepatitis cascade. **Diagnosis and assessment:** Evaluation of diagnostic performance of serological assays (RDTs and immunoassays) and validation of use of non-invasive tests (e.g. both blood-based assays and transient elastography) for staging of liver disease in children and adolescents.

To date, the few paediatric studies that have been published were conducted primarily in a few high-income countries. The paediatric research agenda would benefit from the establishment of new international collaborations, consortia and cohorts of HCV-infected children to inform best practices for the management, care and treatment of children living with HCV infection in high burden settings. There is also a need to ensure inclusion of recommendations for testing and treatment for children in national policies. Finally, global efforts are underway to accelerate paediatric formulations development and introduction.¹¹⁰ These efforts rely on more coordinated and better funded actions by policy-makers, researchers, industry, regulators and other relevant-stakeholders.

Author's contribution

PE, MP, CG and GI conceived the project. GI and PE wrote the first and subsequent drafts of the article. All the authors revised the paper critically, approved the final version to be published and agreed 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. All authors contributed to the final version of the review before submission.

Declaration of interests

GD reports grants and personal fees from Gilead Sciences, personal fees from Abbvie, personal fees from Merck (MSD), outside the submitted work. MJ reports grants from Gilead Sciences, grants from AbbVie, grants from Merck (MSD), during the conduct of the study; grants from Bristol Myers Squibb, grants from Roche/Genentech, other from Gilead Sciences, non-financial support from Echosens, outside the submitted work. CT reports grants from ViiV Healthcare via PENTA Foundation, personal fees from ViiV Healthcare, outside the submitted work. The other authors declared no conflicts of interest.

Legend

Figure 1. Burden of HCV viraemia in children and adolescents in most affected countries (reproduced with permission of professor Manal El-Sayed)⁴

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Table 1. Ongoing clinical trials of direct acting antivirals regimens for hepatitis C virus infected, treatment-naïve and –experienced adolescents (aged 12 to 17 years) and children (aged less than 12 years)

Drugs (ClinicalTrials.gov Identifier)	HCV genotypes	Status	Ages (years)	Estimated enrolment	Countries	Dose	Duration	Estimated Study Completion Date
Ledipasvir/sofosbuvir (fixed dose combination) ± ribavirin (NCT02249182)	1; 4; 5; 6; 3*	Enrolment completed	3-17	200	US, New Zealand, Australia, UK	12 to < 18 years, ≥ 45 kg: 90 mg/400 mg 3 to 6 years, ≥ 17 Kg or 7 to 12, < 45 Kg: 45/200 mg 3 to 6 years, < 17 Kg: 33.7/150 mg	Genotypes 1,4-6: Treatment naïve with or without cirrhosis and treatment-experienced without cirrhosis - 12 weeks; Treatment experienced with cirrhosis - 24 weeks Genotype 3: Treatment-experienced with or without cirrhosis - 24 weeks + ribavirin	August 2018
Sofosbuvir + ribavirin (NCT02175758)	2; 3	Active, not recruiting	3-17	104	US, Australia, Belgium, Germany, Italy, New Zealand, Russia, UK	12 to 17 years: 400mg sofosbuvir, 6 to 11 years: 200 mg sofosbuvir 3 to 5 years, ≥ 17kg: 200 mg; < 17 Kg 150 mg (all groups: + weight-based ribavirin)	Genotype 2: 12 weeks Genotype 3: 24 weeks	September 2018
Ombitasvir-paritaprevir-ritonavir ± dasabuvir ± ribavirin (NCT02486406)	1, 4	Enrolment completed	3-17	74	US, Belgium, Canada, Germany, Puerto Rico, Spain, Switzerland, UK	unknown	Genotypes 1b and 4: 12 weeks; Genotype 1a, with compensated cirrhosis: 24 weeks Genotype 1a without cirrhosis: 12 weeks	
Ledipasvir/sofosbuvir (fixed dose combination) (NCT02868242) **	1, 4	Recruiting	12-17	40	Egypt	90/400 mg	12 weeks	April 2019
Sofosbuvir-daclatasvir (NCT03080415)	4				Egypt	>45 Kg: 400/60 mg; <45 Kg 200/30	12 weeks	May 2018 (completed)
Glecaprevir/pibrentasvir (NCT03067129)	1-6	Recruiting	3-11	110	US, Puerto Rico	12-<18: 300mg/120mg GLE/PIB daily 9-<12 6-<93-<6 Paediatric formulation	8, 12, or 16 weeks depending on genotype, cirrhosis status and prior treatment experience	September 2019

