

## “Epidemiology of Hepatitis C Virus (HCV) Infection”

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### Summary:

*Hepatitis C virus is a significant healthcare problem, affecting more than 170 million people worldwide and as many as 4 million new infections occur annually. Incidence rates across the world fluctuate and are difficult to calculate given the asymptomatic, often latent nature of the disease prior to clinical presentation. Of those exposed to HCV, 80% become*

*chronically infected, and at least 30% of carriers develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. HCV infection also increases the number of complications in persons who are co-infected with HIV. This article reviews an overview of the prevalence, genotype data, transmission risk and prevention.*

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### Prevalence:

The discovery of the hepatitis C virus (HCV) in 1989 was a major breakthrough and it continues to be a major disease burden on the world. WHO estimated a worldwide prevalence of about 3% with the virus affecting 170 million people worldwide.<sup>1,2</sup> (Table-1). Although the virus is found throughout the world, the various genotypes of hepatitis C are distributed differently.<sup>3</sup>

The prevalence of HCV infection varies throughout the world, with the highest number of infections reported in Egypt. The use of parenteral antischistosomal therapy in Egypt is thought to have contributed to a prevalence of antibodies against HCV in various regions ranging from 6 to 28 percent (mean 22 %).<sup>4</sup> In the United States, 1.8 % of population is positive for HCV antibodies.<sup>5, 6</sup> Between Central and South America, the estimated prevalence of HCV in 2001-2002 was 6.3 %.<sup>6</sup> In Europe, general prevalence of HCV is about 1 % but

varies among the different countries.<sup>7</sup> Prevalence rate of HCV antibody is high in Italy (3.2%),<sup>8</sup> and low in Hungary (0.73%).<sup>9</sup>

The estimated prevalence in Australia has been reported as 2.3%.<sup>10</sup> There have been fewer studies in Africa, but lower rate have been reported- 1.6% in Ethiopia and 0.9% in Kenya.<sup>11,12</sup> Intermediate rates of HCV have been reported in Asia. 0.49% in Japan,<sup>13</sup> 1% in China,<sup>14,15</sup> 1.6% in Malaysia<sup>16</sup> and 0.54% in Singapore.<sup>17</sup> In Thailand, the prevalence rates are (3.2%-5.6%).<sup>18</sup> Prevalence rate is 4.5% in Pakistan,<sup>19</sup> 1.8% in Saudi Arabia<sup>20</sup> and 2.1% in Yemen.<sup>21</sup> In New Delhi, India the prevalence rate is 1.85%.<sup>22</sup>

In Bangladesh, a very few data is available regarding prevalence of HCV. Prevalence rate is 1.2% among professional blood donors<sup>23</sup>, 0.6% in rural adult population<sup>24</sup>, < 1% among truck drivers and helpers<sup>25</sup>. In another study the prevalence of HCV infection was higher among intravenous drug abusers (24.8%) in comparison to non-drug abusers (5.8%)<sup>26</sup>.

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### Genotypes of HCV:

On the basis of phylogenetic analysis of nucleotide sequences, multiple genotypes and subtypes of HCV have been identified. The complete HCV genome was determined by Choo et al in 1991<sup>27</sup>. After that several HCV isolates from different parts of the world were obtained and sequenced. This led to the identification of several different types that may differ from each other by as much as 33% over the whole viral genome. In 1994, at the 2<sup>nd</sup> international conference of HCV and related viruses, a consensus nomenclature system was proposed that is to be used

in future studies of HCV genotypes, subtypes and quasispecies.<sup>28</sup> (Table-2). According to this system, HCV is classified on the basis of the similarity of nucleotide sequence into major genetic groups designated genotypes. HCV genotypes are numbered (Arabic numerals) in the order of their discovery. The more closely related HCV strains within some types are designated subtypes, which are assigned lower case letters (in alphabetic order) in HCV genotypes are important epidemiological markers and may alter the sensitivity and specificity of diagnostic assays for detection of HCV. HCV genotyping in combination of other markers, such as quantitative evaluation of HCV RNA may be beneficial in the management of chronic hepatitis C infection and the selection of candidates for interferon treatment. Genotype 1 is less responsive to alpha-interferon therapy compared to genotypes 2 and 3. It is therefore important to track the different genotypes of the HCV virus.<sup>29, 30</sup>

Epidemiologically and clinically 11 genotypes and more than 70 subtypes have been identified. Substantial regional differences appear to exist in the distribution of HCV genotypes.<sup>31</sup> (Table-3). Genotype 1b is the most common genotype globally and is principally transmitted through contaminated blood products. Although HCV genotypes 1, 2 and 3 appear to have a worldwide distribution, their relative prevalence varies from one geographical area to another.

Although the impact of HCV heterogeneity and genotypes on day to day clinical management of chronic HCV infection has not been established, its role as an epidemiological marker has been clearly shown. The exact role of genotypes in the clinical presentation, progression of liver disease, outcome of HCV infection or incidence of HCC are much less well understood than their role as an epidemiological marker.

The geographical distribution and diversity of HCV genotypes may provide clues about the historical origin of HCV.<sup>32</sup> The presence of numerous subtypes of each HCV genotype in some regions of the world, such as Africa and Southeast Asia, may suggest that HCV has been endemic for a long time. Conversely, the limited diversity of subtypes observed in the United States and Europe could be related to the

recent introduction of these viruses from areas of endemic infection.

#### **Transmission:**

Risk factors associated with HCV infection include injection drug use (or intranasal if using a blood contaminated device), receipt of blood products, long term haemodialysis, organ transplantation, receipt of tattoo from an unsanitary facility, vertical transmission during pregnancy and sexual or nosocomial exposure.<sup>33, 34, 35</sup> Sexual transmission of the virus appears to be inefficient means, certainly less efficient than HIV-1;<sup>36</sup> whether this is due to the low levels of the virus in genital fluids and tissues or to a lack of appropriate target cells in the genital tract is not known. Maternal fetal transmission occurs but is infrequent and often associated with coinfection with HIV-1 in the mother.<sup>37, 38</sup> Co infection with HIV-1 appears to increase the risk of both sexual and maternal fetal transmission of HCV.<sup>37, 39</sup>

Virus can be recovered from saliva of infected persons<sup>40</sup> and although chimpanzees have been experimentally infected by the injection of saliva from HCV-infected persons,<sup>41</sup> casual household contact and contact with the saliva of infected persons also appear to be very inefficient modes of transmission.<sup>40, 42</sup> Nosocomial transmission has been documented, such as from patient to patient by a colonoscope,<sup>43</sup> during dialysis,<sup>44</sup> and during surgery.<sup>45, 46</sup> Needle stick injuries in the health care setting continue to result in nosocomial transmission of the virus. The rate of transmission after a needle stick injury, involving known blood, to be ranged from 0% to 10% in various studies.<sup>34, 47</sup> A rough estimate of the comparative risks of transmission through a needle stick injury is provided by the rules of three: HBV is transmitted in 30% of exposures, HCV in 3%, and HIV-1 in 0.3%. These numbers are most likely influenced by the size of the inoculum, the size of the needle and depth of inoculation.

#### **Prevention:**

There is no vaccine against HCV. Research is in progress but the high mutability of the HCV genome complicates vaccine development. Lack of knowledge of any protective immune response following HCV infection also impedes vaccine research. The value of prophylactic immune globulin (IG) is not clear.<sup>48, 49</sup> Post exposure prophylaxes with IG are not effective in preventing infection.

In absence of a vaccine, all precautions to prevent infection of HCV should target reduction of transmission of the virus. The only means of protection are the implementation universal precautions and safe injection practices. Screening and treatment of blood products is the only way to prevent transfusion associated cases.<sup>50,51</sup> Needle exchange programs for injecting drug users may help to limit the spread of HCV infection.<sup>52</sup> Prevention should target those at risk of acquiring the virus and should involve providing education, risk reduction counseling, HCV screening and substance abuse treatment. To date, screening the general population for HCV infection has been controversial.

HCV carriers should be strongly discouraged from drinking alcohol because there is evidence that acts as a cofactor in developing more severe liver injury.<sup>53, 54, 48</sup> Patients who do not have serologic evidence of immunity to hepatitis A and B should be vaccinated,<sup>55, 56, 57</sup> especially since infection with the hepatitis A virus in patients with chronic HCV may result in a more severe infection than in patients without HCV.

Comprehensive strategy to prevent and control hepatitis C virus (HCV) infection and HCV-related disease<sup>58, 59</sup>;

- Primary prevention activities include
  - screening and testing of blood, plasma, organ, tissue, and semen donors
  - virus inactivation of plasma-derived products
  - adequate sterilization of reusable material such as surgical or dental instruments
  - risk-reduction counseling and services
  - implementation and maintenance of infection-control practices
  - needle and syringe exchange programs
- Secondary prevention activities include
  - identification, counseling, and testing of persons at risk
  - medical management of infected persons
- Professional and public education
- Surveillance and research to monitor disease trends and the effectiveness of prevention activities and to develop improved prevention methods.

Prevention of spread of infection should be the main goal at the current time until cost effective therapies become available.<sup>60</sup>

**Table-I**

<i>Worldwide prevalence of HCV</i>			
WHO Region	Total population (Millions)	Hepatitis C Prevalence rate %	Infected population (Millions)
Africa	602	5.3	31.9
Americas	785	1.7	13.1
Eastern Mediterranean	466	4.6	21.3
Europe	858	1.03	8.9
South-East Asia	1500	2.15	32.3
Western Pacific	1600	3.9	62.2
Total	5811	3.1	169.7

**Table-II**

<i>Terminology commonly used in studies related to HCV genomic heterogeneity</i>		
Terminology	Definition	% Nucleotide similarity <sup>a</sup>
Genotype	Genetic heterogeneity among different HCV isolates	65.7- 68.9
Subtype	Closely related isolates within each of the major genotypes	76.9- 80.1
Quasispecies	Complex of genetic variants within individual isolates	90.8- 99

<sup>a</sup> % Nucleotide similarity refers to the nucleotide sequence identities of the full length sequences of the HCV genome.<sup>28</sup>

**Table-III**

<i>Epidemiology of the HCV genotypes</i>		
HCV Genotypes <sup>a</sup>	Geographical distribution	Clinical Significance
1a	United States, Northern Europe	Most common genotypes in the United States. \ May have a more aggressive clinical course than other genotypes and less likely to respond interferon treatment.
1b	United States, Europe, Japan	Often transmitted by transfusion; may have a more aggressive clinical course than other genotypes and higher incidence of HCC; associated with recurrent hepatitis in patients with liver transplants. Less likely to respond interferon treatment.
2a, 2b	Europe, Japan, North America	With genotype 3, excellent treatment responses
2c	Northern Italy	
3a	India, Europe, United States	Associated with intravenous drug use; often associated with hepatic steatosis
4	North Africa, Middle East	
5	South Africa	
6	Hong Kong	
7, 8, 9	Vietnam	
10, 11	Indonesia	

<sup>a</sup> There has been disagreement about the number of genotypes into which HCV isolates should be classified. Investigators have proposed that genotypes 7 through 11 should be regarded as variants of the same group and classified as a single genotype, type 6.<sup>31</sup>

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