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Hepatitis C virus infection in children and adolescents

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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 transformed treatment for HCV infection. Since the 2016 launch 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 the treatment of adults, who bear the greatest burden of morbidity and mortality of HCV-related chronic liver disease. Compared with adults, there has been little attention paid to addressing the response to HCV in children and adolescents, in part because of the scarcity of data to inform specific paediatric management practices and policy. In this Series paper, we summarise knowledge on the epidemiology, natural history, and treatment of chronic HCV infection in adolescents and children, and we highlight key differences from infection acquired in adulthood. The estimated global prevalence and burden of HCV infection in children aged 1–19 years is 0·15%, corresponding to 3·5 million people (95% CI 3·1–3·9 million). HCV infection is usually asymptomatic during childhood, and cirrhosis and hepatocellular carcinoma are rare. Sofosbuvir with ledipasvir and sofosbuvir with ribavirin have received regulatory approval and guidelines recommend their use in adolescents aged 12 years and older with HCV infection. In April, 2019, glecaprevir with pibrentasvir also received regulatory approval for adolescents aged 12–17 years. Key actions to address the current policy gaps and achieve treatment scale-up that is comparable to that in adults include: establishment of a campaign on access to testing and treatment that is 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 prevalence studies of HCV viraemia in priority countries; further validation of non-invasive tests for staging of liver disease in children; and establishment of paediatric treatment registries and international consortia to promote collaborative research agendas.

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,[2] mainly from cirrhosis or hepatocellular carcinoma.[1,2] In addition, there were approximately 1·75 million new infections per year.[2] In 2016, the WHO global health sector strategy on viral hepatitis 2016–21 outlined global targets and priority actions for countries to achieve the goal of eliminating viral hepatitis as a public health threat by 2030.[3] Elimination was defined as a 65% reduction in mortality and a 90% reduction in the incidence of chronic infections. There has been considerable progress in improving access to curative, direct-acting antiviral treatment because of substantial cost reductions of generic medicines. By the end of 2016, approximately 3 million adults had been treated. However, achieving the global targets for mortality reduction will require a substantial scale-up in testing and treatment, because WHO estimates that less than 20% of people who are chronically infected with HCV have been diagnosed, and in 2015, less than 10% of people diagnosed with chronic HCV infection were treated. The predominant focus of the global HCV response has been on the adult population, which bears the greatest burden of morbidity and mortality caused by chronic liver disease. Compared with adults, little attention has been paid to testing, treatment, and preventive strategies among children and adolescents, in part because until 2017 none of the direct-acting antiviral regimens had been approved for use in people younger than 18 years, and there were major gaps in the evidence to inform paediatric management practices and policies. For example, since 2015 there has only been one systematic review of the prevalence of paediatric HCV infection,[4,5] and to date, only three moderately sized prospective studies with long-term follow-up[6–8] have examined the long-term natural history and the risk of complications in children with perinatal HCV acquisition. Although more than eight different direct-acting antiviral combinations are available for treatment in adults, to date only three direct-acting antiviral regimens (sofosbuvir plus ribavirin, sofosbuvir-ledipasvir, and glecaprevir-pibrentasvir) have been approved for HCV treatment in adolescents.[9–11] Very few countries have included recommendations for systematic testing and treatment of adolescents and children in their national policies. As a result, only a small proportion of children or adolescents with HCV infection globally have been diagnosed or treated, especially in low-income and middle-income countries.

The objective of this Series paper is to provide a comprehensive overview of the epidemiology, natural history, and treatment of HCV infection in children and adolescents, and to highlight key differences and similarities with HCV infection in adults. We conclude with key priorities for action, which include addressing critical evidence gaps to inform future policy development

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This is the second in a Series of two papers about viral hepatitis in children and adolescents

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in children, and strategies to promote the scale-up of testing and treatment.

Prevalence and burden

Global estimates of HCV prevalence, burden, morbidity, and mortality are largely based on data from the adult population.[2] WHO estimated that in 2015, there were approximately 71 million people (95% uncertainty interval 64–103 million, or 1% of the global population) living with chronic HCV,[2] with the highest prevalence in the eastern Mediterranean region (2·3%), followed by the European region (1·5%) and the African region (1%).[2] The estimated HIV-HCV antibody co-infection prevalence among people with HIV is 6·2% (IQR 3·4–11·9) or 2·3 million cases (IQR 1·3–4·3 million), of which approximately half are people who inject drugs.[12]

