REVIEW ARTICLE

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Comparison of Seroepidemiology and Transmission Modes of Viral Hepatitis C in Iran and Pakistan

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Hepatitis C virus (HCV) infection is a worldwide problem in health. The seroprevalence of HCV infection is estimated to be 3%. There is considerable geographic and temporal variation in the incidence and prevalence of HCV infection. The researchers conducted the literature search using the electronic database MEDLINE (1966 to January 2008), EMBASE (1980 to October 2007), OVID (1966 to October 2007) and Google (for local websites and medical journals). The following keywords were used: 'Hepatitis C', 'Epidemiology', 'Iran', and 'Pakistan'. HCV infection in Pakistan is more common than in Iran. The most common modes of transmission in Pakistan consist of: IVDs, unsafe injections, transfusion, tattooing and sharing by barbers and in Iran consists of: IVDs, getting wounded in war, extramarital sexual contact and tattooing. The hepatitis C infection is an emerging disease in both countries and requires more governmental support. This article reviews the literature available so far on the epidemiology and potential risks of transmission of HCV and makes recommendations for implementing strategies for the prevention of such transmission in our region.

Keywords: **Hepatitis C, Seroprevalence, Transmission, Prevention, Review**

Introduction

Hepatitis C virus (HCV) infection is a worldwide problem in health. The seroprevalence of HCV infection is estimated to be 3%. Marked geographic variation exists with seroprevalence rates from 0.4% to 1.1% in North America to 9.6% to 20% in North Africa. However, there is considerable geographic and temporal variation in the incidence and prevalence of HCV infection. Using age-specific prevalence data, at least three distinct transmission patterns can be identified. In countries with the first pattern (e.g., United States, Australia), most infections are found among persons 30-49 years old, indicating that the risk for HCV infection was greatest in the relatively recent past (10-30 years ago) and primarily affected young adults. In countries with the second pattern (e.g., Japan, Italy), most infections are found among older persons, consistent with the risk for HCV infection having been greatest in the distant past. In countries with the third pattern (e.g., Egypt), high rates of infection are observed in all age groups, indicating an ongoing high risk for acquiring HCV infection. In countries with the first pattern, injection drug use has been the predominant risk factor for HCV infection, whereas in those with the second or third patterns, unsafe injections and contaminated equipment used in healthcare-related procedures appear to have played a predominant role in transmission. Much of the variability between regions can be explained by the frequency and extent to which different risk factors have contributed to the transmission of HCV [1].

Projections showed that although the prevalence of HCV infection may be declining currently because of the decline in incidence in the 1990s, the

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number of persons infected for ≥30 years could increase substantially before peaking in 2015 [2, 3]. The transmission is parenteral, i.e., commonest by blood transfusion and intravenous drug abusers (IDUs). Risk factor for acquisition of infection in different parts of the world is different. Important risk factors associated with acquiring HCV infection include transfusion of blood and blood products (before 1990) and transplantation of solid organs from infected donors, injecting drug use, occupational exposure to blood (primarily contaminated needle sticks), being born to an infected mother, and having sex with an infected partner, and multiple heterosexual partners. Vertical transmission from mother to child, needle prick, ear piercing, tattooing, barbers, and razors are other risk factors. Another study stated people who use illegal drugs or engage in high-risk sexual behavior account for most persons with HCV infection [4]. This article reviews the literature available so far on the epidemiology and potential risks of transmission of HCV and makes recommendations for implementing strategies for the prevention of such transmission in our region.

Materials and Methods

The researchers conducted the literature search using the electronic database MEDLINE (1966 to January 2008), EMBASE (1980 to October 2007), OVID (1966 to October 2007) and Google (for local websites and medical journals). The following keywords were used: 'Hepatitis C', 'Epidemiology', 'Iran', and 'Pakistan'. In addition a manual search using citation in previous publication was performed. Our research was restricted to English and Persian by language. We excluded the similar result in the articles.

Results

We divide the prevalence of HCV infection in different parts and at first; the situation in Pakistan will be presented.

Geographic characteristics

Pakistan is located in Southern Asia, bordering the Indian Ocean, between India on the east and Iran and Afghanistan on the west and China in the north. Pakistan has an old history. The Indus Valley civilization, one of the oldest in the world and dating back at least 5,000 years, spread over much of what is presently Pakistan. Pakistan is a developing country with a population of 164,741,924.The Burden of HCV related chronic liver diseases had been shown in different studies.

Iran is a developing country with a population of 65,397,521. Iran is located in the Middle East and acts like a bridge between Indian subcontinent, Arabian Peninsula, Middle Asia, and Europe. This geographical situation, mass immigration from Afghanistan and Iraq, frequent travels in western borders to Turkey, and illegal drug traffic from eastern borders with Pakistan and Afghanistan have all affected epidemiology of HCV in the country [5].

Epidemiology of hepatitis C in Pakistan

A community-based study in Hafizabad, Punjab, found a 6.5% seroprevalence of HCV infection, 6.7% in women and 1.3% in children [6, 7]. General sero-prevalence of anti-HCV in healthy adult male population from the northern Pakistan was 5 percent for anti-HCV [8]. This reflects that the population at large is exposed to the same risk factors. In another study among 5,371 young adults, seroprevalence of HCV infection was 3.53% [9]. While few population-based studies are available, the estimate is 10 million infected patients with HCV based on an average sero-prevalence of 6% [10]. Other studies in blood donors revealed that HCV infection is more common in Pakistan than in neighboring countries. The HCV prevalence in blood donors from Armed Forces and Civilian population in Rawalpindi was 4% and the average age was 28 years [11]. Multivariate logistic regression model showed that the cases were more likely than controls to have reported past hospitalization or to have received multiple injections. When a glass syringe was used to give therapeutic injections, it had increased the adjusted odds of being HCV seropositive significantly, more among cases than in controls. This relationship was stronger when injection was given by general medical practitioner than if the injection was given in hospital setting. Cases were more likely than controls to have reported sexual contact with multiple sexual partners. This figure is similar to reported figures for the Pakistani population [12-19]. 50% of blood bank facilities in Karachi regularly use paid blood donors. During pre-donation interviews, only a small minority of donors were asked their history of high-risk behaviors. Laboratory equipment for screening major blood pathogens was present in less than half of the facilities [20]. Moreover, in Karachi, the majority of blood recipients believed that generalized weakness was a valid indication for blood transfusion and were unaware of the risks of blood transfusion [21].

The prevalence of HCV infection in chronic liver disease in Pakistan may be pockets of much higher as other smaller studies have reported a population prevalence of 16% from Lahore and 23.8% from Gujranwala [22]. Chronic hepatitis and cirrhosis of liver due to hepatitis C virus is becoming a major health hazard in Pakistan [23]. In a study from Karachi, the overall seroprevalence of HCV in blood donors was 1.8% [24]. The prevalence of HCV infection in Pakistan has been estimated as high as 35% in some areas [23, 25-28]. HCV and HBV are significant causes of morbidity and mortality in Pakistan, where studies of patients with chronic hepatitis and hepatocellular carcinoma in Rawalpindi and Karachi showed that between 20 and 30% had antibodies to HCV and that 70 to 80% had evidence of past HBV infection [29].

The burden of HCV related chronic liver disease (CLD) clearly seems to be increasing with time. Whereas earlier studies showed that of all patients presenting with CLD, 16.6% were anti-HCV positive [30], more recent data shows nearly 60-70% patients with CLD to be positive for anti-HCV [31]. It has been demonstrated that nearly 50% of patients with HCC in Pakistan are anti-HCV positive [32, 33]. A study included 1074 patients, comprising of 564 of chronic hepatitis (group I) and 510 of cirrhosis liver (group II) in Chandka Medical College Hospital, Larkana from 1997 to 2002. Anti-HCV antibody was present in 51% in group I and 57% in group II. Use of contaminated syringes (62%) was an important risk factor and HCV infection was a leading cause of CLD. The leading risk factor identified is the use of contaminated syringes [34]. In Pakistan, one of the earliest studies shows anti-HCV prevalence of 13.5% in chronic liver disease [35]. Studies conducted recently in Karachi show 43.06% seropositivity in chronic liver diseases and cirrhosis combined, with 45.7% cases of chronic liver disease and 37.7% cases in cirrhosis [36]. In another recent study 44% patients with chronic liver disease had HCV antibodies [37]. In hepatocellular carcinoma, anti-HCV antibodies were detected in 33% of cases [38].

Epidemiology of hepatitis C in Iran

Nearly most of studies regarding estimation of prevalence of HCV infection in general population in Iran have been conducted on healthy blood donors. In the first report that appeared in literature in 1994, Rezvan *et al.* reported 0.3% anti-HCV positive in blood donors [39]. In other studies from blood donors, the prevalence differs from 0.5% to 0.97% [40, 41]. All of Iranian blood donation clinics follow regulations of Iran's Blood Transfusion Organization that exclude high risk groups i.e. persons with a history of jaundice, intravenous drug abuse, extramarital sexual contact, so the major bulk of positive cases are excluded. With more restrict regulations in blood donation, the prevalence has decreased to 0.12% [42]. Generally, it seems that the whole population prevalence is less than 1% in Iran, which is lower than that of the regional countries; 1.1% in Yemen [43], 0.9% in children to 1.8% in adult blood donors in Saudi Arabia [44, 45], and 4% of blood donors and 3% of college students in Pakistan [46, 47]. In chronic liver disease and hepatocellular carcinoma, the HBV infection is more common than HCV infection in Iran [48, 49].

Modes of transmission in Pakistan

HCV is generally transmitted by the parenteral route. It is also transmitted by needle-stick injuries, sexual contact, and vertically from mother to fetus [50]. Family members of infected patients and low socio-economic status also correlate with an increased risk of HCV infection. Non-sexual household contacts such as sharing tooth brushes, nail clippers and razor blades are risk factors for HCV transmission [51-53]. The development of tests for surrogate markers for HCV and screening of blood donors has decreased the risk of HCV transmission to 0.001% per unit of transfused blood in developed countries [54, 55]. However, in developing countries including Pakistan, the risk of HCV transmission through blood transfusion is unknown but considered to be high due to lack of appropriate screening of blood and needs to be more investigated [56].

Nosocomial transmission of HCV seems to occur more frequently in developing countries because optimal precautions may not be taken. Therapeutic injections by health care providers [57], shaving by barbers, tattooing and ear-piercing, known to be associated with HCV infection [58, 59], are common in developing countries. Low educational level and/or low socio-economic status has also been associated with the prevalence of a number of infectious diseases. This is in keeping with Mujeeb *et al.* who described areas of higher prevalence of Hepatitis C located in specific districts and a trend of higher prevalence in less affluent urban areas for the city of Karachi [60]. Blood transfusion is still the major cause of HCV transmission in Pakistan. A survey of blood banks in the large urban centers of the country showed that only about 25% of them tested blood and blood product donations for HCV infection to keep the cost down [61]. It can be safely assumed that testing for HCV in the rural areas of the country is even less frequent, making blood

transfusions still the major cause of HCV transmission in the country.

In a study of volunteer and replacement blood donors in Lahore, Pakistan for the years 1996-2005, the frequency of hepatitis C was 3.01-4.99%. The frequency of hepatitis C amongst Pakistani donors is the highest in the region [62]. This figure is similar to reported figures for the Pakistani population [63, 64]. The seroprevalence for HCV was lowest amongst volunteer donors (all under 35 years of age) and was lower than that in replacement donors of the same age group. This fact is of importance in terms of policy since some of the difference may be due to differences in health behavior and attitudes of volunteer donors versus replacement donors, but may also reflect the possibility that some of the replacement donors may be paid donors brought in by family members to masquerade as replacement/family donors. Pakistan has a larger problem in terms of hepatitis C compared to its eastern and western neighbors (India and Iran) as well as others in the region (Saudi Arabia and Turkey).

Community trends like reuse of disposable and/or glass syringes, repeated use of potentially contaminated razors by barbers, improper dental practices [65] and other risk factors seem to be unchanged. Widespread practices such as unsafe injections, improper disposal of hazardous waste, recycling of used syringes without proper sterilization, sharing of needles by injecting drug users and unsafe sex are believed to facilitate the transmission of these infections, resulting in high prevalence rates in the country [66-69]. There is an enormous dependence on parenteral therapy for treatment, both in the form of injections and infusion of drips, driven by cultural beliefs in the power of parenteral therapy. Additional risk factors that may be important modes of transmission include excessive use of barbers for shaving [70]. In an earlier study, non-sterile syringes and needles were also the source of HCV and HBV infections in a peri-urban community of Karachi [71]. Patients who received more injections were more likely to be infected with HCV [72]. A nationwide survey by the ministry of health in 2002 revealed that as many as 72% therapeutic injections and 50% immunization injections in public health-care facilities were unsafe and potentially dangerous [73]. Hepatitis C exposure and antibody positivity rates among injection drug users have been reported to be higher than 50% compared to 10% in the same general population [74-76]. The use of inadequately sterilized undisposable medical materials, e.g., needles and scalpels, has also been shown to transmit HCV [77].

There is some evidence of occupational and nosocomial transmission of HCV infection. Inadvertent needle-stick injuries and lack of application of universal precautions may be contributing factors [78]. About 80% of HCV-positive surgical operation room personnel in a hospital in Pakistan had more than four needle-stick injuries per year in five years [79]. In one Pakistani community, HCV seroprevalence was 6.5%, and individuals who received more therapeutic injections were found to be at a higher risk of infection [80]. In Pakistan, over a third of the people are living in poverty and have a fragile health structure; many patients cannot afford the costly treatment of these diseases. Pakistan has one of the highest frequencies of injections in the world. The average number of injections per person per year is 8.5 and 49% of patients receive injections at their first outpatient visit [81]. In addition to the unnecessary use of injections, injection practices are not safe in the country. In 18 clinics in peri-urban areas in Karachi, for example, 94% of injections used were not safe [82]. These unsafe injections may be attributed to a lack of knowledge and understanding and a high patient demand for injections [83].

A number of studies also show the relationship between therapeutic injections using non-sterile needles and transmission of HCV [32]. There is enormous dependence on parenteral therapy for treatment, both in the form of injections and infusion of drips, driven by cultural beliefs in the power of parenteral therapy. Additional risk factors that are peculiar to a developing country and may be important modes of transmission are excessive use of barbers for shaving [47]. Other known risk factors for HCV transmission include ear piercing, acupuncture, tattoos, and cultural procedures involving blood contact [48, 63]. Bleeding during facial shaving by barbers was significantly associated with the outcome in this study. Facial shaving by barbers has been repeatedly documented as a risk factor for transmission of hepatitis B and C viruses in various countries along with ear piercing and non-sterile surgical and dental practices of unqualified health care workers (quacks) [64, 84].

In a study of 6095 inhabitants 35 years or older in a community with hyperendemic hepatitis B and C virus infections, in multivariate logistic analyses, alcohol consumption and smoking were significantly associated with elevated ALT levels among anti-HCV-seropositive subjects. Patients who are seropositive for anti-HCV are strongly advised not to smoke and drink alcohol to reduce the possible risk for aggravating the liver dysfunction [65].

Shaving beard and armpits by barbers has also been identified as a risk for hepatitis C by Bari *et al.* [47], providing another avenue of public health intervention for risk reduction. In a study in 947 pregnant women in Shifa International Hospital, Islamabad, the proportion of HCV sero-positivity among pregnant woman in our study was 3.27%. Among all the risk factors under study, previous surgery was found to have a significant association with HCV positive status of women [66]. Dried blood spot samples from mothers and their offspring attending the obstetric and pediatric departments of two hospitals in Lahore, Pakistan, were tested for antibodies to HCV. The seroprevalence of HCV in the women was 6.7% (95% CI: 4.3-9.1), and that in the children was 1.3% (95% CI: 0.34-2.26). Four anti-HCV immunoglobulin G (IgG)-positive children had mothers that were anti-HCV IgG negative, which suggested that their infection was community acquired [7]. It concluded that vertical transmission in the early perinatal period is the least. The sero-prevalence of HCV in children appears to be low in Pakistan, with 0.2% and 0.4% children infected under the age of 12 and between 12-19 years respectively [67].

Several epidemiologic studies have reported the existence of nonsexual intrafamilial HCV transmission. However, actual routes and their relative efficiency have been controversial. The objective of this study was to investigate whether contacts of HCV seropositive index patient living in the same household have similar probabilities of being HCV seropositive with respect to any of the household-level variables, after taking into account the independent effects of individual-level variables. In a study in household members of HCV-infected patients; specifically, their close contact with objects that are contaminated with blood or perhaps saliva of the HCV-seropositive index patient may pose increased risk of HCV transmission. High household intercept variances in different analyses revealed that at there are still unrecognized nonsexual modes of HCV transmission at the household level that need further research [68]. The households' contacts of hepatitis C virus (HCV) seropositive patients have been shown to have an elevated risk of HCV infection [69, 70]. On the contrary, we demonstrated a significant clustering of HCV seropositivity among nonsexual contacts of HCV-seropositive thalassemic patients [71]. Because of shared behaviors and living conditions, family members within a household are likely to be more similar to one another than are family members from different households. Household contacts of HCV-positive patients are considered at increased risk of HCV infection [71].

Modes of transmission in Iran

Today, intravenous drug abuse is the major risk factor for HCV infection. In a study in blood donors, transfusion, undergoing endoscopy, extramarital sexual activities, non-intravenous (IV) drug abuse, IV drug abuse, and receiving wounds at war were found to be independent risk factors of being HCV-positive (Odds ratio: 17, 4, 42.2, 34.4, 52.8 and 5.2, respectively). No apparent risk factors could be demonstrated in 24.5% of the positive cases [35]. There are certain medical procedures, lifestyle patterns, and customs and cultural matters in Iran that predispose people to a number of HCV risk factors [35]. In Iran, the risk factors had shown by a cross-sectional prevalence study to determine the prevalence of HCV and high-risk behaviors in drug abusers admitted to prison in Guilan Province, north of Iran. Of 460 inmates, (45.4%) were HCV antibody positive and 88.9% of intravenous drug abusers were infected. HCV-positive status was significantly associated with intravenous drug use, having skin tattoos and number of times in prison [72]. During a five-year period, a cross-sectional study was conducted among HCV positive individuals referred to Ahwaz Jundi-Shapour University Hospitals (AJSUH) and Hepatitis Clinic from 1999 to 2003. A total of 514 subjects were studied for HCV, of whom 254 were HCV-positive and 260 HCV-negative donors comprised the control group. Transfusion 132 (52%), non-intravenous (n-IV) drug abuse and IV drug abuse 37 (14.5%), hemodialysis 25 (10%), receiving wounds at war and extramarital sexual activities (2.4%), tattooing (3.6%) were found to be independent risk factors of being HCV-positive. No apparent risk factors could be demonstrated in 29 (11.2%) of the positive cases [73].

A total number of 427 drug abuser inmates in the central prison of Hamadan, Iran were studied in 2002. Total number of IV drug abusers (IDA) and non-IV drug abusers (NIDA) was 149 (34.9%) and 278 (65.1%), respectively. The overall rate of antibody positivity among inmates was 30% for HCV. The seroprevalence of HCV infection among drug abuser prisoners in comparison with the general population in Iran is very high (30% vs. 0.2%). The results indicated the importance of policies to prevent transmission of HCV infection during and following incarceration [74]. In a study in 226 gypsies of Southwest of Iran, seven of them were positive for anti-HCV. Tattooing and phlebotomy are very common practices among gypsies [75].

In Iran, to determine whether HCV infection of index cases increases intrafamilial transmission (sexual and nonsexual contacts) of HCV, 300-household contacts of 60 index cases (40 males and 20 females) of HCV infection and 360 pair-matched controls in Ahwaz Jundi-Shapour University Hospitals were enrolled. Only 4 of 300 (1.33%) cases of household contacts without percutaneous risk factors were positive for HCV-Ab while the remaining 296 family contacts were negative for anti-HCV. The mean age of the index cases was 28.4 (Std 15.22) years. The anti-HCV prevalence's in parents, spouses, children of the index cases were 0.87% (1/115), 3.39% (2/59)) and 0.79% (1/126), respectively. The prevalence of positive HCV Ab among household contacts (1.33%) was not significantly higher than that in the controls (1%). Intrafamilial transmission of HCV is not the significant transmission route and sexual transmission does not seem to play a role in the intrafamilial spread of HCV infection. Intrafamilial transmission of HCV is possible but occurs at a low rate [76].

HCV genotypes distribution in Pakistan and Iran

Molecular studies have identified HCV type 3 as the predominate strain in Pakistan [26, 77, 78]. Multiple studies confirm that type 3 is the predominant HCV genotype in Pakistan, with a prevalence of between 75% and 90% [79, 80]. The rest are mostly type 1 and occasionally type 2, with no evidence for other genotypes. Amongst the type 3 infections, subtype 3a is the commonest followed by 3b. In many published data from Iran, genotypes 1 (1a and 1b) and 3 were found in 87 (55.8%) and 45 (28.8%) patients, respectively. The most frequent HCV subtype was 1a (37.8), followed by 3a (28.9%) and 1b (16.7%). We further found that 18 (40%) and 17 (37.8%) patients that were intravenous drug users (IVDU) had genotype 1a and 3a, respectively.

Genotypes 3a and 1a in Iran are less prevalent in IVDU than in Europe and USA, but there is a high similarity between the pattern of genotype in IVDU in both Europe and the United States, and Iran. However, in this case it cannot be due to people's migration to other countries since history of traveling abroad existed only in 6 cases (13.3%) [81]. HCV subtypes were determined in 125 Iranian patients by phylogenetic analysis within the NS5B or 5'-UTR/core regions. Subtypes 1a and 3a were predominant accounting for 47 and 36%, whereas 1b and 4 accounted for 8 and 7%. This subtype distribution differs from that of Turkey and Pakistan, where subtypes 1b and 3a dominate and also from neighboring Arabic countries where subtype 4 is the prevalent genotype. Patients infected by blood products had more frequently subtype 1a (57%); while younger drug users had more frequently subtype 3a (54%). Genotype 4 was over-represented among hemodialysis patients in Tehran. One strain, most similar to genotype 5, was highly divergent in the NS5B region and further analysis is needed to assess the systematic status of this strain [82].

In a study, 2231 patients with hepatitis C were investigated for HCV genotypes. The highest frequency was for genotype 1a, with 886 (39.7%) of subjects. Genotype 3a and 1b were the other frequent genotypes, with 613 (27.5%) and 271 (12.1%) subjects, respectively. Of the samples, 401 (18%) had an undetermined genotype. Mixed genotypes were also found in 33 samples (1.6%). Genotype 1b frequency in patients under 20 years old was 10.2%, while its frequency in patients over 60 years old was 18.5%. Genotype 1b frequency significantly increased by age (P=0.02). This study indicates that the dominant HCV genotype among patients living in Tehran was 1a [83].

Discussion

Hepatitis C is an emerging disease in Pakistan and Iran Table 1. Some projections had shown the decrease in the incidence rate of infection, but

Table 1. Prevalence and risk factors for HCV infection in Pakistan and Iran.

Variables	Pakistan	Iran
Prevalence in general population	6.5% [6]	Less than 1% [35]
Prevalence in blood donors	4% [11]	Less than 1% [34, 35]
Paid blood donors	50% [19]	No
Prevalence in chronic hepatitis	16-23% [21]	Less than 10%
Prevalence in hepatocellular carcinoma	50% [29]	8.5% [39]
Risk factors	IVDs Transfusion [6] Unsafe injections [6] Sharing by barbers [48, 85] Tattooing	IVDs [35] Receiving wounds at war [35] Extramarital sexual contact [35] Tattooing [75]
HCV genotype (predominant)	3a [77, 78]	1a, 3a, 1b [81-83]

without recognition of the modes of transmission and providing proposed intervention, it will be far from reality. Intravenous drug abuse is the main cause of infection in both countries. Otherwise, injections by health care providers, sharing by barbers and tattooing are more important in Pakistan. In conclusion, Awareness and prevention are the main safeguards against the epidemics of viral hepatitis. In Iran, family practitioners who work as primary health care providers along with midwives engaged with active infection screening, patients and their families in the rural areas; also play an important role by increasing public awareness of these diseases.

HCV infection is a major health problem in Pakistan. More scrutiny on blood donors, just use of voluntary donors, use of sensitive screening tests, more control on injection practices in Pakistan is mandatory. Regarding current frequency of diagnosed HCV-infected subjects, unless use of standard medical precautions in health units, and injection practices re-evaluated, Pakistan would be involved in more chronic hepatitis C patients in the future. Continued education of the public and healthcare professionals will play an important part in control of this problem since injections in the healthcare setting in Pakistan are reported as a risk factor for acquisition of hepatitis B and C in adults as well as children [47, 64]. HCV infection could be reduced substantially by efforts to limit injections to those that are medically essential and to ensure the use of sterile equipment [6].

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