HCV transmission in industrialized countries and resource-constrained areas

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Abstract | HCV is a blood-borne virus transmitted by percutaneous exposure to infected blood or blood-derived body fluids. The main routes of transmission are blood transfusions, medical procedures and injection drug use. In industrialized countries, HCV transmission through blood transfusions has been virtually eliminated and iatrogenic transmission occurs only sporadically during local breaches of infection control procedures. As most new cases originate from injection drug use, harm-reduction programmes (including opiate substitution, needle exchange and health education) can greatly reduce HCV transmission. Currently, the main approach to reduce the HCV disease burden is by increasing awareness of both the public and health-care providers to hepatitis C, enhancing screening opportunities and treatment of the infected population. In resource-limited countries, the priority is reducing transmission through blood transfusions and invasive medical procedures. This approach requires training of health-care providers and also structural changes and financial investments in countries where antibody screening, disposable materials and effective sterilization procedures are not routinely available. In these countries, reducing the HCV burden has been hampered by limited access to treatment, largely owing to the cost of drugs. Access to treatment is moving up on the agenda of international and non-governmental organizations in conjunction with the future availability of highly efficacious oral drug regimens.

Thursz, M. & Fontanet, A. *Nat. Rev. Gastroenterol. Hepatol.* **11**, 28–35 (2014); published online 1 October 2013; doi:10.1038/nrgastro.2013.179

Introduction

HCV, an hepatotropic RNA virus from the Flaviviridae family, is responsible for the majority of post-transfusion and non-A, non-B chronic hepatitis infections.[1] Worldwide, 130–170 million people are estimated to be infected with HCV and 350,000 people are predicted to die from the consequences of HCV infection each year.[2,3] HCV is also thought to be the cause of ~25% of all liver cancers worldwide[2] and it is the underlying aetiology of ~30% of all liver transplantations in developed countries.[4]

HCV is a blood-borne virus transmitted by percutaneous exposure to infected blood or blood-derived body fluid.[5] Infection is limited to humans and, in artificial situations, non-human primates;[6] however, no animal reservoir exists for the virus.[7] On the basis of HCV sequence variability, six genotypes have been defined,[8] with different distributions according to region. HCV genotypes 1 and 3 are more common in Western countries, genotype 2 in west Africa, genotypes 1 and 4 in central Africa and the Middle East, and genotypes 3 and 6 in southern and eastern Asia.[8] Sequence diversity suggests that HCV has been endemic in sub-Saharan Africa and southeast Asia for considerable time, and only emerged during the 20th century in Western and non-tropical countries.[9,10] Understanding the routes of transmission for HCV is essential for designing and implementing control strategies to reduce the prevalence of infection and burden of disease. The main routes of transmission described so far are blood transfusions, medical injections and procedures and injection drug use; more marginal routes of transmission are sexual, mother-to-infant and minor percutaneous exposures.

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Competing interests
The authors declare no competing interests.

Routes of transmission

Blood transfusions

For some time prior to the discovery of HCV, a pathogen with viral characteristics was known to be responsible for the majority of non-A, non-B post-transfusion hepatitis infections.[11] After the identification of HBV and the implementation of donor hepatitis B surface antigen (HBsAg) screening in the 1970s, HCV became the most important source of blood-borne hepatitis infection.[12] Before the onset of donor HCV screening, the rate of post-transfusion hepatitis, now known to be attributable to HCV, reflected the background prevalence of the infection in the blood donor population. The rate in the UK was only ~0.5%, compared with 11% in Spain and 13% in Greece.[13,14] The use of paid blood donors, in contrast to volunteers, was associated with an increased rate of post-transfusion HCV infection and, amongst paid donors, transmission rates were higher in those who had certain characteristics including: previously received blood products, injection drug use, intranasal cocaine use or sexual promiscuity.[15,16] Transmission of HCV was not only associated with whole blood transfusion, but was also transmitted by blood products. Administration of contaminated batches of anti-D immune globulin to Irish and German women to prevent rhesus isoimmunization led to two large outbreaks with

Key points

- The main route of HCV transmission in industrialized countries is injection drug use, whereas in resource-limited countries the major routes are iatrogenic, blood transfusions and medical procedures
- HCV transmission through sexual activity is rare amongst heterosexual couples, but is increasingly recognised amongst men who have sex with men, in whom traumatic sexual practices and HIV infection are associated with increased risk
- HCV transmission amongst people who inject drugs can be reduced by implementation of needle-exchange and opiate-substitution programmes
- Cheap, reliable and robust nucleic acid testing assays for screening pooled blood donations are urgently required in resource-limited settings to reduce HCV transmission
- Training in hospital infection control procedures and their regulation are required to reduce iatrogenic transmission of HCV in resource-limited settings
- Drug treatment might prove to be an effective method of reducing transmission in populations with a high prevalence of HCV infection

known dates of transmission, enabling long-term evaluation of hepatitis infection outcomes.[17,18] The risk of infection was particularly high in those who had received pooled blood products, such as clotting factor concentrates used for treatment of haemophilia.[19]

Identification of HCV led to the development of assays—initially ELISA then recombinant immunoblot assays (RIBA)—to detect antibodies formed against viral proteins and so reveal infection in potential blood donors.[20] Refinements have led to the production of ELISA tests with high sensitivity and specificity, making the RIBA test redundant.[21] By 2002, use of these tests to screen blood donors reduced the risk of post-transfusion hepatitis C from 7.7% to 1 in 276,000 donations in the USA and from 3.5% to 1 in 127,000 donations in Italy.[22,23]

During an acute infection, HCV RNA is present in the blood for up to 6 weeks before antibodies can be detected.[24] As such, this 'window period' creates vulnerability in the blood supply when antibody screening is used. Nucleic acid testing (NAT) on small pools of donor serum has been applied in most developed countries since the early 2000s.[23] This additional level of screening has virtually eliminated the risk of HCV transmission through transfusion. For example, in Italy, NAT reduced the risk of HCV transmission by 83% to 1.3 per million transfusions.[22] The risk of HCV transmission in the USA is now down to 1 in 1,935,000.[23]

In contrast to blood donor screening in developed countries, the blood supply in many low-income countries is poorly controlled.[25] The 2011 WHO Global Database Blood Safety Report showed that in 40 countries, <25% of the blood supply is collected from voluntary unpaid blood donors, and in 39 countries, blood donations are not routinely tested for transfusion-transmissible infectious agents, including HCV.[26] Furthermore, use of rapid test assays and poor quality control procedures might result in low sensitivity for detecting potential infections; a multinational study in 17 African countries reported sensitivities as low as 80.0% for HCV, 81.4% for HIV and 75.6% for HBsAg.[27] A similar situation exists in Pakistan where use of paid donors and poor screening practices are associated with high rates of HCV prevalence in recipients of multiple blood transfusions.[28] NAT is currently out of reach financially for most sub-Saharan African countries, suggesting a role for HCV antigen-based assays in these regions. These assays detect the core protein of HCV and become positive at an earlier phase in the window period than antibody-based screening assays.[29] The HCV core antigen assay is not as sensitive as NAT, limiting the size of donor pools that can be tested simultaneously. Although the assay has been used with reasonable sensitivity when the HCV antigen was tested in donor pool sizes up to six, the use of pooled donor screening is still controversial and a cheap, reliable and robust assay is still urgently required for screening blood donations in resource-limited settings.[30–32]

Iatrogenic

Increases in the number of medical injections and blood transfusions after the second World War drove the expansion of the HCV genotype 1b epidemic, preceding the expansion of HCV genotype 1a among injecting drug users by 16 years.[10] Historically, outbreaks of hepatitis C were first documented among patients in haemodialysis units.[33] Further outbreaks were described in relation to the use of contaminated multiple dose vials,[34] spring-loaded finger sticks,[35] surgery[36] and gastrointestinal endoscopy.[12,37] Studies from the past 5 years investigating the routes of HCV transmission after outbreaks during endoscopy or myocardial perfusion suggest that unsafe injections with syringe reuse and multiple dose vials, notably for anaesthesia, were at the source of contamination, rather than the procedures themselves.[38–40] Transmission from infected surgeons to their patients during invasive procedures is well documented,[41] but is still a rare event. Although iatrogenic transmission of HCV has become less common in industrialized countries, breakdown in control of infection and clinical hygiene procedures might result in transmission, indicating that vigilance and investment of resources in infection control must be maintained.[42,43] Data from Eastern Europe also suggest that medical and dental procedures continue to be responsible for HCV transmission in this region.[44]

In resource-limited countries, iatrogenic transmission has a key role in the initiation of large epidemics. Egypt has the highest HCV prevalence worldwide (14.7% among individuals aged 15–59 years).[45] It is widely accepted that HCV was transmitted during campaigns in the 1960s and 1970s to treat the parasitic disease schistosomiasis using the injectable tartar emetic with reusable syringes and multiple dose vials.[46] Similar, past mass-treatment approaches or vaccination campaigns are suspected to be at the origin of epidemics in central Africa where high prevalence rates are observed among people >50 years in Cameroon,[47] Gabon,[48] Central African Republic[48] and Democratic Republic of Congo.[49] In Egypt, the HCV incidence rate remains high with >150,000 new infections each year,[50] most of which are unexplained. In 2010, a case–control study in Egypt examined potential risk factors for HCV transmission in patients presenting with acute HCV infection, comparing them with controls with acute hepatitis A virus infection.[51] The main risk factor that emerged was attendance at medical facilities; sutures, intravenous access, catheterization and dental

work were all also associated with risk of HCV infection, accounting for ~40% of acute cases. In Cameroon, treatment of malaria and trypanosomiasis by injection, as well as blood transfusions, have contributed to the rise in HCV prevalence in the first half of the 20th century.[52,53] Reuse of syringes and needles remains the predominant route of HCV transmission in resource-limited countries,[54–56] despite improvements in availability of disposable material during the past decade.[57]

Injection drug use

Injection drug use, practised by ~16 million people worldwide,[58] is universally accepted as an important route of HCV transmission. Indeed, it has now become the main source of incident HCV infections in industrialized countries after the decline of iatrogenic transmission with implementation of blood donor screening and infection control procedures. Injecting drug use is also prevalent in resource-limited countries and contributes to HCV transmission, although data are scarce from these regions.[51,59,60] The prevalence of HCV infection ranges from 45% to >90% in drug users and annual incidence rates are 6–40%.[61] The incidence rates are often reported to be highest in the early years of intravenous drug use when behaviour is often chaotic and sharing of equipment is common.[62–64] HCV transmission is also frequent in people who do not use recreational drugs intravenously but who use cocaine intranasally.[65] This mode of transmission seems to be facilitated by the damaging effect of cocaine on the nasal mucosa, which induces bleeding.

A number of public health interventions could be used to interrupt transmission of HCV by injecting drug use. These interventions include those aimed at altering behaviour, opiate-replacement therapy, increasing syringe access, syringe disinfection and multicomponent interventions. Opiate-substitution programmes reduce the use of street drugs and promote safer practices. In two meta-analyses, opiate substitution was associated with a 30–65% reduction in HCV transmission.[63,66] Needle substitution or disinfection programmes were also evaluated and produced mixed results.[63] Combining several approaches seems to be the preferred solution and can achieve >75% reduction in HCV transmission.[63]

A novel approach to reduce harm amongst injection drug users is the concept of 'treatment as prevention'. The principle here is fairly straightforward: as the rate of HCV transmission is strongly determined by the prevalence of infection in the population of injecting drug users, if the prevalence of infection can be reduced by treatment, then the rate of transmission should also diminish. To date, the only evidence in support of this approach is based on mathematical modelling. Even modest rates of treatment and sustained virological response rates seem to be both clinically effective and cost-effective.[67–69] However, many teams have treatment programmes operating amongst active injection drug users and their experiences have been mixed. A limited number of programmes report impressive adherence rates and treatment outcomes in these populations, but the majority of unreported experiences, communicated anecdotally, are less optimistic.[70,71] The adverse effect profile of interferon-based regimens coupled with the need for prolonged treatment are clearly a major barrier to success amongst this population, and it is reasonable to expect that all oral 12-week treatment courses are likely to engender higher adherence rates and sustained virological response rates than standard treatment approaches.

Sexual

As other blood-borne viruses (such as HIV and HBV) are transmitted sexually, it is reasonable to assume that the same pertains to HCV. However, the situation for HCV is not clear cut (reviewed elsewhere[72]). In some studies, but not all, HCV has been isolated from semen and cervical secretions.[73–75] Case reports and small case series have identified couples who are both infected with exactly the same strain of the virus,[76] but these findings do not confirm sexual transmission, as it is impossible to exclude common nonsexual routes of transmission, such as shared needles.[77] Male partners of females infected with HCV after receiving contaminated anti-D immune globulin had low levels of HCV infection, suggesting that female-to-male transmission is rare.[78] A number of studies now seem to confirm that heterosexuals in regular partnerships hardly ever transmit HCV infection.[79–81] However, several studies have documented an increased risk of transmission amongst individuals with multiple sexual partners,[82,83] established sexually transmitted disease[84] and HIV infection.[77] Estimates based on a large cross-sectional study of 500 HCV-positive, HIV-negative individuals and their long-term heterosexual partners suggest that the risk of heterosexual HCV transmission is approximately 1 per 190,000 sexual contacts.[85]

Since 2000, numerous cases of acute HCV infection have been reported amongst men who have sex with men (MSM) who are HIV positive. These reports mainly originate from high-income countries in Europe,[86–88] North America[89,90] and Australia.[91] Longitudinal serological testing and phylogenetic analysis have been used to trace the source of the virus and often the social event when the virus was transmitted. Although sexual transmission does seem to occur amongst MSM who are not HIV positive, HIV positivity is clearly one of the main risk factors.[92] In addition, the risk of transmission is high in men who have multiple sexual partners, indulge in anoreceptive intercourse, traumatic sexual practices and the use of recreational drugs during sex.[93]

Vertical

The risk of transmission of HCV from infected mothers to infants has been estimated to be ~4–7% when the mother is viraemic, and twofold to fourfold higher when she is co-infected with HIV.[85,94–97] Diagnosis in children relies on two positive HCV RNA tests at least 6 months apart. Of note, HCV antibodies passively transmitted from the mother to the infant can persist for up to 18 months.[98,99] The timing of transmission is not well known, and both intrauterine and perinatal transmission are likely to occur.[99] However, no evidence indicates that caesarean section rather than vaginal delivery reduces the risk of transmission.[98,100,101] Breastfeeding is considered safe, but

should be avoided if nipples are cracked or in cases of coinfection with HIV.[102]

Needlestick injury

In the USA, an estimated 400,000 needlestick injuries occur each year and each one has an appreciable risk of HBV, HCV and HIV transmission.[103] Pooled estimates of the risk of HCV transmission from an infected source are 0.5–1.9%.[104–106] Large needle size, increased depth of penetration and an injury sustained from a hollow bore needle increase the risk of infection transmission.[107,108] The risk of injury might be reduced by provision of ubiquitous sharps containers, thereby avoiding recapping needles, and by the use of self-capping hypodermic needles. Transmission of HCV by blood or body fluids coming into contact with mucosal surfaces (such as mouth or eye) is anecdotal.[109]

If health-care workers sustain a needlestick injury, they should be tested immediately for the presence of anti-HCV antibodies and HCV RNA to document the absence of infection at the time of injury.[103] They should then be tested periodically (usually at 1 month intervals) for HCV RNA. Health-care workers who seroconvert should be treated immediately with PEG-IFN, as the success rates of treatment for acute infection are substantially higher than in patients with chronic infection.[110] However, no evidence supports the use of post-exposure prophylactic treatment with PEG-IFN.[111]

Other routes

HCV transmission has been associated with tattooing and acupuncture when there is poor hygiene and reuse of needles.[112] Tribal scarification and circumcision have also been postulated as a mode of transmission, but evidence supporting these risk factors is scarce. Routes of transmission other than those discussed could also account for cryptogenic transmission of HCV in the community. Transmission might also lead to transient infection without seroconversion (where the innate immune system eliminates the virus).[113,114] This observation suggests that establishing persistent infection might require a minimal viral dose threshold, which some parenteral routes of transmission rarely exceed.

Reducing the burden of HCV

In 2010, the World Health Assembly adopted a resolution calling for a comprehensive approach for the prevention, control and management of viral hepatitis.[115] In passing this resolution, member states recognized the tremendous burden of viral hepatitis. In line with this resolution, the WHO established a Global Hepatitis Programme and released a framework in 2012 for global action on viral hepatitis, outlining four axes for action with suggested approaches for member states to adopt or adapt as they see fit.[116] As these axes are from a global point of view, each country should adapt actions depending on the local burden of disease and routes of transmission.

Industrialized countries

As described earlier, in developed countries, the level of HCV transmission through blood transfusions and invasive medical procedures is now very low, occurring as an outbreak during local breaches of infection control procedures. The most important source of new HCV infections in these countries is injecting drug use, through sharing of needles. Improving harm-reduction programmes including opiate substitution, needle exchange and health education has a clear effect on HCV transmission in this high-risk community. Furthermore, over the next 5 years, oral drug regimens will become available on the market, with cure rates >90% and a shorter treatment duration than the current standard of care.[117] With these new drugs, it is conceivable to implement treatment as prevention programmes and so assess the effectiveness of this strategy on reducing HCV transmission in this high-risk group.

Now that HCV transmission is effectively controlled in the majority of developed countries, the emphasis is gradually shifting from reducing transmission towards reducing the burden of disease (that is, treating those who are already infected to prevent long-term complications). This trend will gain more momentum now that new highly efficacious treatments are on the horizon. The proposed strategy relies on raising the awareness of the public and health-care providers about hepatitis C, therefore enhancing screening opportunities. Although most infected individuals and individuals with hepatitis C are asymptomatic, HCV meets the majority of criteria for screening programmes (Box 1). In the USA, special age groups including 'baby boomers'—individuals born between 1945 and 1965, and comprising 75% of the currently infected population[118]—are the target of the current campaign. Such actions are integrated within more comprehensive plans, such as the one released in 2011 by the US Department of Health & Human Services.[119] In Australia, the first National Strategy was released in 1999, and great progress has been achieved in the past decade in identification of infected individuals.[120] In Europe, French and Scottish plans are globally recognized as models of good practice.[121,122] Indeed, France has the highest proportion of treated individuals among all of those infected of any country in Europe.[123] However, many developed countries still lack a coordinated approach, resulting in a failure to reduce the prevalence of infection and morbidity and mortality related to infection. In a European analysis of public health policies related to viral hepatitis undertaken by the European Liver Patients Association in 2013,[122] several Eastern European countries scored badly, despite a high prevalence of infection.

Resource-constrained countries

In resource-limited countries, the priority is aimed at reducing transmission via blood transfusions and invasive medical procedures. The screening of blood products using antibody-based assays remains insufficient in place and time owing to a shortage of reagents. In addition, the choice of proper serological assays would benefit from standardized evaluations performed by the WHO. Implementing infection control procedures is a big challenge in resource-limited countries where disposable devices are too expensive or not routinely available, and

Box 1 | Wilson and Jungner classic screening criteria

1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognized disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognizable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case-finding should be a continuing process and not a "once and for all" project

where proper sterilization procedures are not followed. Structural changes and large financial investments will be needed, together with the training of health-care workers, to reduce HCV transmission in medical facilities. Unfortunately, ministries of health struggle with constrained budgets and have limited control of what is happening outside of facilities under their authority (for example, in the private sector); elaborate systems for delivering and renewing licenses might therefore be required to implement infection control beyond their facilities. Raising awareness about blood-borne infections in the general public might also prove efficient, if it can help to reduce unnecessary injections and make the public more critical about syringes and medical devices being reused. In Egypt, illiteracy has consistently been associated with increased risk of HCV infection;[45,124] further studies are required to see whether this increased vulnerability is related to lack of public knowledge about HCV transmission routes.

Injection drug use has mostly been investigated in industrialized countries, but this route of transmission also participates in HCV transmission in resource-limited settings. As injection drug users are often stigmatized in these countries, harm-reduction programmes are usually managed by non-governmental organizations. To scale up these actions, recognition of this issue at a national level is a necessary first step, before the implementation of harm-reduction programmes.

Access to treatment is moving up the agenda of international and non-governmental agencies,[125] although few countries are in a position to implement treatment activities.[126] Egypt is a notable exception; a national programme has managed to treat >200,000 patients in the past 6 years, thanks to a dramatic reduction in the cost of PEG-IFN after the introduction on the market of a locally produced biosimilar.[127] Access to new and highly effective direct-acting antivirals at a reduced price will become a priority in resource-limited countries, and will benefit from the experience acquired in the field of HIV treatment in the same countries.[125]

A vaccine for HCV

The observation that a proportion of individuals who are exposed to HCV spontaneously clear the virus raises the possibility that a vaccine could be developed to elicit immune responses and so prevent transmission of infection. However, experiments in chimpanzees suggest that either previous infection or vaccination reduces the duration and magnitude of subsequent infection, rather than stimulating sterilizing immunity.[128] If this phenotype could be replicated in human vaccination studies, it would be sufficient to meet the public health target of preventing chronic HCV infection. Spontaneous resolution of infection has been associated with a polyclonal, multispecific and high magnitude $CD4^+$ and $CD8^+$ T-cell response, which has been difficult to replicate with current vaccine candidates.[129] The role of antibodies in protection from chronic infection is unclear, as all infected patients develop antibody responses to both structural and nonstructural viral proteins even in the face of chronic infection.[130] Viral envelope proteins are a particularly difficult target for obtaining an antibody response as they are highly variable in amino acid sequences.[131] Furthermore, the virus circulates as a lipoviral particle, which probably makes it inaccessible for effective antibody binding.[130]

A prophylactic vaccine to prevent infection is widely believed to be a valuable tool in reducing HCV transmission. In resource-limited settings with a high prevalence of HCV infection (such as Egypt), it is easy to comprehend how a universal vaccine could be used to reduce the high incidence rate of HCV. However, the incidence rates of HCV in European and North American countries are low, which affects both the commercial motivation for vaccine development and the potential cost-effectiveness of vaccine deployment. At present, the prospect of an effective vaccine remains rather remote and only a small number of prospective vaccines have made it to clinical trials in humans, owing to the associated technical, commercial and immunological challenges.[128] Control of the transmission of HCV must therefore rely on alternative health measures.

Conclusions

All of the major routes of HCV transmission are probably now known. There is wide global variation in the importance of different transmission routes: intravenous and recreational drug use is the most important in industrialized countries; medical practices, including the reuse of needles and syringes as well as poor quality screening of blood products in transfusion centres, account for the majority of new HCV infections in resource-limited countries. These routes of transmission should be considered as completely avoidable. Education and close regulation of health-care workers, along with education of patients about iatrogenic risks could result in a major reduction in HCV transmission in many resource-constrained countries.

Review criteria

The articles cited in this review were identified from the authors' personal libraries and from the database PubMed. Only full-text English language papers were reviewed.

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Acknowledgements
The authors would like to thank A. Bernier for critical reading of the manuscript and helpful suggestions.

Author contributions
The authors contributed equally to all aspects of this article.