The prevalence and burden of HCV infection in children and adolescents are less well understood than they are in adults. Historical reports from small, hospital-based cohorts found prevalence of HCV infection of up to 20% among adolescents and children who had been treated in hospital for malignancy or renal failure, or who had had haemodialysis, or surgery of any type.[13] A systematic review updated in 2016[4,5] (as yet unpublished) of the prevalence of HCV viraemia in children and adolescents aged 1–19 years, based on studies from 102 countries, estimated a 0·3% prevalence in high-income countries and a 0·6% prevalence in low-income countries, with an overall burden of 3·5 million cases (95% CI 3·1–3·9 million) or 0·15% of the global population (figure).[4,5] The 19 countries shown in the figure accounted for 80% of infections worldwide. Data were sparse, based on outdated studies, or missing, even from western Europe and the USA, and were too limited to generate regional prevalence estimates. As a result, the true prevalence of HCV in adolescents and children might be underestimated in some countries.[14] Data from the USA show an increasing HCV prevalence in adolescents, which has been linked to the opioid epidemic and increasing rates of HCV infection in women of reproductive age.[15] HIV-HCV co-infection in children now appears to be rare, because HIV vertical transmission rates have declined worldwide.[16]

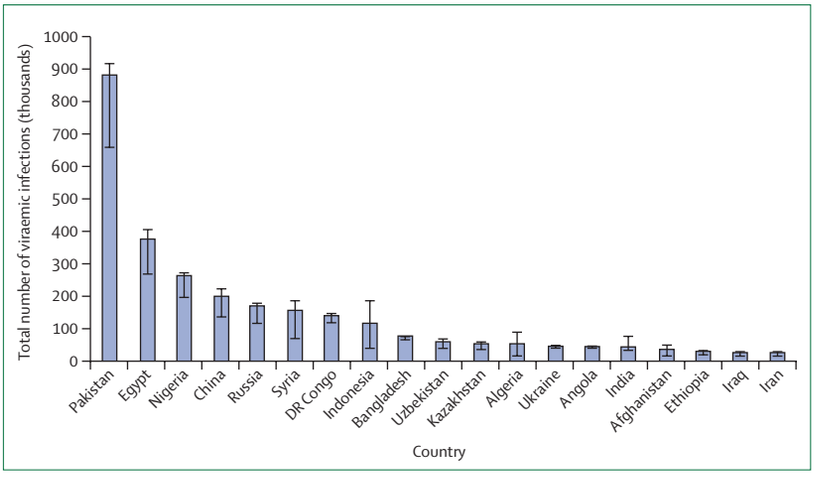

Figure: **Burden of chronic hepatitis C infection in children and adolescents in the 19 most affected countries**
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Routes of transmission

In many middle-income and high-income countries, injection drug use accounts for a large number of HCV infections, particularly in settings where sharing needles and syringes remains common and access to harm reduction is scarce. Sexual transmission of HCV has mainly been reported in men who have sex with men,[12] including people who are infected with HIV and people who are taking pre-exposure prophylaxis for HIV,[17] with several outbreaks among men who have sex with men in Europe, Australia, and the USA.[18] By contrast, in low-income and some middle-income countries, HCV infection in adults, adolescents, and children is most commonly associated with unsafe injection practices, and inadequate infection control practices in health-care facilities, such as in renal dialysis units.[2]

Since the introduction of routine screening for HCV infection in blood transfusion services, vertical transmission is now the principal route of HCV acquisition among children,[19] with a transmission rate of about 5% from mothers with HCV monoinfection, and about 10% from mothers with HIV-HCV co-infection.[20] The transmission rate is increased with a higher maternal HCV viral load, longer labour duration, use of amniocentesis or fetal scalp monitoring, and prolonged rupture of membranes.[19–21] The scarcity of serosurvey data from antenatal clinics has precluded the generation of reliable estimates of new infections from vertical transmission in children. In low-income settings, iatrogenic transmission and exposure to unsafe medical interventions also contribute to transmission, especially among children with malignancy or renal failure requiring haemodialysis, or who have surgery.[13] Horizontal and intrafamilial transmission is generally considered to play a minor role in HCV acquisition.[22] In high-income countries, especially the USA, the number of reports of adolescents acquiring HCV (and HIV) infection through injection drug use is increasing.[23,24] This finding highlights the need to monitor trends in adolescents closely, and to ensure that barriers to harm reduction services faced by adolescents are addressed.[23,24] Adolescents are also at risk of infection through high-risk sexual practices, especially among men who have sex with men, and through tattooing in unregulated settings.[18,25]

Natural history of hepatitis C infection

The natural history of HCV infection in adults has been ascertained through several large prospective studies.[26,27] Spontaneous clearance of acute HCV infection generally occurs within 6 months of infection in around 30% (range

15–45%) of cases, in the absence of treatment.[28] Overall, the 20-year cumulative incidence of developing cirrhosis is 15–30%,[26,27] and the risk of hepatocellular carcinoma is 2–4% per year in people with cirrhosis.[29] Extrahepatic manifestations are reported in up to 74% of adults with HCV infection,[30] the most common of which are diabetes mellitus (15% of adults with HCV infection) and chronic renal disease (10% of adults with HCV infection).[13]

Key studies on the natural history of HCV infection in adolescents and children are summarised in the appendix (pp 1–3). Although there have been several large and long-term cohort studies in adults, there have only been two moderate-sized (>100 patients) prospective studies with long-term follow-up (>4 years) in children and adolescents.[6,7] One study of 504 Italian children and adolescents had a mean follow-up of 5·9 years (SD 3·8) after recruitment, and 10·6 years (SD 6·0) after the putative time of infection.[6] The European Paediatric HCV Network multicentre prospective study of 266 children born to women with HCV infection had a median follow-up of 4·2 years (range 3·2–15·9).[7] There have also been three other large observational studies with long-term follow-up: a cohort of 113 patients from the USA who were HCV-seropositive and had paediatric cancer, who were followed up for a median of 30 years (IQR 28–36) after cancer diagnosis;[31] a national cohort of 348 children from Japan who were followed up for 30 years;[8] and a UK cohort of 1049 people who were infected with HCV in childhood, of whom 53% were infected through injection drug use in adolescence, and 24% were infected through receipt of contaminated blood products.[32] There have also been several other smaller prospective[33,34] and retrospective cohorts and case studies.[35–45]

After vertical acquisition of HCV, between 25% and 40% of infected children spontaneously clear the infection in the first 4 years of life,[6,7,34] which is slightly higher than the rate that is reported in adults. A further 6–12% of children with chronic HCV infection are expected to clear the virus before adulthood,[39,46,47] whereas the remainder will develop chronic infection that persists into adulthood. The spontaneous clearance rate of vertically acquired HCV infection is affected by host factors, such as the *IL28B* gene (the rs12979860 single nucleotide polymorphism located on chromosome 19),[48,49] and natural killer cell cytolytic function,[50] as well as by viral characteristics, such as HCV genotype.[34]

Chronic HCV infection is usually asymptomatic during childhood,[6,7,39,51] and tends to have a more indolent course than that in adults.[51] For 25 (10%) of 266 children in the European Paediatric HCV Network study,[7] hepatomegaly was the only clinical finding, but almost 50% of the patients had a persistently abnormal alanine aminotransferase concentration during follow-up. The histological course of chronic HCV infection in adolescents and children is unpredictable. Although patients can have a normal liver on histology, cirrhosis is reported in around 1–2% of chronically infected adolescents and children, including decompensation[6,7,35,36,39,47,51–62] and a few case reports of hepatocellular carcinoma.[63] Advanced liver disease and decompensated cirrhosis have been identified in children as young as 3 years old and as early as 1 year after infection,[35,53,54,57] although 80% of the individuals enrolled in two paediatric studies with long-term follow-up had normal liver biopsies over two to three decades of follow-up.[36,47] However, evidence of disease progression is considerably increased in patients with longer follow-up and duration of infection, and progression is more likely 10 years after the onset of infection.[11,58,63] In an analysis of a UK cohort, cirrhosis developed in a third of patients who were infected in childhood, and the median time to diagnosis was 33 years (range 12–53), independent of the age or route of acquisition.[32] Some studies have shown that the extent of fibrosis is closely associated with the severity of histological necroinflammation,[43,53,55,56,60] the age of the patient,[36,54,57,60] and the duration of infection,[56,57,59,61] indicating slower progression in young children compared with those infected later in life. However, these associations have not been confirmed in other studies.[39,53] Heterogeneity in the characteristics of the studied populations (age, mode of acquisition, and duration of infection) and in the duration of follow-up explain many of the differences observed.[52] More rapid disease progression also occurs in adults because of the presence of additional risk factors and comorbidities, such as alcohol consumption and HIV co-infection. In adolescents and children, comorbidities, such as haematological diseases with iron overload, obesity, cancer, and viral co-infections (HIV and hepatitis B virus [HBV]) can also accelerate the development of hepatic fibrosis.[52–54] Negative effects of HCV infection on quality of life and cognitive functioning have been reported in children.[64,65] By contrast with adults, HCV-related extrahepatic manifestations have not been systematically studied in children, but they are less common. The findings of several small studies and case reports suggest an association between chronic HCV infection and thyroid disease,[66] membranoproliferative glomerulonephritis,[67] cryoglobulinaemia,[63] myopathy, and opsoclonus-myoclonus syndrome.[68] Impairment of both psychosocial and cognitive functioning have been reported even in asymptomatic children with HCV infection compared with non-infected peers.[64,65]

See Online for appendix

Prevention

In the absence of a vaccine to prevent new cases or re-infection of HCV, strategies to prevent HCV transmission among adults are focused on harm reduction interventions in people who inject drugs, safe blood transfusions, and avoidance of unnecessary or unsafe injections in health-care settings. These strategies run in parallel to widespread treatment scale-up that will reduce the prevalence of viraemia and therefore transmission, especially in high-risk populations, such as people who inject drugs.

In adolescents and children, the major targets for prevention of HCV transmission are vertical infection[19] and transmission associated with unsafe injections and health-care practices. WHO recommends that pregnant women with risk factors for HCV infection, and all pregnant women in high-endemic settings, should be tested for HCV alongside testing for HIV and HBV.[69] A systematic review of 18 observational studies showed that none of the observed interventions—including caesarean delivery and avoidance of breastfeeding—significantly reduced the risk of vertical HCV transmission.[69] Nevertheless, both the US Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy during labour in women who are HCV positive to avoid contact between maternal HCV-infected blood and the neonate.[70] Effective antiretroviral treatment in pregnant women with HIV-HCV co-infection appears to be associated with a reduced risk of HCV and HIV vertical transmission.[16,21] Although preemptive treatment and cure of women infected with HCV before they become pregnant would help to prevent vertical transmission, this strategy requires a diagnosis to be made before pregnancy. Direct-acting antiviral therapy has not yet been approved for use in pregnant or breastfeeding women, but it would have the compelling advantage of curing both maternal HCV infection and preventing vertical transmission. A phase 1 pharmacokinetic and safety trial (NCT02683005) is underway to evaluate ledipasvir-sofosbuvir use in pregnancy. To reduce transmission associated with high-risk sexual behaviours or drug use behaviours, adolescents should be given appropriate counselling and harm reduction services.

Diagnosis, staging, and monitoring

Diagnosis of HCV infection across all age groups consists of initial screening for past or current HCV infection with an HCV serological assay (antibody or antibody-antigen), using either a rapid diagnostic test or a laboratory-based immunoassay that meets minimum safety, quality, and performance standards (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.[71] Since the regulatory approval of pangenotypic direct-acting antiviral regimens and the recommendation of their use in international guidelines,[72] WHO guidelines no longer recommend genotyping to guide treatment in adults. However, genotyping might still be required for children until pangenotypic combinations are approved for use and are more widely available in this age group.

Because transplacental maternal antibodies can persist until around 18 months of age, HCV infection in infants and children younger than 18 months can only be confirmed by detection of HCV RNA. In guidelines from WHO[71] and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition,[73] serological testing in children is only recommended after 18 months. However, because HCV from vertical transmission could be spontaneously cleared up to the age of 4 years,[6,7,34] confirmation of chronic viraemic infection can be postponed until after this age.

Similar to the guidelines for HCV testing in adults, WHO recommends testing of high-risk adolescents (ie, those with a history of injecting drugs and men who have sex with men).[71] Testing is also recommended for adults, adolescents, and children with clinical suspicion of chronic viral hepatitis (ie, symptoms, signs, and laboratory markers that indicate infection), and for the children of infected mothers.[71]

Staging of liver disease

Although liver biopsy was previously the reference method for grading necroinflammatory activity and staging of fibrosis in adults, it has now been widely replaced by non-invasive methods with use of both serological markers (aspartate aminotransferase to platelet ratio index, Fibrosis 4 score, and FibroTest) and transient elastography, as recommended by key professional and international guidelines.[72,74–76]

Little evaluation has been done on the use of these non-invasive methods for staging of liver fibrosis in children or adolescents. Five studies have evaluated the role of transient elastography in 140 children with chronic HCV infection,[42,77–80] although a formal comparison with liver biopsy results was only available for a subset of 58 children. Transient elastography reliably distinguished between stages of liver fibrosis in children with HCV infection. Two of the studies,[79,80] which included children with autoimmune hepatitis, non-alcoholic fatty liver disease, liver transplantation, and viral hepatitis, found sensitivity and specificity values of 72% and 76%, respectively, for detection of fibrosis at stage F3 and higher,[79] and 79% and 83%, respectively, for detection of fibrosis at stage F4 and higher.[80] Although the use of non-invasive methods in routine clinical practice in children is not yet formally recommended in professional society guidelines,[73,81] their use can be considered pending the completion of studies on performance.

Antiviral treatment and indications for treatment

The development of highly effective, oral, direct-acting antiviral regimens (with durations as short as 8 weeks) has transformed the treatment of HCV, resulting in cure rates of more than 90% and few serious adverse events. Many of the newer regimens have pan-genotypic activity.

As of December, 2017, ten direct-acting antivirals had been approved for use in adults as part of multidrug regimens: daclatasvir, elbasvir-grazoprevir, glecaprevir-pibrentasvir, ombitasvir-paritaprevir-ritonavir, ombitasvir-paritaprevir-ritonavir-dasabuvir, simeprevir, sofosbuvir, sofosbuvir-ledipasvir, sofosbuvir-velpatasvir,

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and sofosuvir-velpatasvir-voxilaprevir. Guidelines from WHO and three professional societies recommend pangenotypic regimens as the preferred treatment for all treatment-naive and treatment-experienced people with HCV, regardless of age, sex, fibrosis stage, risk group, or HIV co-infection.[72,74–76]

The use of a fixed-dose combination of sofosbuvir-ledipasvir for adolescents (12–17 years old and ≥35 kg) infected with HCV genotype 1, 4, 5, or 6, and sofosbuvir plus ribavirin for adolescents infected with HCV genotype 2 or 3, was approved by the US Food and Drug Administration in April, 2017, and the European Medicines Agency in June, 2017, and July, 2017, on the basis of two studies (appendix pp 4–6).[9,10] In one study, 100 treatment-naive and treatment-experienced adolescents infected with genotype 1 HCV were given sofosbuvir-ledipasvir (400 mg sofosbuvir and 90 mg ledipasvir) as a single tablet once a day for 12 weeks.[9] The sustained virologic response 12 weeks after the end of treatment (SVR12) was 98%, with good tolerability and a satisfactory pharmacokinetic profile. The efficacy and safety profile of this regimen was confirmed in two Egyptian studies that enrolled a total of 184 adolescents with HCV genotype 4 infection (SVR12 99%).[82,83] Treatment with sofosbuvir and weight-based ribavirin was studied for 12 weeks in 52 adolescents with genotype 2 or 3 infection.[10] The SVR12 rates were 100% (13 of 13) in patients with HCV genotype 2 and 97% (38 of 39) in patients with HCV genotype 3. No serious adverse effects leading to treatment discontinuation or marked abnormalities in laboratory results were reported.[10] Substantial improvements in social functioning and school performance domains following attainment of a sustained virological response were shown in adolescents who received direct-acting antivirals.[84,85] In April, 2019, the pangenotypic fixed-dose combination of glecaprevir-pibrentasvir was approved by the European Medicines Agency for use in adolescents (12–17 years) infected with HCV, on the basis of the high SVR12 (100%; 47 of 47 patients) reported in the Dora study.[11] Similarly high SVR rates and good tolerability were reported in preliminary studies of other direct-acting antiviral regimens (ombitasvir-paritaprevir-ritonavir with or without dasabuvir and with or without ribavirin,[86] and sofosbuvir-daclatasvir[87–90]) that included adolescents with and without cirrhosis. In the sofosbuvir plus ribavirin trial[10] and the trial of ombitasvir-paritaprevir-ritonavir with or without dasabuvir and with or without ribavirin,[86] the use of ribavirin was not associated with any significant laboratory adverse events. Ongoing clinical trials for other direct-acting antiviral regimens in adolescents (12–17 years) and children (3–6 years and 6–11 years) are summarised in table 1.

The only approved treatment for children younger than 12 years is 24–48 weekly injections of peginterferon alfa-2a or peginterferon alfa-2b with twice-daily ribavirin, according to the HCV genotype (24 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4).[81] Overall, 11 clinical trials (one randomised and ten open-label, non-randomised) have been done on the use of peginterferon alfa in adolescents and children younger than 12 years.[91–101] In genotype 1 HCV, the SVR**12** of peginterferon alfa and ribavirin was worse than that for the direct-acting antiviral, with an SVR12 of only 52% in those with HCV genotype 1 and 4, and 89% in genotypes 2 and 3.[81,102] Peginterferon alfa and ribavirin are associated with prominent side-effects during treatment, and potentially irreversible long-term side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications, and growth impairment.[91–101] In clinical practice, interferon alfa treatment has been mainly restricted to the small number of children with persistently elevated serum aminotransferases, progressive liver disease (ie, fibrosis on liver histology), or HIV co-infection,[103] whereas for most children, follow-up without treatment until adulthood has been preferred.[73]

Studies have been done on a fixed-dose combination of sofosbuvir-ledipasvir in treatment-naive or treatment-experienced children aged 6–11 years and 3–5 years (200 mg of sofosbuvir and 45 mg of ledipasvir if weight is ≥17 kg, and 150 mg of sofobuvir and 33·75 mg of ledipasvir if weight is <17 kg) and infected with HCV genotypes 1, 3, and 4,[82,104,105] and on sofosbuvir plus ribavirin in treatment-naive or treatment-experienced children aged 3–11 years and infected with HCV genotypes 2 and 3.[106] In the sofosbuvir-ledipasvir registration trial,[104,105] SVR12 was 99% (89 of 90 patients) for children aged 6–11 years and 97% (33 of 34 patients) for children aged 3–5 years; two patients with genotype 3 were given 24 weeks of sofosbuvir-ledipasvir and ribavirin, at the end of which they had achieved a sustained virological response.[104,105] Only one 3-year-old patient discontinued treatment after 4 days because of abnormal drug taste and vomiting.[105] The treatment was well tolerated, with only mild to moderate adverse events.[104] There were no ribavirin-related adverse events in the two children who were given ribavirin.[104] Data on the pharmacokinetics of sofosbuvir-ledipasvir in 12 children aged 6–11 years,[107] and in 15 children aged 3–5 years,[108] showed similar plasma exposure of sofosbuvir and ledipasvir to that in adults. In a pilot prospective study,[109] 20 Egyptian children, aged 6–12 years, were given sofosbuvir-ledipasvir (200 mg of sofosbuvir and 45 mg of ledipasvir) once a day for 12 weeks. The SVR12 rate was 95% (19 of 20 patients; 95% CI 76·4–99·1). Data on the pharmacokinetics of sofosbuvir (200 mg once daily) plus ribavirin in 12 children aged 6–11 years showed similar plasma exposure of sofosbuvir to that in adults.[107] In the sofosbuvir plus ribavirin registration trial, the SVR12 rate among patients aged 6–11 years was 100% (41 of 41), and among patients aged 3–5 years old was 92% (12 of 13).[106]

Further studies on direct-acting antivirals are projected to be completed in children aged 6–11 years in 2019, with anticipated regulatory approval. According to ClincialTrials.gov, trials on ombitasvir-paritaprevir-ritonavir with or without dasabuvir and

	ClinicalTrials.gov number	HCV genotypes	Status	Ages (years)	Estimated number of patients enrolled	Countries	Doses	Treatment durations	Estimated study completion date
Sofosbuvir-ledipasvir (fixed-dose combination) with or without ribavirin	NCT02249182	1,3–6	Enrolment completed	3–17	200	USA, New Zealand, Australia, UK	12–17 years and ≥45 kg: 90 mg ledipasvir and 400 mg sofosbuvir; 3–6 years and ≥17 kg, or 7–12 years and <45 kg: 45 mg ledipasvir and 200 mg sofosbuvir; 3–6 years and <17 kg: 33·7 mg ledipasvir and 150·0 mg sofosbuvir	Genotypes 1 or 4–6, and treatment-naive with or without cirrhosis or treatment-experienced without cirrhosis: 12 weeks; genotypes 1 or 4–6, and treatment-experienced with cirrhosis: 24 weeks; genotype 3 and treatment-experienced with or without cirrhosis: 24 weeks plus ribavirin	August, 2018 (completed)
Sofosbuvir-ledipasvir (fixed-dose combination)	NCT02868242	1,4	Recruiting	12–17	40	Egypt	90 mg ledipasvir and 400 mg sofosbuvir	12 weeks	April, 2019
Sofosbuvir plus ribavirin	NCT02175758	2,3	Enrolment completed	3–17	104	USA, Australia, Belgium, Germany, Italy, New Zealand, Russia, UK	12–17 years: 400 mg sofosbuvir; 6–11 years: 200 mg sofosbuvir; 3–5 years and ≥17 kg: 200 mg sofosbuvir; 3–5 years and <17 kg: 150 mg sofosbuvir; plus weight-based ribavirin in all groups	Genotype 2: 12 weeks; genotype 3: 24 weeks	September, 2018 (completed)
Ombitasvir-paritaprevir-ritonavir with or without dasabuvir and with or without ribavirin	NCT02486406	1,4	Enrolment completed	3–17	74	USA, 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	November, 2020
Sofosbuvir-daclatasvir	NCT03080415	4	Enrolment completed	8–17	40	Egypt	>45 kg: 400 mg sofosbuvir and 60 mg daclatasvir; <45 kg: 200 mg sofosbuvir and 30 mg daclatasvir	12 weeks	May, 2018 (completed)
Glecaprevir-pibrentasvir	NCT03067129	1–6	Recruiting (12–17 years enrolment completed)	3–17	110	USA, Puerto Rico	12–17 years: 300 mg glecaprevir and 120 mg pibrentasvir daily; 3–11 years: paediatric formulation	8, 12, or 16 weeks depending on genotype, cirrhosis status, and prior treatment experience	August, 2022
Sofosbuvir-velpatasvir	NCT03022981	1–6	Recruiting (12–17 years enrolment completed)	3–17	200	USA, Belgium, Italy, UK	12–17 years: 400 mg sofosbuvir and 100 mg velpatasvir fixed-dose combination; 3–6 years and ≥17 kg or 7–12 years and <45 kg: 50 mg velpatasvir and 200 mg sofosbuvir; 3–6 years and <17 kg: 37·5 mg velpatasvir and 150 mg sofosbuvir	12 weeks, including pharmacokinetics lead-in phase (7 days)	January, 2020
Elbasvir-grazoprevir	NCT03379506	1,4	Recruiting	3–17	56	USA, Germany, Poland, Sweden	12–17 years: 50 mg elbasvir and 100 mg grazoprevir; 3–11 years: dose to be determined	12 weeks	June, 2020

HCV=hepatitis C virus. NCT02985281 is recorded in ClinicalTrials.gov but with no update since 2016.

Table 1: **Ongoing clinical trials of direct-acting antiviral regimens for adolescents and children infected with HCV**

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	Who to treat	Drug regimen
American Association for the Study of Liver Diseases[75]	Treatment is recommended for all children >3 years old who are infected with HCV because they will benefit from antiviral therapy regardless of disease severity Treatment of children aged 3–11 years with chronic HCV should be deferred until interferon-free regimens are available	Genotype 1: sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks for patients who are treatment-naive and without cirrhosis or with compensated cirrhosis, or who are treatment-experienced and without cirrhosis Genotype 1: sofosbuvir (400 mg) and ledipasvir (90 mg) for 24 weeks for patients who are treatment-experienced with compensated cirrhosis Genotype 2: sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks for patients who are treatment-naive or treatment-experienced and without cirrhosis or with compensated cirrhosis Genotype 3: sofosbuvir (400 mg) plus weight-based ribavirin for 24 weeks for patients who are treatment-naive or treatment-experienced and without cirrhosis or with compensated cirrhosis Genotypes 4–6: sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks for patients who are treatment-naive or treatment-experienced and without cirrhosis or with compensated cirrhosis
European Association for the Study of the Liver[74]	Treatment is recommended in adolescents aged ≥12 years with HCV who are treatment-naive or treatment-experienced, and without cirrhosis or with compensated (Child-Pugh A) cirrhosis In children <12 years old, treatment should be deferred until direct-acting antivirals, including pangenotypic regimens, are approved for this age group	Genotypes 1 and 4–6: fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks for adolescents aged ≥12 years who are treatment-naive or treatment-experienced and without cirrhosis or with compensated (Child-Pugh A) cirrhosis Genotypes 2 and 3: adolescents aged ≥12 years who are treatment-naive or treatment-experienced and without cirrhosis or with compensated (Child-Pugh A) cirrhosis can be given other regimens approved for adults, with caution pending more safety data in this population
WHO[72]	Treatment should be offered to all individuals diagnosed with HCV infection who are ≥12 years old, irrespective of disease stage	Genotypes 1 and 4–6: sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks Genotype 2: sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks Genotype 3: sofosbuvir (400 mg) plus weight-based ribavirin for 24 weeks
Asian Pacific Association for the Study of the Liver[76]	No recommendation	No recommendation
European Society for Paediatric Gastroenterology, Hepatology and Nutrition[81]	All treatment-naive and treatment-experienced children with chronic HCV infection should be considered for therapy Treatment can generally be deferred in younger age groups for which combined peginterferon and ribavirin is the only treatment option currently available	Genotypes 1 and 4: children >12 years old or who weigh >35 kg should be given a combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once a day for 12 weeks; the recommended duration of therapy for treatment-experienced children with HCV genotype 1 infection and compensated cirrhosis is 24 weeks Genotype 2: children >12 years old or who weigh >35 kg should be given sofosbuvir (400 mg) once a day plus weight-based ribavirin (15 mg/kg in two divided doses) for 12 weeks Genotype 3: children >12 years old or who weigh >35 kg should be given sofosbuvir (400 mg) once a day plus weight-based ribavirin (15 mg/kg in two divided doses) for 24 weeks

HCV=hepatitis C virus.

Table 2: **Comparison of international guidelines for treatment of chronic HCV infection in children and adolescents**

with or without ribavirin (NCT02486406), glecaprevir-pibrentasvir (NCT03067129), and sofosbuvir-velpatasvir (NCT03022981) are projected to complete in November, 2020, August, 2022, and January, 2020, respectively, although it is likely that these trials will complete earlier. In high-income countries, a relatively small number of adolescents and children diagnosed with chronic HCV infection are available for recruitment into clinical studies, and there is a need for more proactive case finding, as well as for enrolment of patients from low-income and middle-income countries, to accelerate completion.

The criteria for treatment in children were revised in 2018 by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition,[81] the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America,[75] and WHO[72] (table 2). The recommendation from these organisations is to defer treatment across age groups until oral direct-acting antiviral regimens are approved, because of the overall low efficacy, prolonged treatment duration, and pronounced side-effects of interferon-based treatments, as well as the generally low morbidity of chronic HCV in children younger than 12 years, and the anticipated

approval of more direct-acting antivirals in 2019 or 2020.[72,75,81] Eventually, recommendations for use of pangenotypic direct-acting antiviral regimens might be made consistent between adults, adolescents, and children, which would simplify procurement in low-income and middle-income countries and reduce fragmentation of what is already a low-volume market in children. When direct-acting antivirals are approved in children aged 3–12 years, treatment with direct-acting antivirals can then be considered for all children to eradicate the infection as early as possible, irrespective of liver disease stage and rate of disease progression. Children will then be able to grow up free from the potential stigma and psychological consequences of having a chronic transmissible infection.

Testing and service delivery

The expansion of direct-acting antiviral 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 mothers who are infected with HCV (which will, in turn, require more systematic screening of pregnant women and women of child-bearing age), and of adolescents and children with a clinical suspicion of chronic viral hepatitis, based on clinical symptoms, signs, abnormal serum amino-transferase, or ultrasound.[71] This approach will require additional advocacy because in some countries, access to treatment still remains restricted to people 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 restrict adolescents' access to services.

Search strategy and selection criteria

We did a comprehensive narrative literature review using PubMed 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. We searched for English language publications with the use of broad search terms: "hepatitis C virus" AND ("child" OR "adolescent") AND "epidemiology", "transmission", "natural history", "prevention", "diagnosis", or "treatment" from Jan 1, 2010, to Dec 31, 2017. The age limit "birth–18 years" was applied. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports. Animal studies and in-vitro studies were excluded. We also searched reference lists of articles identified by this strategy and included additional relevant studies. The final list of eligible studies was based on those of direct relevance to the key topics of this review. For each of the topics, we summarised the findings to highlight the main differences in data and management strategies in adults compared with children and adolescents. For the purpose of this review, we defined an adult as a person who is aged 18 years or older; an adolescent as a person who is 12–17 years old; and a child as a person who is younger than 12 years, unless stated otherwise. These definitions were consistent with the age categories used in most of the studies evaluated.

Conclusions, research agendas, and future strategies

To date, the focus of the global hepatitis response has been on treatment and prevention in the adult population, which bears the greatest burden of morbidity and mortality for HCV. However, to achieve the goal of eliminating HCV infection as a public health threat globally,[3] all affected populations, including children and adolescents, must be included. If adolescents and children are to benefit from the global, regional, and national strategies to eliminate HCV infection, critical gaps in the evidence on prevention, treatment, and management must be addressed to inform policy and management guidelines, and challenges in implementation and scale-up of treatment must be overcome.

Key actions are the inclusion of children and adolescents in national hepatitis strategies and policies, the establishment of a campaign on access to testing and treatment that is targeted at children and adolescents, fast-track evaluation of pangenotypic regimens for children and adolescents, and accelerated approval of paediatric formulations. An opportunity for accelerated evaluation and approval of paediatric formulations for direct-acting antiviral regimens is provided by the increasing emphasis that stringent regulatory authorities (eg, the US Food and Drug Administration and the European Medicines Agency) now place on extrapolation from adult efficacy trials paired with safety and dose-finding phase 1 or 2 clinical studies of 30–40 children.

Key evidence gaps and research needs were also identified. For treatment, these include an evaluation of the effectiveness and safety of pangenotypic direct-acting antiviral regimens, including sofosbuvir-velpatasvir and sofosbuvir-daclatasvir, in adolescents and children. Pharmacokinetic and drug interaction studies should be done to guide the development of paediatric formulations in younger children. Registries of treated and cured children and adolescents should also be established, with long-term follow-up to confirm non-progression of liver disease. In terms of prevention, the safety and effectiveness of direct-acting antivirals in pregnancy should be evaluated, with the dual aim of reducing vertical transmission and curing mothers, and continued research is required on the development of an effective HCV vaccine. To evaluate the prevalence and burden of HCV, age-stratified serosurveys of HCV antibody prevalence and HCV viraemia should be done in different populations of children and adolescents (high-risk populations and the general population), and estimates should be made of burden, morbidity, and treatment need by region. Children and adolescents should also be included in routine national data collection and global reporting on the viral hepatitis cascade of diagnosis, treatment, and cure. To improve

diagnosis and assessment, the diagnostic performance of serological assays (rapid diagnostic tests and immunoassays), and the use of non-invasive tests (eg, blood-based assays and transient elastography) for staging of liver disease, should be evaluated in children and adolescents.

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

Contributors

GI, PE, CG, and MP conceived the project. GI and PE wrote the first and subsequent drafts of the article. All authors 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. All authors contributed to the final version of the review before submission.

Declaration of interests

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