Sofosbuvir/Velpatasvir (NCT03022981)	1-6?	Recruiting	3-17	200	US, Belgium, Italy, UK	12-<18 years: 400/100 sofosbuvir /velpatasvir FDC 6-<12: dose TBD 3-<6: dose TBD	12 weeks, including PK lead- in (7 days)	December 2019
Elbasvir/Grazoprevir (NCT03379506)	1, 4	Recruiting	3-17	56	US, Germany, Poland, Sweden	12-<18 years: 50 mg/100 mg 6-<12: dose TBD 3-<6: dose TBD	12 weeks	June 2020
Gratsovir (sofosbuvir) + Ribavirin (NCT02985281)	1-6?	Enrolling by invitation	10-18	41	Egypt	sofosbuvir : 20-29.9kg: 200mg daily, 30-39.9kg: 1.5 tab 200mg daily, >40kg: 2 tab 200mg daily All groups: sofosbuvir + ribavirin weight- based dosing 15mg/kg/daily	Arm 1: 24 weeks Arm 2: Participants with undetectable HCV RNA after 2 weeks - 16 weeks, rest will complete 24 weeks	September 2017 (last update December 2016)

Table 2. Comparison of the recommendations for treatment of chronic hepatitis C virus infection in children and adolescents from four international guidelines AASLD⁷⁶, EASL⁷⁵, WHO⁷³, APASL⁷⁷ and ESPGHAN⁸²

Guideline	Recommendations for adolescents
AASLD⁷⁶	<ul style="list-style-type: none"> • treatment is recommended for all HCV-infected children older than 3 years as they will benefit from antiviral therapy, independent of disease severity • treatment of children aged 3 to 11 years with chronic hepatitis C should be deferred until interferon-free regimens are available • ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks for patients with genotype 1, treatment-naïve without cirrhosis or with compensated cirrhosis, or treatment-experienced without cirrhosis • ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks for patients with genotype 1 who are treatment-experienced with compensated cirrhosis • sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks for patients with genotype 2 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis • sofosbuvir (400 mg) plus weight-based ribavirin for 24 weeks for patients with genotype 3 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis • ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks for patients with genotype 4, 5, or 6 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis
EASL⁷⁵	<ul style="list-style-type: none"> • adolescents aged 12 years and above infected with genotype 1, 4, 5 or 6 who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks • adolescents aged 12 years and above infected with genotype 2 or 3 who are treatment-naïve or treatment experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with other regimens approved for adults, with caution pending more safety data in this population • in children younger than 12 years, treatment should be deferred until DAAs, including pangenotypic regimens, are approved for this age group
WHO⁷³	<ul style="list-style-type: none"> • it is recommended to offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage • ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks for patients with genotype 1, 4, 5 and 6 • sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks for patients with genotype 2 • sofosbuvir (400 mg) plus weight-based ribavirin for 24 weeks for patients with genotype 3
APASL⁷⁷	<ul style="list-style-type: none"> • no recommendation
ESPGHAN⁸²	<ul style="list-style-type: none"> • it is recommended that all treatment-naïve and treatment-experienced children with chronic HCV infection are considered for therapy • treatment can be generally deferred in age-cohorts where combined pegylated interferon and ribavirin is the only treatment option • it is recommended that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 1 or 4, are treated with the combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with a single tablet administered once daily for 12 weeks. The recommended duration of therapy for treatment-experienced children with HCV genotype 1 infection and with compensated cirrhosis is 24 weeks • it is recommended that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 2 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg in 2 divided doses) for 12 weeks (C1) • it is recommended that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 3 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg in 2 divided doses) for 24 weeks

Legend: AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of Liver; WHO, World Health Organization; APASL, Asian Pacific Association for the Study of Liver; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition.