Title: Hepatitis C: Global Epidemiology and Strategies for Control

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Abstract

Hepatitis C virus (HCV) is a single strained RNA virus formally identified as the main cause of non-A non-B chronic hepatitis in April 1989. There are no accurate evidence about the actual prevalence of HCV chronic infection, however recent meta-analyses estimate that currently about 130-150 million people lives with chronic hepatitis C and that HCV causes about 500,000 deaths each year. The prevalence of infection is the highest in lower and middle income countries where incidence of new case of infection are mainly associated to iatrogenic transmission. In developed countries the infection is mainly due to at risk exposures and prevalence is still high among special groups such as person who injects drugs and jailed people. There is no vaccine against HCV, however since recently new drugs with a direct antiviral activity (DAA) has made chronic hepatitis C a curable condition. These drugs assure all oral therapy with efficacy approaching 100%, optimal tolerability and no absolute contraindications. The extraordinary clinical performance of DAA has renew the hope for developing public health interventions to reduce the burden of diseases and cut down new HCV infections at global level. We review the global epidemiology of HCV and intervention strategies for achieving global control of HCV infection. We also summarize the key elements of the World Health Organization's first-ever global health sector strategy for addressing the viral hepatitis pandemic, 2016-2021.

Introduction

Hepatitis C virus (HCV) is a single strained RNA virus formally identified as the main cause of non-A non-B hepatitis in April 1989.[1] It is a leading cause of liver related mortality worldwide and was estimated to have caused 333 000 deaths in 1990, 499 000 in 2010 and 704 000 in 2013.[2-4] Humans are the only natural host of HCV. Symptoms of acute infection are generally mild and the majority of cases of acute infection are asymptomatic and remain undiagnosed. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15–45% of infected individuals in the absence of treatment.[5]

Infection with HCV does not result in long term immunity and re-infection after recovery has been largely reported.[6] Furthermore, in settings with high HCV prevalence, mixed HCV genotype infections, a consequence of multiple exposures, are also frequent.[7] The inability to mount an effective protective immune response and the high variability of HCV genotypes (7 genotypes and 67 confirmed subtypes)[8] has hindered progress in vaccine development. However, new oral direct-acting antivirals (DAA) treatments have transformed the treatment of HCV, with cure rates higher than 90%, using short duration oral regimens and providing pan-genotypic efficacy.[9]-[10]-[11] The extraordinary clinical efficacy of DAA is now being advanced as a public health intervention to control the HCV infection at global level. [11-12]

We review the global epidemiology of HCV and intervention strategies for achieving global control of HCV infection. We also summarize the key elements of the World Health Organization (WHO) first-ever global health sector strategy for addressing the viral hepatitis pandemic, 2016-2021.

Methodological notes

This narrative review represents experts' personal interpretation of the different perspectives about the public health strategies to scale-up the control of HCV epidemic at global level after the introduction of DAA.

Information used to write the manuscript was collected from: PubMed search, Scopus, Web of Science, WHO website, google scholar, hand searches of the references of retrieved literature and personal experience of participating experts.

Global epidemiology of HCV infection

Global estimates of HCV prevalence and burden

Hanafiah and colleagues[13] estimated that in 2005 there was an overall global prevalence of 2.8% (95% CI 2.6%-3.1%) and in excess of 185 million persons who were HCV antibody positive (95% CI 169 to 201 million) based on a systematic review of 232 studies.2 A key limitation of this review was that since the focus was on regional picture of prevalence, the results do not capture the potential heterogeneity that exists between sub-populations within countries. A more recent systematic review by Gower and colleagues[14] was based on 4901 studies from 87 countries that included unpublished reports, and that also excluded older studies. This has generated substantially lower estimates of global HCV antibody prevalence at 115 million cases (95% CI 92 to 149 million) and an HCV viraemic population of 80 million people (95% CI 64 to 103 million).

In high income countries (HIC), the prevalence of chronic hepatitis C is generally below 2%.[13-14] However, there is variability and differences within countries with similar socio-economic conditions due to both differences a) the size and prevalence of infection in key higher risk populations, such as PWID (people who injects drugs); and b) access to prevention, diagnosis and treatment.[15] Even in a relatively homogenous settings such as Western Europe, prevalence of viraemic HCV infection may range between 0.4% (Austria, Cyprus, Germany, Denmark, France, United Kingdom) to 1.5% (Israel, Italy).13

Available data indicate that countries with the highest HCV prevalence (≥5%) are mainly low-middle income countries (LMIC), including: Egypt 9.8%-15.0%,[16]-[17] Gabon 4.9%-11.2%;[18] Uzbekistan 11.3%, Cameron 4.9%-13.8%,[19] Mongolia 9.6%-10.8%,[20-21] Pakistan 6.8%,[22] Nigeria 8.4%, Georgia 6.7%.[23]

Health-care associated transmission

In LMIC poor standards of infection control and injection safety are responsible for a significant proportion of new HCV infections. A nationwide systematic review and meta-analysis indicates that exposures to medical

procedures was a major driver of HCV infection in Egypt between 1989 and 2013[24] This is confirmed by studies from India[25], Nigeria[26] and Gabon.[27] Several studies from LMIC report that HCV seroprevalence approaches 10–20% among children who have been treated in hospital for malignancy, those who received haemodialysis and those who have undergone surgical procedures.11 It is also estimated that there are around 16 billion injections administered yearly around the world and 40% of these are considered to be unsafe and/or unnecessary (mainly in LMIC).[28] Between 2000 and 2010, there was a reduction of 83% in infections of hepatitis C virus due to unsafe injections. However, medical injections still account for an estimated 157,000-315,000 HCV infections annually.[29] The WHO global database on blood safety indicated that in 2011 39 countries did not routinely screened blood transfusions for blood-borne viruses.[30]

Although, HCV outbreaks due to transmission in health care settings are uncommon in HIC, between 2008 and 2014, the US Centers for Disease Control and Prevention reported a total of 22 HCV outbreaks associated with 239 new cases of infection and more than 90,400 at-risk persons notified for screening.[31] HCV outbreaks within healthcare settings have been reported in Europe too.[32-34] A study carried out in 18 Spanish hospitals indicated that a medical procedure was the only exposure for 67% of new sporadic HCV infections reported between 1998 and 2005.[35]

HCV transmission in other groups

PWID behaviours (sharing needles and paraphernalia) are responsible for the highest number of the infections among young adults at global level. A longitudinal study from UK identified a high HCV incidence (42/100 person-years) among PWID aged less than 30 years.[36-37] Furthermore, the risk of HCV re-infection after virus clearance among PWID is estimated to occur at a rate between 1.8 and 46.7 cases per 100 person-years.6 HCV transmission and acquisition in PWID is also strongly associated with incarceration.[38] A cross sectional study in Ireland indicate that about 20% of PWID who had been imprisoned had their first use of drug by injection in prison, of them and 71% reported sharing needles while in prison.[39]

Heterosexual transmission is unlikely to play a significant role in the HCV epidemic, nationally or regionally. A large prospective study carried out on 500 monogamous heterosexual couples in USA indicated that the probability of being infected by heterosexual contacts is about 1 in 190,000.[40] Nonetheless, HCV transmission has recently contributed to multiple outbreaks among HIV-positive men who have sex with men (MSM). [11,41-42] A case control study indicated that among HIV-positive MSM, factors independently associated with HCV infection are: low CD4 cell count, injecting drug use, unprotected receptive anal intercourse, sharing sex toys, fisting, sharing straws for snorting drugs and recent diagnosis of a sexually transmitted infection.[43] There is more limited evidence about the risk of HCV infectionamong HIV-negative MSM.[44]

Mother-to-infant vertical transmission of HCV is the most common HCV transmission route in children [45] with a risk of about 4%-8% and 11-25% in new-borns from HCV mono-infected or HIV/HCV co-infected mothers,

respectively.[11] Several factors have been reported to influence the transmission rate including maternal HCV viral load, labour duration, use of amniocentesis or foetal scalp monitoring and prolonged rupture of membranes. However, a systematic review of 18 observational studies comprising [32,64] participants showed that no primary prevention measure can significantly reduce the risk of mother-to-infant HCV transmission. [46-49] Therefore, pre-emptive treatment of women before pregnancy represents the best strategy to prevent peri-natal infection with HCV.[11]

There is growing evidence that cosmetic practices such as tattooing or scarification may have a prominent role of HCV transmission. In particular, in Western Africa several studies have shown a high risk of HCV among those who underwent tribal scarification and traditional circumcision.[7,50]

Opportunities for intervention and action

Implementing evidence-based prevention interventions

HCV transmission can be dramatically reduced through effective primary prevention interventions, including ensuring blood safety, enhancing infection control and provision of adequate harm reduction services.

Firstly, although entirely preventable, transmission of HCV through the transfusions still occurs because of poor or absent screening.[30] Therefore, ensuring the availability of safe blood and blood products is a vital public health measure for every national government. Secondly, consistent implementation of infection control practices, including safe injection measures, staff training and effective sharps waste management will reduce transmission of HCV to both patients and healthcare workers. Reducing unnecessary injections is also a critical measure in many HCV high burden countries. Implementation of the WHO injection safety policy and global campaign, launched in 2015, will help to address this major public health risks.[51] Thirdly, a package of harm reduction services for PWID that includes sterile needle/injecting paraphernalia programmes and opioid substitution therapy can be highly effective in preventing the transmission of blood-borne infections.[52] Finally, other effective primary prevention interventions are the rapid identification and control of local outbreak by enhancing surveillance systems, improving infection control measures in healthcare settings.[53]

New DAA therapy: a key strategy for achieving global HCV control

Recent clinical trials have shown extraordinary efficacy and safety of the newest combination therapies of DAA. In particular all-oral therapy with nucleotide analogue inhibitors of NS5B in combination with NS5A inhibitor can lead to complete viral clearance of HCV in 85%-100% of patients regardless HCV genotype, stage of diseases, response to previous therapy and pre-existence of viral resistance.[9-11]

ASTRAL 1[54] and ASTRAL 2[55] studies demonstrated that a 12 week treatment with sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor) had high level efficacy (97%-100% virus clearance) and tolerability

(about 2% side effects) in patients with genotype 1, 2, 4, 5, 6. ASTRAL 355 study indicated that complete virus clearance can also be obtained in 95% of patients with genotype 3 infection by a 24 week course of sofosbuvir and velpatasvir with a similar safety profile. Beside ASTRAL [4,56] study provided evidence that the new DAAs are also effective and safe (>80% efficacy <20% severe side effect) in patients with decompensated liver disease. Similar pan-genotypic activity has been observed also for combination of sofosbuvir with other, already approved, NS5A inhibitors such as ledipasvir [9,57] and daclatasvir [9,58].

Complete HCV clearance is considered a proxy for HCV cure [9] and is associated with a reduction in the risk of liver cancer by 76% and of death from any cause by 50%.[7,9-10] In addition, from a societal perspective, HCV clearance offers a direct strategy to reduce the force of infection[59] and represents an important public health measure to control HCV at a regional and global level.[60]

A major barrier to treatment scale-up are costs of diagnostics and drugs. Prioritization strategies have been proposed to optimize the impact of DAA on reducing the burden of disease in several settings.[9,61-62] One approach is to prioritise those with advanced liver disease to improve in the immediate patients life quality and survival .9-11,[63] A further approach is to target persons at highest risk of transmitting infection, regardless of the stage of disease, to reduce the infection pool and so prevent new infections (treatment as prevention).[9,11,64] This strategy may include prioritizing treatment for HCV infected persons who frequently undergo percutaneous procedures (e.g. renal replacement), healthcare workers who undertake exposure prone procedures (e.g. surgeons), PWID, HIV positive MSM, incarcerated population and child bearing women. A recent model estimates that doubling treatment rate of PWID, could reduce the overall incidence of HCV in Scotland to less than 50 cases/year in 10 years. However, prioritizing PWID rather than patients with moderate and advanced fibrosis would also reduce the immediate impact on burden of diseases (i.e. liver morbidity and mortality).[62]

Infection control, elimination and eradication

Though all infections can, in principle, be *controlled* only few can *eradicated*. [65]-[66]-[67] Three epidemiological conditions are considered essential to make eradication achievable: a) an effective intervention to interrupt transmission of the agent; b) an accurate diagnostic test to identify carriers; and that c) humans should be essential for the life-cycle of the agent. Although these criteria are largely met by the new DAA treatments, satisfaction of epidemiological conditions alone are insufficient for an eradication programme to be successful. Other requirements that must also be meet include: a) the local stakeholder must perceive the infection as a relevant health issue; b) the elimination/eradication programme must be economically convenient; and c) the elimination/eradication programme must be supported by adequate institutional commitment.

In several countries, commitment for broad access to new DAAs, unrestricted by the stage of disease, is increasing with the view that HCV elimination is both technically feasible and socially sustainable.[68] For example, the Canadian government estimate that about 250,000 individuals are chronically infected with HCV. Over the next

20 years, it is estimated that these people would require a 60% increase of healthcare expenditure due to HCV associated morbidity, with a lifetime cost per patient of about $64,694 excluding antiviral treatments.[69]-[70] This compares to a current cost of DAAs in Canada which is between $50,000-$120,000 and likely to continue declining over the next few years. In the scenario offering unrestricted access to DAA would save on expected increasing cost of HCV related morbidity[71] as well as spare future generation the risk of infection with an eventual economic gain in the medium and long term. LMICs are also exploring potential elimination strategies, including Egypt, Mongolia, Georgia and Rwanda. All such strategies should include a combined strategy of testing and treatment scale-up with key preventative interventions of injection safety and harm reduction services.11 Model-based analysis demonstrates that prioritizing patients according to the stage of the disease may be the most effective strategy to maximize the impact of DAA in LMIC[72] where there are generally low rates of diagnosis and heterogeneous modes of transmission.

Current challenges to control of HCV epidemic

Although new opportunities provide hope for the elimination HCV, there remain several significant barriers that will need to be addressed to realize this goal:

- ***Inadequate surveillance data****:* the true public health impact of the HCV is poorly understood in many countries making it difficult to plan for focused action and prioritize resources; [73]
- ***Coverage of prevention programmes is limited****:* prevention programmes (which proved to be effective for other blood borne infections such as HIV) are generally of limited scope and coverage, for example, global coverage of harm reduction programmes for PWID, is less than 10%;[74]
- ***Few people know their hepatitis status and have access to treatment****:* early diagnosis and staging of chronic hepatitis disease is compromised by both the lack of simple and reliable diagnostics and effective testing services (it is estimated that even in Egypt, with a high-profile treatment programme, only 3.8% of persons with chronic HCV infection have access to test;[75] in HIC diagnosis rate is generally much higher, though infrequently exceed 50%);[76]-[77]
- ***Medicines and diagnostics are unaffordable for most****.* although DAA have revolutionized the treatment of HCV, their high price remains a major barrier to access in most countries;
- ***A public health approach to hepatitis is lacking:*** few countries have public health programmes that deliver comprehensive HCV services; [73]
- ***Leadership and commitment is uneven****:* at present, few countries have national HCV strategies or plans, and even fewer have designated units and budgets within their health ministries to lead, guide and coordinate their hepatitis responses. [73]

New WHO Global Health Sector Strategy on viral hepatitis

In response to the 2010[78] and 2015[79] World Health Assembly resolutions and target 3.3 of the 2030 Agenda for Sustainable Development Goals,[80] WHO has recently developed the first-ever global health sector strategy on viral hepatitis to guide a coherent global public health response.[81]

The strategy addresses all five hepatitis viruses (hepatitis A, B, C, D and E), but has a strong focus on hepatitis C. The strategy outlines a vision, goals, a series of ambitious impact targets (incidence and deaths) and service delivery coverage targets (access to testing and treatment, blood safety, safe injection practices and harm reduction services) for 2020 and 2030 towards elimination of viral hepatitis as a major public health concern, as well as priority actions to be taken by countries and WHO to achieve these targets.

The Global health sector hepatitis strategy 2016–2021 would be expected to deliver a 70% reduction in HCV incidence by 2030 (50% reduction by 2020) compared with 2010, and 60% reduction in HCV-related deaths by 2030 compared with 2010, which will require reaching ambitious service coverage milestones: in blood safety, safe injection practices, harm reduction services and in access to HCV diagnosis and treatment. In particular, the strategy calls for a major increase in diagnosis of chronic infection, and for treatment coverage ofeligible persons by 2030. The priority actions are summarized in five strategic directions and are summarized in figure 1.

Conclusions

With effective global scale-up of the new DAA treatment alongside evidence-based interventions for primary prevention, control of HCV is a feasible goal. [82]-[83] Complete eradication of HCV although desirable is not yet in reach. Key barriers to elimination especially in LMICs that will need to be addressed include current low implementation of primary prevention measures, poor definition of local HCV epidemiology and relatively weak diagnostics capability. A key challenge is how to make the treatments affordable and ensure that they are accessible to all who need them. The demand for affordable treatment for HCV requires comprehensive price reduction strategies for medicines and diagnostics, that could include fostering generic competition, including voluntary licences, differential pricing and direct price negotiations with manufacturers.[84]-[85] The global response in HCV control can also learn from successful public health programmes in other areas, including those for HIV and tuberculosis. Innovative HIV service delivery approaches for marginalized and vulnerable populations, for example, can be adapted for reaching those key populations most affected by HCV. Effective implementation of the global hepatitis strategy will depend on effective collaboration with partners, including multilateral and bilateral donor and development agencies, funds and foundations, and civil society.

Figure

Figure 1. Framework for the global health sector strategy on viral hepatitis, 2016-2021

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Conflict of interest

Authors declare no conflicts of interest

Reference

[1] Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989 Apr 21;244(4902):359-62. PubMed PMID: 2523562.

[2] WHO Hepatitis C Fact sheet N°164 Updated July 2015 available at http://www.who.int/mediacentre/factsheets/fs164/en

[3] R. Lozano, M. Naghavi, K. Foreman, S. Lim, K. Shibuya, V. Aboyans, et al., Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet Lond. Engl. 380 (2012) 2095–2128. doi:10.1016/S0140-6736(12)61728-0.

[4] Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Aug 22;386(9995):743-800. doi: 10.1016/S0140-6736(15)60692-4 PubMed PMID: 26063472

[5] Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014 Nov;61(1 Suppl):S58-68. doi: 10.1016/j.jhep.2014.07.012. PubMed Epub 2014 Nov 3. Review. PubMed PMID: 25443346.

[6] Cunningham EB, Applegate TL, Lloyd AR, Dore GJ, Grebely J. Mixed HCV infection and reinfection in people who inject drugs--impact on therapy. Nat Rev Gastroenterol Hepatol. 2015 Apr;12(4):218-30. doi: 10.1038/nrgastro.2015.36. Epub 2015 Mar 17. Review. PubMed PMID: 25782091.

[7] Layden JE, Phillips RO, Owusu-Ofori S, Sarfo FS, Kliethermes S, Mora N, Owusu D, Nelson K, Opare-Sem O, Dugas L, Luke A, Shoham D, Forbi JC, Khudyakov YE, Cooper RS. High frequency of active HCV infection

among seropositive cases in west Africa and evidence for multiple transmission pathways. Clin Infect Dis. 2015 Apr 1;60(7):1033-41. doi: 10.1093/cid/ciu965. Epub 2014 Dec 4. PubMed PMID: 25477425

[8] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, Simmonds P. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology. 2014 Jan;59(1):318-27. doi: 10.1002/hep.26744. PubMed PMID: 24115039; PubMed Central PMCID: PMC4063340.

[9] European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015 Jul;63(1):199-236. doi: 10.1016/j.jhep.2015.03.025. PubMed Epub 2015 Apr 21. PubMed PMID: 25911336.

[10] IDSA AASLD Recommendations for Testing, Managing, and Treating Hepatitis C March 10, 2016. Available at Downloaded from http://www.hcvguidelines.org

[11] WHO Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection Updated version, April 2016 2016. Available at http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

[12] Ippolito G, Capobianchi MR, Lanini S, Antonelli G. Is hepatitis C virus eradication around the corner only 25 years after its discovery? Int J Antimicrob Agents. 2015 Feb;45(2):111-2. doi: 10.1016/j.ijantimicag.2014.09.001. PubMed Epub 2014 Sep 6. PubMed PMID: 25249016.

[13] Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013 Apr;57(4):1333-42. doi: 10.1002/hep.26141. Epub 2013 Feb 4. Review. PubMed PMID: 23172780.

[14] Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014 Nov;61(1 Suppl):S45-57. doi: 10.1016/j.jhep.2014.07.027. PubMed Epub 2014 Jul 30. Review. PubMed PMID: 25086286.

[15] Shire NJ, Sherman KE. Epidemiology of Hepatitis C Virus: A Battle on New Frontiers. Gastroenterol Clin North Am. 2015 Dec;44(4):699-716. doi: 10.1016/j.gtc.2015.07.002. PubMed Review. PubMed PMID: 26600215

[16] Abd Elrazek AE, Bilasy SE, Elbanna AE, Elsherif AE. Prior to the oral therapy, what do we know about HCV-4 in Egypt: a randomized survey of prevalence and risks using data mining computed analysis. Medicine (Baltimore). 2014 Dec;93(28):e204. doi: 10.1097/MD.0000000000000204.

[17] El-Zanaty, Fatma and Way, Ann. 2009. Egypt Demographic and Health Survey 2008. Cairo, Egypt: Ministry of Health, El-Zanaty and Associates, and Macro International. Available at: http://dhsprogram.com/pubs/pdf/fr220/fr220.pdf

[18] Njouom R, Caron M, Besson G, Ndong-Atome GR, Makuwa M, Pouillot R, Nkoghé D, Leroy E, Kazanji M. Phylogeography, risk factors and genetic history of hepatitis C virus in Gabon, central Africa. PLoS One. 2012;7(8):e42002. doi:10.1371/journal.pone.0042002. Epub 2012 Aug 1. PubMed PMID: 22870274; PubMed Central PMCID: PMC3411564.

[19] Riou J, Aït Ahmed M, Blake A, Vozlinsky S, Brichler S, Eholié S, Boëlle PY, Fontanet A; HCV epidemiology in Africa group. Hepatitis C virus seroprevalence in adults in Africa: a systematic review and meta-analysis. J Viral Hepat. 2016 Apr;23(4):244-55. doi: 10.1111/jvh.12481. Epub 2015 Oct 19. PubMed PMID: 26477881.

[20] Tserenpuntsag B, Nelson K, Lamjav O, Triner W, Smith P, Kacica M, McNutt LA. Prevalence of and risk factors for hepatitis B and C infection among Mongolian blood donors. Transfusion. 2010 Jan;50(1):92-9. doi: 10.1111/j.1537-2995.2009.02387.x. Epub 2009 Sep 25. PubMed PMID: 19788639

[21] Saraswat V, Norris S, de Knegt RJ, Sanchez Avila JF, Sonderup M, Zuckerman E, Arkkila P, Stedman C, Acharya S, Aho I et al Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 2. J Viral Hepat. 2015 Jan;22 Suppl 1:6-25. doi: 10.1111/jvh.12350. PubMed PMID: 2556083

[22] Umer M, Iqbal M. Hepatitis C virus prevalence and genotype distribution in Pakistan: Comprehensive review of recent data. World J Gastroenterol. 2016 Jan 28;22(4):1684-700. doi: 10.3748/wjg.v22.i4.1684. Review. PubMed PMID: 26819533; PubMed Central PMCID: PMC4721999.

[23] Sharvadze L, Nelson KE, Imnadze P, Karchava M, Tsertsvadze T. Prevalence of HCV and genotypes distribution in general population of Georgia. Georgian Med News. 2008 Dec;(165):71-7. PubMed PMID: 19124921.

[24] El-Ghitany EM, Abdel Wahab MM, Abd El-Wahab EW, Hassouna S, Farghaly AG. A comprehensive hepatitis C virus risk factors meta-analysis (1989-2013): do they differ in Egypt? Liver Int. 2015 Feb;35(2):489-501. doi: 10.1111/liv.12617. Epub 2014 Jul 8. PubMed PMID: 24923487.

[25] Parveen Malhotra, Vani Malhotra, Naveen Malhotra, Ishita Singh, Ajay Chugh and Abhishek Chaturvedi Epidemiological Profile of Hepatitis C Patients at India's New Hub –Haryana Adv Res Gastroentero Hepatol Volume 1 Issue 1 - August 2015 1-6 PubMed Adv Res Gastroentero Hepatol 1(1): ARGH.MS.ID.555554 (2015)

[26] Eze JC, Ibeziako NS, Ikefuna AN, Nwokoye IC, Uleanya ND, Ilechukwu GC. Prevalence and risk factors for hepatitis C and human immunodeficiency virus coinfection among children in enugu, Nigeria. Afr J Infect Dis. 2014;8(1):5-8. PubMed PMID: 24653810; PubMed Central PMCID: PMC3957207

[27] Rerambiah LK, Rerambiah LE, Bengone C, Djoba Siawaya JF. The risk of transfusion-transmitted viral infections at the Gabonese National Blood Transfusion Centre. Blood Transfus. 2014 Jul;12(3):330-3.

doi:10.2450/2013.0144-13. Epub 2013 Dec 3. PubMed PMID: 24333085; PubMed Central PMCID: PMC4111813.

[28] Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. Bull World Health Organ. 1999;77(10):801–7.

[29] Pépin J, Abou Chakra CN, Pépin E, Nault V, Valiquette L. Evolution of the global burden of viral infections from unsafe medical injections, 2000-2010. PLoS One. 2014 Jun 9;9(6):e99677. doi: 10.1371/journal.pone.0099677. eCollection 2014.PubMed PMID: 24911341; PubMed Central PMCID: PMC4049770

[30] Global database on blood safety. In: Blood transfusion safety [webpage]. Geneva: World Health Organization; 2011 (http://www.who.int/bloodsafety/global_database/en/, accessed 10 March 2016).

[31] CDC Healthcare-Associated Hepatitis B and C Outbreaks Reported to the Centers for Disease Control and Prevention (CDC) 2008-2014 available at http://www.cdc.gov/hepatitis/outbreaks/healthcarehepoutbreaktable.htm

[32] de Lédinghen V, Trimoulet P, Mannant PR, Dumas F, Champbenoît P, Baldit C, Foucher J, Faure M, Vergniol J, Castéra L, Bertet J, Fleury H, Couzigou P, Bernard PH. Outbreak of hepatitis C virus infection during sclerotherapy of varicose veins: long-term follow-up of 196 patients (4535 patient-years). J Hepatol. 2007 Jan;46(1):19-25. Epub 2006 Sep 22. PubMed PMID: 1703045

[33] Lanini S, Abbate I, Puro V, Soscia F, Albertoni F, Battisti W, Ruta A, Capobianchi MR, Ippolito G. Molecular epidemiology of a hepatitis C virus epidemic in a haemodialysis unit: outbreak investigation and infection outcome. BMC Infect Dis. 2010 Aug 27;10:257. doi: 10.1186/1471-2334-10-257. PubMed PMID: 20799943; PubMed Central PMCID: PMC2940904.

[34] Ross RS, Viazov S, Khudyakov YE, Xia GL, Lin Y, Holzmann H, Sebesta C, Roggendorf M, Janata O. Transmission of hepatitis C virus in an orthopedic hospital ward. J Med Virol. 2009 Feb;81(2):249-57. doi: 10.1002/jmv.21394. PubMed PMID: 19107970.

[35] Martínez-Bauer, E. et al. Hospital admission is a relevant source of hepatitis C virus acquisition in Spain. J. Hepatol. 48, 20–27 (2008).

[36] Negro F. Epidemiology of hepatitis C in Europe. Dig Liver Dis. 2014 Dec 15;46 Suppl 5:S158-64. doi: 10.1016/j.dld.2014.09.023. PubMed Epub 2014 Oct 22. Review. PubMed PMID: 25453870.

[37] Judd A, Hickman M, Jones S, McDonald T, Parry JV, Stimson GV, Hall AJ. Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study. BMJ. 2005 Jan 1;330(7481):24-5. Epub 2004 Nov 12. PubMed PMID: 15533854; PubMed Central PMCID: PMC539846

[38] Vescio MF, Longo B, Babudieri S, et al. Correlates of hepatitis C virus sero-positivity in prison inmates: a meta-analysis. Journal of Epidemiology andCommunity Health 2008;62:305–13.

[39] Allwright S, Bradley F, Long J, et al. Prevalence of antibodies to hepatitis B,hepatitis C, and HIV and risk factors in Irish prisoners: results of a nationalcross sectional survey. British Medical Journal 2000;321:78–82.

[40] Terrault NA, Dodge JL, Murphy EL, Tavis JE, Kiss A, Levin TR, Gish RG, Busch MP, Reingold AL, Alter MJ. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: the HCV partners study. Hepatology. 2013 Mar;57(3):881-9. doi: 10.1002/hep.26164. Epub 2013 Feb 7. PubMed PMID: 23175457; PubMed Central PMCID: PMC4384338.

[41] Martin NK, Thornton A, Hickman M, Sabin C, Nelson M, Cooke GS, Martin TC,Delpech V, Ruf M, Price H, Azad Y, Thomson EC, Vickerman P. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clin Infect Dis. 2016 Feb 16. pii: ciw075. [Epub ahead of print] PubMed PMID: 26908813.

[42] Hullegie SJ, van den Berk GE, Leyten EM, Arends JE, Lauw FN, van der Meer JT, Posthouwer D, van Eeden A, Koopmans PP, Richter C, van KasterenME, Kroon FP, Bierman WF, Groeneveld PH, Lettinga KD, Soetekouw R, Peters EJ, Verhagen DW, van Sighem AI, Claassen MA, Rijnders BJ. Acute hepatitis C in the Netherlands: characteristics of the epidemic in 2014. Clin Microbiol Infect. 2016 Feb;22(2):209.e1-3. doi: 10.1016/j.cmi.2015.10.012. PubMed Epub 2015 Oct 17. PubMed PMID: 26482267.

[43] Vanhommerig JW, Lambers FA, Schinkel J, Geskus RB, Arends JE, van de Laar TJ, Lauw FN, Brinkman K, Gras L, Rijnders BJ, van der Meer JT, Prins M; MOSAIC (MSM Observational Study of Acute Infection With Hepatitis C) Study Group, van der Meer JT, Molenkamp R, Mutschelknauss M, Nobel HE, Reesink HW, Schinkel J, van der Valk M, van den Berk GE, Brinkman K, Kwa D, van der Meche N, Toonen A, Vos D, van Broekhuizen M, Lauw FN, Mulder JW, Arends JE, van Kessel A, de Kroon I, Boonstra A, van der Ende ME, Hullegie S, Rijnders BJ, van de Laar TJ, Gras L, Smit C, Lambers FA, Prins M, Vanhommerig JW, van der Veldt W. Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study. Open Forum Infect Dis. 2015 Aug 6;2(3):ofv115. doi: 10.1093/ofid/ofv115. eCollection 2015 Sep. PubMed PMID: 26634219; PubMed Central PMCID: PMC4665384.

[44] McFaul K, Maghlaoui A, Nzuruba M, Farnworth S, Foxton M, Anderson M, Nelson M, Devitt E. Acute hepatitis C infection in HIV-negative men who have sex with men. J Viral Hepat. 2015 Jun;22(6):535-8. doi: 10.1111/jvh.12366. Epub 2014 Nov 21.PubMed PMID: 25412826.

[45] El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. World J Gastroenterol. 2013 Nov 28;19(44):7880-8. doi: 10.3748/wjg.v19.i44.7880. Review. PubMed PMID: 24307782; PubMed Central PMCID: PMC3848136.

[46] Tovo PA, Calitri C, Scolfaro C, Gabiano C, Garazzino S. Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression. World J Gastroenterol. 2016 Jan 28;22(4):1382-92. doi: 10.3748/wjg.v22.i4.1382.Review. PubMed PMID: 26819507; PubMed Central PMCID: PMC4721973.

[47] Benova L, Awad SF, Miller FD, Abu-Raddad LJ. Estimation of hepatitis C virusinfections resulting from vertical transmission in Egypt. Hepatology. 2015Mar;61(3):834-42. doi: 10.1002/hep.27596. Epub 2015 Jan 22. PubMed PMID:25366418; PubMed Central PMCID: PMC4365684.

[48] Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014 Sep 15;59(6):765-73. doi: 10.1093/cid/ciu447. Epub 2014 Jun 13. Review. PubMed PMID: 24928290; PubMed Central PMCID: PMC4144266.

[49] Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013 Jan 15;158(2):109-13. Review. PubMed PMID: 23437438.

[50] Luma HN, Eloumou SA, Malongue A, Temfack E, Noah DN, Donfack-Sontsa O, Ditah IC. Characteristics of anti-hepatitis C virus antibody-positive patients in a hospital setting in Douala, Cameroon. Int J Infect Dis. 2016 Feb 22;45:53-58. doi: 10.1016/j.ijid.2016.02.013. [PubMed Epub ahead of print] PubMed PMID: 26905319

[51] WHO Injection safety policy and global campaign available at http://www.who.int/injection_safety/global-campaign/en/

[52] Palmateer NE, Taylor A, Goldberg DJ, Munro A, Aitken C, Shepherd SJ, McAllister G, Gunson R, Hutchinson SJ. Rapid decline in HCV incidence among people who inject drugs associated with national scale-up in coverage of a combination of harm reduction interventions. PLoS One. 2014 Aug 11;9(8):e104515.doi: 10.1371/journal.pone.0104515. PubMed PMID: 25110927.

[53] UK Home office Advisory Council on the Misuse of Drug The Primary Prevention Of Hepatitis C Among Injecting Drug Users 2009 available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119144/acmdhepcreport2.pdf

[54] Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai CL, Chan HL, Mazzotta F, Moreno C, Yoshida E, Shafran SD, Towner WJ, Tran TT, McNally J, Osinusi A, Svarovskaia E, Zhu Y, Brainard DM, McHutchison JG, Agarwal K, Zeuzem S; ASTRAL-1 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. 2015 Dec 31;373(27):2599-607. doi: 10.1056/NEJMoa1512610. Epub 2015 Nov 16. PubMed PMID: 26571066

[55] Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Conway B, Ruane P, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg W, Agarwal K, Stedman CA, Mo H, Dvory-Sobol H, Han L, Wang J, McNally J, Osinusi A, Brainard DM, McHutchison JG, Mazzotta F, Tran TT, Gordon SC, Patel K, Reau N, Mangia A, Sulkowski M; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med. 2015 Dec 31;373(27):2608-17. doi: 10.1056/NEJMoa1512612. Epub 2015 Nov 17. PubMed PMID: 26575258.

[56] Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, Reddy KR, Lawitz E, Flamm SL, Schiano T, Teperman L, Fontana R, Schiff E, Fried M, Doehle B, An D, McNally J, Osinusi A, Brainard DM, McHutchison JG, Brown RS Jr, Charlton M; ASTRAL-4 Investigators. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med. 2015 Dec 31;373(27):2618-28. doi: 10.1056/NEJMoa1512614. Epub 2015 Nov 16. PubMed PMID: 26569658

[57] Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, Stedman CA. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology. 2015 Nov;149(6):1454-1461.e1. doi: 10.1053/j.gastro.2015.07.063. PubMed Epub 2015 Aug 7. PubMed PMID: 26261007

[58] Yang SS, Kao JH. Daclatasvir-containing all-oral regimens for the treatment of hepatitis C virus infection. Hepatol Int. 2016 Mar;10(2):258-66. doi:10.1007/s12072-015-9668-3. Epub 2015 Nov 5. PubMed PMID: 2654206

[59] Castro-Sánchez A, Shkedy Z, Hens N, Aerts M, Geskus R, Prins M, Wiessing L, Kretzschmar M. Estimating the force of infection for HCV in injecting drug users using interval-censored data. Epidemiol Infect. 2012 Jun;140(6):1064-74. doi: 10.1017/S0950268811001750. Epub 2011 Sep 12. PubMed PMID: 21910930.

[60] Ward JW, Mermin JH. Simple, Effective, but Out of Reach? Public Health Implications of HCV Drugs. N Engl J Med. 2015 Dec 31;373(27):2678-80. doi: 10.1056/NEJMe1513245. Epub 2015 Nov 17. PubMed PMID: 26575359.

[61] Lanini S, Nanni Costa A, Grossi PA, Procaccio F, Ricci A, Capobianchi MR, Terrault NA, Ippolito G. Liver transplant recipients and prioritization of anti-HCV therapy: an Italian cohort analysis. Liver Int. 2016 Mar;36(3):410-7. doi: 10.1111/liv.12938. Epub 2015 Sep 21. PubMed PMID: 26264452.

[62] Innes H, Goldberg D, Dillon J, Hutchinson SJ. Strategies for the treatment of hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? Gut. 2015 Nov;64(11):1800-9. doi: 10.1136/gutjnl-2014-308166.Epub 2014 Nov 6. PubMed PMID: 25378522.

[63] Bruno S, Di Marco V, Iavarone M, Roffi L, Crosignani A, Calvaruso V, Aghemo A, Cabibbo G, Viganò M, Boccaccio V, Craxí A, Colombo M, Maisonneuve P. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. J Hepatol. 2016 Jun;64(6):1217-23. doi:10.1016/j.jhep.2016.01.034. PubMed Epub 2016 Apr 5. PubMed PMID: 27059129.

[64] Edlin BR, Winkelstein ER. Can hepatitis C be eradicated in the United States? Antiviral Res. 2014 Oct;110:79-93. doi: 10.1016/j.antiviral.2014.07.015. PubMed Epub 2014 Aug 7. PubMed PMID: 25110202.

[65] Aylward B, Hennessey KA, Zagaria N, Olivé JM, Cochi S. When is a disease eradicable? 100 years of lessons learned. Am J Public Health. 2000 Oct;90(10):1515-20. PubMed PMID: 11029980; PubMed Central PMCID: PMC1446384.

[66] Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ 1998;76 Suppl 2:23-5

[67] Heymann DL. Control, elimination, eradication and re-emergence of infectious diseases: getting the message right. Bull World Health Organ. 2006 Feb;84(2):82. Epub 2006 Feb 23. PubMed PMID: 16501719; PubMed Central PMCID: PMC2626

[68] Peltekian KM. With all the new treatment regimens, complete elimination of hepatitis C virus in Canada is a possibility! But when will Canadians have access these drugs? Can J Gastroenterol Hepatol. 2014 Sep;28(8):417-8. PubMed PMID: 25229463; PubMed Central PMCID: PMC4210230.

[69] Public Health Agency of Canada. Hepatitis C in Canada: 2005-2010 Surveillance Report. Centre for Communicable Diseases and Infection Control, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada; 2011.

[70] Myers RP, Krajden M, Bilodeau M, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol 2014;28:243-50.

[71] Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Dig Liver Dis. 2011 Jan;43(1):66-72. doi: 10.1016/j.dld.2010.05.006. PubMed Epub 2010 Jun 17. PubMed PMID: 20739252.

[72] Obach D, Yazdanpanah Y, Esmat G, Avihingsanon A, Dewedar S, Durier N, Attia A, Anwar WA, Cousien A, Tangkijvanich P, Eholié SP, Doss W, Mostafa A, Fontanet A, Mohamed MK, Deuffic-Burban S. How to optimize hepatitis C virus treatment impact on life years saved in resource-constrained countries. Hepatology. 2015 Jul;62(1):31-9. doi: 10.1002/hep.27691. Epub 2015 Feb 27. PubMed PMID: 25581111

[73] WHO Draft global health sector strategy on viral hepatitis, 2016-2021 - the first of its kind available at http://www.who.int/hepatitis/strategy2016-2021/Draft_global_health_sector_strategy_viral_hepatitis_13nov.pdfaccessed on 17/07/2016

[74] The Global State of Harm Reduction 2012 Towards an integrated response available at http://www.ihra.net/files/2012/07/24/GlobalState2012_Web.pdf

[75] El-Zanaty F, Way A. Egypt Demographic and Health Survey 2008. Cairo, Egypt, Ministry of Health, Cairo, 2009. Available at: http://pdf.usaid.gov/pdf_docs/PNADO806.pdf.

[76] Dore GJ, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward). J Viral Hepat 2014;21 Suppl 1:1-4.

[77] Aghemo A, Dore GJ, Hatzakis A, et al. Estimating HCV disease burden – volume 3. J Viral Hepat 2015;22 Suppl 4:1-3.

[78] Viral Hepatitis Resolution – Sixty-Third World Health Assembly, World Health Organization, 2010. http://www.who.int/mediacentre/news/releases/2014/WHA-20140522/en/ (accessed January 27, 2016)

[79] World Health Assembly approves resolution on hepatitis and mechanism to coordinate noncommunicable disease response, World Health Organization, 2014. http://www.who.int/mediacentre/news/releases/2014/WHA-20140522/en/ (accessed January 27, 2016).

[79] Resolution WHA64.17 (2010) and resolution WHA68.6 (2015) [80] Sustainable Development Goals, target 3.3: “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.”

[81] United Nations General Assembly resolution A/RES/70/1 – Transforming our world: the 2030 Agenda for Sustainable Development, see http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E (accessed 30 October 2015).

[82] Sixty-Seventh World Health Assembly 24 May 2014 available at http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R6-en.pdf

[83] Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. 2015 Mar 17;162(6):397-406. doi: 10.7326/M14-1336. PubMed PMID: 25775312; PubMed Central PMCID: PMC4435698.

[84] Gilead Science CHRONIC HEPATITIS C TREATMENT EXPANSION Generic Manufacturing for Developing Countries available at http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf