Special Series: Communicable Diseases

Viral hepatitis in India

S. K. ACHARYA, KAUSHAL MADAN, S. DATTAGUPTA, S. K. PANDA

INTRODUCTION

Viral hepatitis, caused by hepatitis viruses A through E, is a major public health problem in India. Since 1955, several epidemics of hepatitis have been reported. Although hepatitis A virus (HAV) and hepatitis E virus (HEV), both enterically transmitted, are highly endemic in India, HEV has been responsible for most of these epidemics. In India, HEV infection is responsible for 30%–70% of cases of acute sporadic hepatitis and is the major cause of acute liver failure (ALF). Among children, HAV is the predominant cause of acute hepatitis, and dual infection with HAV and HEV have been more frequently reported among children with ALF.

In India, hepatitis B virus (HBV) infection is of intermediate endemicity, with nearly 4% of the population being chronic HBV carriers, i.e. about 40 million people. Most of them are asymptomatic (high endemicity >8%, intermediate 2%–8%, low <2%). The frequency of hepatitis C virus (HCV) infection, as evaluated by anti-HCV antibody positivity, has been reported to be 1%–2% among voluntary blood donors and 0.87% in the community; these figures are similar to those from developed countries such as Japan and the USA. HBV and HCV are parenterally transmitted and cause both acute as well as chronic disease. About 15%–30% of acute hepatitis in India is due to HBV. However, HCV is an infrequent cause of acute icteric hepatitis, but causes most of post-transfusion hepatitis. HBV is the major cause of chronic hepatitis, cirrhosis and primary liver cell cancer in India. About 50% of chronic liver disease (CLD) is due to HBV and 20% is due to HCV infection. Hepatitis D virus (HDV) infection is found in fewer than 10% of patients with acute or chronic HBV infection.

Based on data from Indian hospitals, annually about 250,000 people die of viral hepatitis or its sequelae. This article reviews the epidemiological, clinical, biochemical, histological and treatment data related to viral hepatitis in India published in the English literature. However, this effort is limited by the lack of a hepatitis registry, and of good community-based epidemiological and seroepidemiological studies.

HEPATITIS E VIRUS (HEV)

HEV infection is the most frequent cause of acute sporadic and epidemic hepatitis in India. HEV has a positive-stranded, 7.5 kb RNA genome with 3 open reading frames (ORFs). It is transmitted predominantly through faecal contamination of water and food. During the past 5 decades, several epidemics of HEV infection have been documented in India. HEV is also the major cause of ALF in India. It has been recently shown to be a common cause of acute superinfection and liver damage among patients with chronic liver disease due to various causes. Thus, HEV is a major public health problem in India and its importance may not have been fully realized yet by public health professionals, clinicians and basic scientists.

Epidemiology

The first and the most well-studied epidemic of HEV affected 29,300 people in Delhi between December 1955 and January 1956. Most of the information on the epidemiological aspects of HEV has been derived from this epidemic. Several well-studied epidemics reported subsequently (Table I) have had similar epidemiological features. In these epidemics, faecal contamination of the source of drinking water was documented. The contamination of drinking water was due to backflow of sewage during floods, leaking sewers located close to corroded drinking water pipes, and contamination of shallow well water during the rainy season.

Unlike other faeco-orally transmitted viral infections (HAV, rotaviruses and polioviruses), person-to-person transmission of HEV is much less frequent. During HEV epidemics, secondary attack rates among household contacts of HEV-infected individuals are 0.7%–2%, 0.87% in the community; these figures are similar to those from developed countries such as Japan and the USA. HBV and HCV are parenterally transmitted and cause both acute as well as chronic disease. About 15%–30% of acute hepatitis in India is due to HBV. However, HCV is an infrequent cause of acute icteric hepatitis, but causes most of post-transfusion hepatitis. HBV is the major cause of chronic hepatitis, cirrhosis and primary liver cell cancer in India. About 50% of chronic liver disease (CLD) is due to HBV and 20% is due to HCV infection. Hepatitis D virus (HDV) infection is found in fewer than 10% of patients with acute or chronic HBV infection.

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documented among children. In India, HEV infection has also been associated with severe liver disease. During epidemics, pregnant women in their second and third trimesters get infected more frequently (12%–20%) than men and non-pregnant women (2%–4%). The frequency of ALF is higher (10%–22%) among pregnant women with HEV infection than among men and non-pregnant women (1%–2%). Hence, the mortality rate is significantly higher among pregnant women who develop hepatitis during epidemics (10%–39%) than in the general population affected with hepatitis (0.06%–12%; Table I). In the sporadic setting, evidence of HEV infection has been detected in 30%–45% of patients with ALF. Among children, combined HEV and HAV infection is frequently associated with ALF. In patients with compensated chronic liver disease, superinfection with HEV has been reported to cause decompensation. However, patients with HEV infection do not develop any chronic sequelae.

**Serology**

The structural region of the HEV genome (ORF2 and ORF3) has been cloned and its encoded polyproteins have been expressed. Commercial enzyme immune assays (EIAs) are now available to detect IgG and IgM antibodies against ORF2- and ORF3-encoded peptides. Most commercial EIAs use both these peptides. In non-endemic regions, the presence of either IgM or IgG antibodies in a patient’s serum is considered evidence of acute HEV infection. During HEV epidemics, anicteric hepatitis E virus (HEV) infection is the detection of HEV RNA in the serum. The recent development of HEV replication that express reporter genes should also help in this direction.

The current understanding of the replication strategy of HEV is based on similarities with other positive-strand RNA viruses. Apart from the detection of negative-strand RNA in infected rhesus macaque liver and presence of subgenomic RNA in experimentally infected cynomolgus macaque and cell culture systems, only one study provides evidence of HEV replication. However, several issues in HEV replication remain unresolved; these include the mechanism of ORF1 polyprotein processing, functions of viral replicase and protease included in the ORF1 polyprotein, regulatory factors controlling HEV gene expression, and the mechanisms of ORF1 polyprotein processing.

**Pathology**

During the 1955–56 epidemic in Delhi, 78 needle liver biopsy specimens from patients with acute hepatitis E were studied. The prominent feature observed in 45 of these was the presence of canicular and intracanalicular cholestasis with formation of pseudoglandular structures resembling embryonal bile ducts. In addition, mononuclear infiltration was prominent in the portal tracts and hepatic lobules, along with ballooned hepatocytes. Similar histological features have been described subsequently.

**Molecular biology**

Tam et al. in 1991 sequenced the entire HEV genome and described its genomic organization. Even after 15 years, little is understood about its mechanisms of replication and transcription, primarily because of the non-availability of a reliable in vivo propagation system. Several authors have reported propagation of HEV in cell culture systems but their work needs independent confirmation. HEV can infect several commonly available macaques and these infected animals have served as the source material for HEV for several years. The development of an infectious cDNA clone for HEV by Panda et al. provides a useful tool for the study of mechanisms involved in viral replication and gene expression during HEV infection. The recent development of HEV replication that express reporter genes should also help in this direction.

Table I. Major epidemics of hepatitis E virus (HEV) infection in India

<table>
<thead>
<tr>
<th>Location (year)</th>
<th>Number affected</th>
<th>Incubation period (days)</th>
<th>Attack rate (%)</th>
<th>Mortality</th>
</tr>
</thead>
</table>
| Delhi* (1955–56) | 29,300          | 18–64                   | 2.3            | 6.5 (0.22) | 10.5$ |}
| Kharagpur† (1960) | 65              | —                       | —              | 0 (0)     | —     |}
| Aurangabad‡ (1961) | 865             | —                       | —              | 3 (0.34) | —     |}
| Siliguri (1966) | 4287            | 28–70                   | 2.5–7.2        | 4 (0.09) | na     |}
| Ahmedabad* (1975–76) | 2572          | —                       | —              | 62 (2.4)  | —     |}
| Kashmir (1978) | 275             | 10–40                   | 1.65           | 10 (3.6)  | 75l   |}
| Azamgarh* (1979–80) | 152            | na                      | na             | 18 (12)   | 39¶   |}
| Kanpur* (1990–91) | 79,091         | 14–56                   | 3.76           | 48 (0.06) | na**  |}

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* serology negative for hepatitis B and A virus † presumed aetiology, serological studies not done ‡ positive serology for HEV § Of 275 affected persons, 8 were pregnant women of whom 6 (75%) died, compared with 4 of 267 (1.4%) men and non-pregnant women
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Mortality among non-pregnant women was 13.4% and among men was 8.4%
** Of 48 deaths, 13 (27%) occurred in pregnant women

$\alpha$-globulin in the serum.
cis-acting elements involved in viral gene expression and replication, and the translation mechanics of ORF2 and ORF3 proteins.

**Genotypes**

Arankalle et al. undertook HEV genotyping of 17 Indian HEV isolates from epidemic and sporadic cases occurring between 1971 and 1991. By sequencing the RNA polymerase (RdRp) region, they divided HEV isolates into 3 genotypes (>15% heterogeneity). Genotype 1 was further subdivided into 1A, 1B, 1C and 1D. The majority of Indian isolates belonged to genotype 1A. In Indian cities that had 2 outbreaks 10 years apart, there was a shift in the subgenotype from 1B (Ahmedabad, 1976) to 1A (Ahmedabad, 1984) and from 1A (Kolkata, 1981) to 1D (Kolkata, 1991). Aggarwal et al. sequenced short ORF1 and ORF2 subgenomic regions from isolates obtained during 3 different outbreaks. They found that sequences within an outbreak were 99.3%–100% identical in both ORF1 and ORF2 regions. However, HEV isolates from different outbreaks had genomic sequence homology of 97.1%–99.2% and 96.4%–100% in the ORF1 and ORF2 regions, respectively.

Despite considerable genomic variability, all the HEV genotypes belong to one serotype.

**Preventive strategy**

In rural India, defaecation in the open is common. This is the major cause of well water contamination, especially during the rainy season. Better sanitation, provision of clean drinking water, proper sewage disposal and public education are the mainstays for prevention of HEV infection. However, since these are difficult to achieve in developing countries with limited resources, the development of a vaccine may be a useful preventive strategy.

Recent studies have evaluated recombinant HEV ORF2 proteins as candidate vaccines. An ORF2-derived 62 kD recombinant protein prepared from the Burmese HEV strain and expressed in baculovirus has shown protection against biochemical or histological hepatitis in monkeys upon challenge with a large dose of a heterologous HEV strain. However, the protection was short-lived. DNA vaccine administered through the gene gun has confers immunity to a large proportion of the population.

**Hepatitis A Virus (HAV)**

HAV is an RNA virus which is transmitted through contaminated water and food. HAV infection is highly endemic in most developing countries including India. However, unlike HEV infection, HAV infection is associated with the development of protective immunity. Further, HAV infection is frequently mild and asymptomatic in childhood. In developing countries, HAV infection is common during childhood, is often subclinical, and confers immunity to a large proportion of the population. Therefore, HAV hepatitis usually occurs in children, and infection in adults is extremely infrequent. However, in the paediatric population dual infection with both the enteric hepatitis viruses (HAV and HEV) is not infrequent and may cause ALF. Parenteral and vertical transmission of HAV is unusual. In contrast, in the developed world, lack of exposure to HAV during childhood results in a large non-immune adult population. In adults, HAV infection has been reported to cause more severe liver disease such as cholestatic and relapsing hepatitis, which has a prolonged course. However, mortality due to HAV is extremely low (0.05%–0.1%). HAV superinfection in patients with pre-existing chronic liver disease has been reported to cause liver failure and death, particularly in the West. Therefore, routine HAV vaccination is recommended in the West for patients with chronic liver disease.

A few recent hospital-based studies suggest that the prevalence of anti-HAV antibodies among Indian adults has declined to <70%, possibly due to improved sanitation and urbanization (Table II). This decline was more marked among the higher socioeconomic group. However, these latter studies were not community-based and included select populations. In community-based studies among unselected schoolchildren, anti-HAV antibodies were detected in nearly 80% of children by the age of 5 years and in nearly all children by the age of 16 years (Fig. 1, Table III). Similarly, anti-HAV antibody was detected in around 97% of

**Table II. Hepatitis A virus antibody (anti-HAV) prevalence rates among children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Anti-HAV positivity n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age ≤5 years</td>
</tr>
<tr>
<td>Dhawan et al.</td>
<td>120 (56)</td>
</tr>
<tr>
<td>Mall et al.</td>
<td>408 (52.2)</td>
</tr>
<tr>
<td>Acharya et al.</td>
<td>206 (86)</td>
</tr>
</tbody>
</table>

**Table III. Age-wise prevalence of hepatitis A virus antibody (anti-HAV) in schoolchildren in New Delhi**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>n</th>
<th>Anti-HAV positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–7</td>
<td>206</td>
<td>178 (86.4)</td>
</tr>
<tr>
<td>8–12</td>
<td>574</td>
<td>528 (91.2)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>644</td>
<td>622 (96.6)</td>
</tr>
</tbody>
</table>

**Fig. 1. Age-stratified prevalence of anti-HAV antibody among Indian schoolchildren aged 4 to 18 years.**

**Hepatitis A virus**

- An enterically transmitted RNA virus
- Causes mild, self-limited hepatitis
- Chronic infection does not occur
- India is hyperendemic for HAV infection
- Mortality due to HAV infection is infrequent
- In India, frequent exposure during childhood makes most people immune by adolescence
- Acute hepatitis A is rare in Indian adults
- Adult infection, if it occurs, results in a prolonged cholestatic or relapsing hepatitis
- Acute liver failure or superinfection are rare
- A safe effective vaccine is available, but its need in India is minimal
Indian patients with chronic liver disease. A large study found no increase in the number of cases of acute hepatitis A (Fig. 2) or ALF due to hepatitis A over a decade (Fig. 3).

The preventive strategies for HAV infection are similar to those for HEV infection. However, unlike HEV, an effective safe, immunogenic, live, attenuated HAV vaccine is commercially available in India and is being marketed aggressively. Among non-immune people, it provides seroconversion rates of >90% and nearly 100% after one and two doses (4–6 weeks apart), respectively.

The extremely high prevalence of anti-HAV antibody in the general population in India implies that a mass immunization programme against HAV would not be cost-effective. As the anti-HAV test is cheaper than the HAV vaccine, it may be cost-effective to do this test before administering the HAV vaccine.

HEPATITIS B VIRUS (HBV)

Chronic HBV infection, a major global public health problem, can lead to the development of liver cirrhosis and liver cancer. Despite the presence of a substantial HBV disease burden, India has not yet embarked on a national programme for the control of this infection.

Prevalence

In India, the frequency of HBV infection has been studied in 4 distinct population groups: (i) blood donors and pregnant women, (ii) general population, (iii) subjects at high risk of acquiring HBV infection, and (iv) patients with various liver diseases.

Blood donors. Table IV shows the HBsAg positivity rates among Indian blood donors. The studies done in the 1970s used less sensitive techniques such as gel diffusion, immunoelectrophoresis or counter-immunoelectrophoresis, whereas those in 1990s used more sensitive techniques such as EIAs or reverse passive haemagglutination assays (RPHA). Despite the variation in tests used, hepatitis B surface antigen (HBsAg) prevalence

**Table IV. Prevalence of hepatitis B surface antigen (HBsAg) positivity among the normal population**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Place</th>
<th>n</th>
<th>Method</th>
<th>Positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillis et al. (1970)</td>
<td>West Bengal</td>
<td>100*</td>
<td>GD</td>
<td>0</td>
</tr>
<tr>
<td>Sama et al. (1973)</td>
<td>Delhi</td>
<td>952†</td>
<td>GD</td>
<td>0.1</td>
</tr>
<tr>
<td>Pal et al. (1973)</td>
<td>Chandigarh</td>
<td>146†</td>
<td>IEOP</td>
<td>1.6</td>
</tr>
<tr>
<td>Sama et al. (1973)</td>
<td>Delhi</td>
<td>879*</td>
<td>CIEP</td>
<td>2.74</td>
</tr>
<tr>
<td>Shannanagam et al. (1973)</td>
<td>Vellore</td>
<td>741†</td>
<td>CF</td>
<td>4.2</td>
</tr>
<tr>
<td>Dutta et al. (1972)</td>
<td>Delhi</td>
<td>796*</td>
<td>GD</td>
<td>2.6</td>
</tr>
<tr>
<td>Singhvi et al. (1990)</td>
<td>Vellore</td>
<td>8569†</td>
<td>ELISA</td>
<td>0.7–3.8</td>
</tr>
<tr>
<td>Elavia et al. (1991)</td>
<td>Mumbai</td>
<td>10 433†</td>
<td>RPHA</td>
<td>2.02</td>
</tr>
<tr>
<td>Irshad et al. (1994)</td>
<td>Delhi</td>
<td>20 435†</td>
<td>RPHA</td>
<td>2.6</td>
</tr>
<tr>
<td>Nigawat et al. (1997)</td>
<td>Jaipur</td>
<td>69 330*</td>
<td>ELISA</td>
<td>2.1–3.1</td>
</tr>
<tr>
<td>Choudhury et al. (2005)</td>
<td>West Bengal</td>
<td>7653*</td>
<td>ELISA</td>
<td>2.97</td>
</tr>
</tbody>
</table>

* voluntary donors † voluntary and professional donors # General rural population GD gel diffusion IEOP immuno electro-osmophoresis CIEP counter-immunoelectrophoresis CF complement fixation RPHA reverse passive haemagglutination

**Table V. Hepatitis B surface (HBsAg) and e (HBeAg) antigen prevalence among pregnant women**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>HBsAg positivity (%)</th>
<th>Among HBsAg-positive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandon et al. (1986)</td>
<td>837</td>
<td>3.6</td>
<td>40</td>
</tr>
<tr>
<td>Nayak et al. (1987)</td>
<td>8575</td>
<td>3.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Sehgal et al. (1992)</td>
<td>4137</td>
<td>2.6</td>
<td>na</td>
</tr>
<tr>
<td>Gill et al. (1995)</td>
<td>2000</td>
<td>5.0</td>
<td>na</td>
</tr>
<tr>
<td>Prakash et al. (1998)</td>
<td>—</td>
<td>9.5</td>
<td>12</td>
</tr>
</tbody>
</table>

na not available
rates were 1%–4.2% in these studies. The HBsAg positivity rates among pregnant women have also been similar (Table V). Whether or not these rates are representative of those in the general population continues to be debated. Further, all these studies were point prevalence studies and did not meet the defining criterion for HBsAg carrier—HBsAg positivity lasting for at least 6 months. In a recent report a correction was applied to the available HBsAg positivity rates for false positivity and false negativity of HBsAg tests and it was calculated that the true HBsAg positivity rate may lie between 1% and 2%. However, based on studies in blood donors and the general population, we still believe that the prevalence rate for HBsAg lies between 2% and 4%. Moreover, 70% of the Indian population lives in rural areas and one large study that systematically sampled a rural population reported the HBsAg prevalence rate to be 2.97%. General population. Community data on HBsAg and antibody to hepatitis B surface antigen (anti-HBs) positivity in the Indian population are scarce. In 2 such recent studies that included about 7653 and 730 healthy individuals, the HBsAg positivity rate was reported to be 2.9% and 2.1%, respectively, and that of antibody to hepatitis B core antigen (anti-HBc) was reported to be 19.5% and 16.5%, respectively. Thus, most studies among blood donors, pregnant women and the general population indicate an HBsAg carrier frequency of 2%–4% and anti-HBs positivity of around 18%–20%.

Indian studies on age-stratified HBsAg positivity rates indicate that a carrier rate of 2%–3% is reached by the age of 5 years and does not increase further with age. However, the anti-HBs positivity rates continue to increase with age (Fig. 4). This indicates that the HBV carrier state is acquired mainly in early childhood and that control strategies against chronic HBV infection should focus on children.

High risk populations. The high risk groups reported from India include (i) individuals with repeated parenteral exposure such as multitransfused patients with thalassaemia/haemophilia, patients undergoing haemodialysis and professional sex workers, (ii) professional blood donors, (iii) healthcare workers with occupational exposure, (iv) household contacts of individuals with chronic HBV infection, and (v) individuals living in specific hyperendemic geographical areas.

In patients with thalassaemia and haemophilia, HBsAg and anti-HBs positivity rates of 6%–60% and 29%–70%, respectively, have been reported (Table VI). HBsAg positivity among professional blood donors has been reported to be 15%–20%, and HBsAg positivity has been reported to be 1.7%–40%. Recently, 2 studies have shown that within India hyperendemic regions for HBV infection may exist—HBsAg positivity of 23.3% among the tribal population in the Andaman and Nicobar Islands, and 5.2% among the Lambada tribe of Andhra Pradesh. Further studies to identify the route of transmission and risk factors for acquisition of HBV infection in these areas may help in developing appropriate control strategies.

Household contacts, particularly spouses and children of persons with chronic HBV infection, are known to be at an increased risk of acquiring HBV infection. Therefore, such household contacts need to be screened for HBV infection and preventive steps taken if they are not already infected.

A substantial proportion of patients with various acute and chronic liver diseases have HBV infection—12.5%–21% of those with acute hepatitis (Table VII), 40% with subacute hepatic failure, 11%–27% with acute liver failure, 35%–60% with cirrhosis of the liver, and 60%–80% with primary liver cell cancer. Asymptomatic HBV carriers may also have superinfection with another virus such as HEV leading to severe liver disease.

**Transmission**

As mentioned previously, the HBV carrier pool in India reaches a plateau by the age of 5 years. The predominant route of transmission among children is horizontal during the preschool and early school years. A well-designed study by Nayak et al. which included 8575 pregnant women found 3.7% of them to be HBsAg positive. Of these, only 7.8% were HBeAg positive; a frequency much lower than that in Southeast Asian countries but similar to that in sub-Saharan Africa where horizontal HBV transmission occurs. The HBV infection rate was 19% among children of HBsAg-positive mothers compared with 3% among those of HBsAg-negative mothers. Among children born to HBsAg-positive mothers, the rate of HBV infection was 87.5% among the offspring of hepatitis B e antigen (HBeAg)-positive mothers and <10% among children of HBeAg-negative mothers.

---

**Table VI.** Prevalence (%) of serological markers of hepatitis B and C (HCV) virus in multitransfused populations

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Place</th>
<th>n</th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
<th>Overall</th>
<th>Anti-HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mittal et al. (1988)</td>
<td>Delhi</td>
<td>27</td>
<td>14.8</td>
<td>48.1</td>
<td>51.8</td>
<td>74.1</td>
<td>–</td>
</tr>
<tr>
<td>Kapil (1989)</td>
<td>Delhi</td>
<td>50</td>
<td>10.0</td>
<td>40.0</td>
<td>62.0</td>
<td>80.0</td>
<td>–</td>
</tr>
<tr>
<td>Bhattacharya et al. (1992)</td>
<td>Calcutta</td>
<td>70</td>
<td>6.0</td>
<td>73.0</td>
<td>49.0</td>
<td>76.0</td>
<td>17.5</td>
</tr>
<tr>
<td>Gulati et al. (1992)</td>
<td>Chanderigarh</td>
<td>100</td>
<td>6.0</td>
<td>73.0</td>
<td>49.0</td>
<td>76.0</td>
<td>17.5</td>
</tr>
<tr>
<td>Amarapurkar et al. (1992)</td>
<td>Bombay</td>
<td>40</td>
<td>45.0</td>
<td>–</td>
<td>–</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>William et al. (1992)</td>
<td>Delhi</td>
<td>54</td>
<td>7.4</td>
<td>–</td>
<td>59.2</td>
<td>66.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Jolly et al. (1992)</td>
<td>Lucknow</td>
<td>251</td>
<td>15.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Choudhary et al. (1995)</td>
<td>Delhi</td>
<td>102</td>
<td>35.2</td>
<td>29.4</td>
<td>1.0</td>
<td>65.7</td>
<td>30.3</td>
</tr>
</tbody>
</table>

*Anti-HBsAg positivity of 44% was observed in the donor blood  anti-HBs antibody to hepatitis B surface antigen  anti-HBc antibody to hepatitis B core antigen*
These data suggest that in the general population about 75% of carriers acquire the infection by horizontal spread during early childhood and the remaining acquire it by vertical (mother-to-child) transmission. A multicentric study and a WHO collaborative study evaluating age-stratified HBsAg prevalence rates as well as studies assessing HBV infection rates among household contacts indicate that horizontal spread of infection may be the predominant route of transmission responsible for the HBV carrier state.

The introduction of mandatory screening of blood donors for HBsAg in India during the 1990s has resulted in a marked decrease in post-transfusion HBV infection. However, despite donor screening for HBsAg, about 25% of post-transfusion hepatitis is still due to HBV. A recent report indicated that about 25% of voluntary blood donors who were HBsAg negative but anti-HBc positive were HBV DNA positive. It may be possible to prevent post-transfusion hepatitis B using anti-HBc screening of blood donors. However, due to the shortage of donated blood in India, discarding anti-HBc positive blood may be difficult. To develop a rational policy in this regard, one would need more data on the frequency of post-transfusion HBV infection following HBsAg donor screening, the proportion likely to be prevented by discarding anti-HBc positive blood, and the effect on the availability of blood.

Another possible route of transmission of HBV infection is the use of non-disposable glass syringes in rural India. Data on the importance of other routes of HBV transmission in India such as tattooing, visits to barbers, body piercing practices and homosexual behaviour are scarce.

**Mutants**

Immune pressure leads to selection of various mutant HBV strains in asymptomatic HBV carriers as well as persons with HBV-associated liver disease. Core promoter (CP) and precore (PC) mutants of HBV are unable to produce HBeAg and have been described predominantly among patients with HBeAg-negative, chronic hepatitis B (CH-B). Though data on HBV mutants in India are limited, these may account for 15%–20% of patients with CH-B.

The classical HBsAg mutation (G145A) has been identified among patients with CH-B in one report. However, HBeAg-negative, HBV DNA-positive (occult HBV) patients with CLD have also been reported. In a recent study, about 10% of patients with HBsAg-negative CLD had HBV DNA in their sera. These patients were also anti-HBe positive. Further, 25% of HBsAg-negative, anti-HBe positive donors had HBV DNA in their sera. The frequency of HBV transmission, disease occurrence, chronicity and the natural course of such HBV mutants (HBsAg negative) are not yet known.

**Genotypes**

HBV genotypes A and D appear to be the most predominant among Indian patients with HBV-induced acute and chronic liver diseases. Further, the prevalence in India of genotype A (Aa) has been found to be different from that in Europe (Ae). HBSAg carriers with the Aa genotype are less likely to be HBeAg positive (31% v. 49%, p=0.033) and have significantly lower HBV DNA levels regardless of the HBeAg status (3.46 v. 6.09 log copies/ml; p<0.001) than Ae infected individuals. The relevance of these genotypes to disease manifestations, natural course, transmission efficiency and response to therapy needs further evaluation.

**Treatment: Indian scenario**

Currently, it is difficult to treat patients with cirrhosis of the liver due to HBV infection. Treatment is directed predominantly at patients with CH-B. In these patients, suppression of HBV replication as evidenced by HBeAg seroconversion to presence of antibody to hepatitis B e antigen (anti-HBe), loss or reduction of HBV DNA to levels <10^5 copies/ml, and normalization of alanine aminotransferase (ALT) are associated with a survival benefit and prevention of serious complications such as cirrhosis and primary liver cancer.

Whereas HBeAg-positive CH-B is more amenable to therapy, HBeAg-negative CH-B (CP/PC HBV mutants) is difficult to treat. Similarly, CH-B patients with associated chronic renal failure, liver or kidney transplantation, or HCV or HIV infection are difficult to treat, with response rates of only 10%–15%, compared with 30%–50% in other patients.

Interferon-α 2b, interferon-β 2a, pegylated interferons and nucleoside analogues such as lamivudine, adefovir, entecavir and tenofovir have been used to treat HBV infection. The results of these therapies have been reported predominantly from western and Southeast Asian countries. Unfortunately, therapeutic data from the Indian subcontinent are scarce.

Two published trials from India, using low dose interferon-α 2b (3 million units thrice weekly for 6 months) have reported sustained virological response (SVR) in more than 60% of treated patients. However, the results of interferon therapy have been unsatisfactory among HBeAg-negative patients; despite achieving an optimal decrease in HBV DNA load, these patients relapse frequently (80%) after the drug is stopped.

Using a Markov transitional probability mathematical model, Aggarwal et al. showed that the cost incurred to gain 1 year of life using interferon treatment was Rs 432 000. The cost for each quality-adjusted life-year gained was Rs 275 000. These estimates were 20.5 and 13.1 times greater than the per capita GNP of the Indian population. They, therefore, recommended that interferon treatment should not be supported from public funds.

Lamivudine, a nucleoside analogue, has been reported to be either as effective or more effective than interferon for the treatment of HBeAg-positive CH-B. However, long term use of this drug is associated with the emergence of lamivudine-resistant HBV (YMDD) mutants. Unfortunately, no head-to-head comparison of lamivudine and interferon therapy in patients with CH-B has been done. Studies on the efficacy of lamivudine therapy among Indian patients are also scarce. At our institution, a recent prospective study showed that 3-year therapy with lamivudine had a significantly better response (54%) than 4–6 months of interferon treatment among HBeAg-positive patients, whereas both the drugs had similar efficacy among HBeAg-negative patients (20% response).

Phyllanthus amarus, a plant product, has been shown to suppress HBV replication. However, except for one Indian study, other studies have failed to establish a definite therapeutic role for this product in CH-B.

Studies on treatment with pegylated interferon and adefovir among Indian patients are limited.
In China and Southeast Asia, transmission of HBV infection associated with the development of chronic HBV infection is predominantly vertical; in the West it occurs in adults due to intravenous drug abuse. In India it is due to horizontal transmission in childhood. The HBV genotypes in China and Southeast Asia are predominantly B and C, which are more frequently associated with liver cancer and progressive liver disease, whereas in India and the West the prevalent genotypes are A and D. Further, recent studies have shown that the subtype of genotype A prevalent in India (Aa) has a lower HBV replication rate and lower HBV DNA load than that of the genotype A prevalent in the West. These differences may explain the better response rates observed in a few available Indian studies. Thus, it seems that HBV infection in India has characteristics that are distinct from the infection seen in Southeast Asia, China, and western countries.

**Epidemiology and prevention strategies in India**

HBV vaccination is a cost-effective method of preventing mortality due to such diseases. According to the Yaounde Declaration of WHO, to which India is a signatory, by 2000 all countries in the world would adopt universal HBV vaccination. Universal HBV vaccination has already been documented to decrease the carrier frequency and disease burden in Taiwan.

From the epidemiological data, it is evident that HBV causes a considerable disease burden in India with substantial loss of human life. Therefore, India requires an appropriate preventive strategy to target identified population groups. However, there are several gaps in the available epidemiological data that need to be addressed before a comprehensive policy can be devised for control of HBV infection in India.

The population prevalence of HBsAg positivity is about 4% as estimated from data derived predominantly from select populations such as blood donors and pregnant women. Some skeptics argue that this rate is likely to be about 1%–2%. Large, community-based prevalence studies are needed to resolve this issue. However, despite conflicting views on HBV carrier frequency, it is clear that immunization against HBV remains the most cost-effective strategy for India.

In India, HBV is believed to have a predominantly horizontal transmission, based on a large study in which the HBsAg positivity rate among HBsAg-positive pregnant women was reported to be <10%. However, some small studies have reported higher HBeAg positivity rates of up to 48%. In a multicentric cross-sectional study from India, the carrier rates were similar among children aged <1, 1–5 and >5 years. Another multicentric study also suggested that horizontal transmission may not have a major role to play. There is a clear need for large studies on age-specific HBV seroprevalence rates in India. Despite the lack of such data, it is clear that childhood infection is the major cause of the HBV carrier state (Fig. 5) and universal childhood HBV immunization will be the most effective HBV control strategy in India. However, if vertical transmission is dominant, then it may be important to administer the first dose of HBV vaccine at birth.

Inclusion of the HBV vaccine in the universal immunization schedule is likely to be the most cost-effective strategy to decrease HBV carrier frequency and disease burden in India. Aggarwal et al. have reported that universal immunization would be more cost-effective than selective immunization. While adopting universal immunization, efforts will be needed to ensure a high coverage rate in countries where HBV vaccination has successfully decreased the carrier frequency and disease burden, at least 80% of the target population has been vaccinated. "Catch up" immunization of adolescents is unlikely to be cost-effective. More data on this are needed from India before any recommendation can be made.

Quality control of donor screening in India is another area where more efforts are needed. In a study from New Delhi, 6% of HBsAg-negative units of blood from various blood banks in Delhi were found to be HBsAg positive on re-testing using a sensitive micro-ELISA technique.

Awareness campaigns on the routes of community-acquired infection and on steps to prevent household and nosocomial spread of HBV infection need to be launched. All household contacts and medical/paramedical staff should be vaccinated against HBV. High risk groups need to be identified, screened for HBsAg and vaccinated against HBV.

While adopting universal immunization, for a successful HBV control programme it is necessary to evaluate the durability of protection, appearance of vaccine escape mutants and compliance of the population. Unless 80% of the target population is vaccinated, the impact on horizontal transmission may be-obtained (in countries where HBV vaccination has decreased the carrier frequency and disease burden, at least 80% of the target population has been vaccinated). The dynamics of post-needlestick HBV transmission are not available from India. Therefore, post-needlestick injuries should be dealt with as anywhere else, i.e. with passive and active immunization combining hepatitis B immunoglobulin and HBV vaccine.

**HEPATITIS C VIRUS (HCV)**

HCV has a single-stranded, positive-sense, RNA genome, approximately 9600 nucleotides in length. Its genome has an
untranslated region (UTR) at each end with one ORF located in between, which encodes for a nearly 3000 amino acid long polyprotein. The 5′-UTR binds with the host cell ribosome to begin the process of translation, whereas the 3′-UTR is necessary for viral replication. The two UTRs represent the most conserved regions of the viral genome. HCV RNA replication occurs in the cytoplasm, during which a mixed population of RNA sequences (quasispecies) are produced. Over time, natural selection occurs under the influence of host immune pressure, leading to gradual drift of the HCV genome and evolution of HCV genotypes, which can vary by up to 35% in their nucleotide sequences. Till now, 11 genotypes and 70 subgenotypes have been described; of these, genotypes 1–6 are the major ones. Genotypes 1 and 4 are associated with resistance to therapy, whereas genotypes 2, 3, 5, and 6 are more amenable to treatment. The genotypes 1 and 4 are prevalent in Japan and the USA; genotype 3 is more common in India.\(^7^,\^9\)

HCV causes both acute and chronic liver disease, including liver cancer. Unlike HBV infection, which becomes chronic in <5% of infected immunocompetent adults, up to 80% of adults with HCV infection develop chronic viraemia. However, only a quarter of chronically infected patients develop chronic hepatitis, a quarter of whom progress to cirrhosis. Among those who develop cirrhosis, 1%–4% progress to liver cancer annually. The rate of progression of HCV-related liver disease is slow and it takes 25–30 years for clinically important liver disease to develop. However, progression may be faster in immuno-compromised persons, alcoholics and obese people.\(^7^,\^9\)

### Prevalence

HCV infection is usually diagnosed by detecting hepatitis C virus antibody (anti-HCV) (ELISA/RIBA) and/or HCV RNA (RT-PCR) in the serum. Data are available on the prevalence of HCV infection in India among blood donors, the general community, high risk groups such as multitransfused patients with thalassaemia and healthcare workers. Reports are also available on the disease burden due to HCV infection.

Using third-generation ELISA, the prevalence of anti-HCV antibody among voluntary or replacement blood donors has been reported in India in 5 large studies that included 57,671 blood donors\(^3^,\^12^,\^41^,\^48^\) and has ranged from 0.7% to 1.8% (Table VIII). Overall, 902 donors (1.5%) were found to be anti-HCV positive.

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**Hepatitis C virus infection**

- Chronic viral infection (50%–80%)
- Chronic hepatitis (25% in 25–30 years)
- Cirrhosis (~25%)
- Hepatocellular cancer (1%–4% per year)

![Fig 6. Natural course of hepatitis C virus infection](HCV_infection_diagram.png)

Among similar populations in the USA and Japan, the prevalence rate is about the same. However, the frequency of HCV viraemia (detectable HCV RNA) in the Indian population has not been reported. In contrast to developed countries where HCV is the aetiological agent in 30%–50% of CLD, in India, of patients attending a large tertiary care hospital, HCV infection was the cause of CLD in only 14%. Long term follow up studies on these anti-HCV positive persons are not available.

The anti-HCV prevalence rate in blood donors may not be representative of the situation in the general population. Two studies have evaluated the community prevalence of HCV in India. Chadha et al.\(^4^,\^5\) screened 1054 healthy volunteers in 4 villages of Bohr Taluka in Pune and found only 1 person to be positive for anti-HCV as well as HCV RNA. In another study, Chowdhury et al.\(^7^,\^9\) used a systematic sampling procedure to select 3579 individuals from among 10,737 inhabitants of 9 villages in the Birbhum district of West Bengal; of these, 2973 individuals (83%) could be screened for anti-HCV antibody using a sensitive third-generation commercial ELISA. The frequency of anti-HCV in this population was 0.87% (26 of 2973); 81% (21 of 26) of those who were anti-HCV positive were viraemic (HCV RNA positive).

Further, only 0.3% of children (2 of 646) below 10 years of age were anti-HCV positive, and the positivity rate increased with age (Table IX), indicating that HCV infection in India is a disease of adults. These data suggest that about 10 million Indians are anti-HCV positive and 5 million of them may be viraemic. Of these, nearly 25%, i.e. over 1 million, may develop CLD within 2 decades and 1%–4% of them may develop liver cancer. Treatment of such a large number of persons with CLD would need a massive infrastructure.

### High risk groups

Since HCV is transmitted parenterally, people who have received multiple transfusions of blood and blood products such as those with thalassaemia and haemophilia, patients with renal failure undergoing haemodialysis, patients who have had a renal transplant and healthcare workers are at an increased risk of contracting HCV infection. The point prevalence of HBV and HCV markers among such a large number of persons with CLD would need a massive infrastructure.

---

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Donor population</th>
<th>n</th>
<th>Anti-HCV positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Das et al. (2000)(^41)</td>
<td>Voluntary and replacement</td>
<td>22245</td>
<td>330 (1.4)</td>
</tr>
<tr>
<td>Arankalle et al. (1995)(^42)</td>
<td>Voluntary and professional</td>
<td>2726</td>
<td>21 (0.7)*</td>
</tr>
<tr>
<td>Jain et al. (2003)(^43)</td>
<td>Voluntary</td>
<td>15898</td>
<td>249 (1.6)</td>
</tr>
<tr>
<td>Kumar et al. (1997)(^44)</td>
<td>Voluntary</td>
<td>780</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Pangrahi et al. (1997)(^45)</td>
<td>Voluntary</td>
<td>15922</td>
<td>295 (1.8)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>57671</td>
<td>902 (1.5)</td>
</tr>
</tbody>
</table>

*RIBA-III test used. All others used ELISA-III*

---

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>n</th>
<th>Anti-HCV positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>646</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>10–19</td>
<td>723</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>20–39</td>
<td>935</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>40–59</td>
<td>507</td>
<td>5 (0.99)</td>
</tr>
<tr>
<td>≥60</td>
<td>162</td>
<td>3 (1.85)</td>
</tr>
</tbody>
</table>

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\(^{210}\) THE NATIONAL MEDICAL JOURNAL OF INDIA \ VOL. 19, NO. 4, 2006
among multitransfused individuals (Table VI) has been reported to be very high (11%–62%). However, these studies were conducted before 2002 when mandatory screening of blood donors for anti-HCV was introduced in India. Thus, the current rates may be lower. For instance, among patients undergoing haemodialysis, the anti-HCV rates (initially 24%–28%) have come down to about 4%,108 with the use of dedicated haemodialysis units for HCV-infected patients and screening of blood donors.

The point prevalence of anti-HCV among healthcare workers in India is similar to the general population (0%–1.5%).142,147,149 However, one report from Rajasthan showed an anti-HCV positivity rate of 5.4% among dentists.109 Larger studies are needed among healthcare workers of various categories, as they may be transmitting HCV infection to their patients. A report from Kolkata has estimated the frequency of seroconversion to anti-HCV following a needlestick injury to be 9% (6 of 68).109 In India, anti-HCV prevalence data have not been reported among intravenous drug abusers, sex workers and homosexuals.

Transmission
HCV infection is transmitted predominantly by the parenteral route. Sexual and vertical transmission is infrequent except when HIV co-infection is present.10 In India, HCV infection is acquired most often through transfusion of blood or blood products.31,173,174 Community-acquired infection is another major route.35

In a report from northern India, about half the patients with chronic hepatitis C (CH-C) had received blood transfusion(s).175 A study from Vellore in southern India reported that 61% of 90 patients with chronic HCV infection had acquired the infection following blood transfusion.176 In another report, 7% of patients who had undergone coronary artery bypass surgery and transfusion developed post-transfusion hepatitis; 80% of them had evidence of HCV infection.177 In a community study, 81% of anti-HCV positive individuals reported having received injections using unsterile glass syringes and none had received a transfusion.35 The presence of HCV infection was associated with the use of glass syringes with a crude odds ratio of 3.8, but not with age, sex, educational status, socioeconomic status, shaving by community barber, transfusion, tattooing or dental therapy.35

A study from Pune did not detect anti-HCV in any of 430 pregnant women or children <5 years of age (n=86).180 In a recent survey of 5–17-year-old schoolchildren (n=1900) in Delhi, none was positive for anti-HCV.34 These figures suggest that sexual and vertical transmission of HCV is negligible in India. Recently, a study from Punjab reported an anti-HCV positivity rate of 16% among household contacts of index cases.181 However, in this study only 50% of household contacts had been evaluated. Thus, there is a need for further studies on this subject.

In India, several traditional body-piercing practices are prevalent in rural and tribal populations. However, data on the prevalence of anti-HCV in these select populations are lacking.

Viral characteristics
Certain viral characteristics have been associated with the progression and severity of HCV-related liver disease and therapeutic response. Genotype 1 HCV infection is resistant to treatment and is associated with progressive disease.182 A viral load >3.5 million copies/ml has been associated with a poor therapeutic response;183 however, a relationship with disease severity has not been established.102

Several published reports from India describe the relative frequency of various HCV genotypes (Table X).13,172–177 in the northern172,173,176 and southern175,177 parts. In these studies, genotype 3 was found in 54%–90% of HCV-infected patients; overall, 60% of patients had genotype 3, 25% had genotype 1, 8% had genotype 2 and 2% had genotype 4 infection. HCV genotype 1 infection was more frequent in southern India than in the rest of the country.

Data on viral load estimation in Indian patients with HCV infection are scarce. In a study from southern India (n=73), the mean HCV viral load using the commercial Amplicor assay was 10^6 copies/ml (range 1.2×10^6–2.5×10^9 copies/ml); in the northern172,173,176 study only 50% of household contacts had been evaluated. Thus, there is a need for further studies on this subject.

Table X. Genotypic distribution of HCV in India

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Region</th>
<th>Genome region</th>
<th>Method</th>
<th>n</th>
<th>Genotype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vallannai et al. (1995)175</td>
<td>Southern</td>
<td>5' UTR, NS5</td>
<td>Direct sequencing</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Panigrahi et al. (1996)172</td>
<td>Northern</td>
<td>Core, NS5</td>
<td>Direct sequencing</td>
<td>11</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Amaraparakur et al. (2001)174</td>
<td>Western</td>
<td>5' UTR</td>
<td>Direct sequencing</td>
<td>61</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Raghuraman et al. (2003)177</td>
<td>Southern</td>
<td>Core</td>
<td>Type-specific primers, PCR</td>
<td>90*</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Chowdhury et al. (2003)175</td>
<td>Eastern</td>
<td>Core</td>
<td>Type-specific primers, PCR</td>
<td>21</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Hazari et al. (2004)173</td>
<td>Northern</td>
<td>Core, NS5</td>
<td>Direct sequencing</td>
<td>51</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Hissar et al. (2006)180</td>
<td>Northern</td>
<td>UTR, NS5</td>
<td>Direct sequencing</td>
<td>398</td>
<td>52 (13.1)</td>
</tr>
</tbody>
</table>

* 11 patients could not be genotyped. UTR, untranslatable region; NS5, non-structural region 5; PCR, polymerase chain reaction.

In India, several traditional body-piercing practices are prevalent in rural and tribal populations. However, data on the prevalence of anti-HCV in these select populations are lacking.

**Disease burden**
Of patients with CLD, HCV is the aetiological agent in 14%–26%,31,132,133,193 and 14%–20% of patients with hepatocellular cancer in India.13,194

Among 247 patients with sporadic acute viral hepatitis, 9% had HCV viraemia.35 Similarly, HCV RNA could be detected in 7 (14%) of 50 patients with ALF.185 5 of these 7 patients had associated HBV and 2 had associated acute HEV infection. HCV is rare in ALF in other parts of the world except in Japan where active HCV infection has been documented in about 40% of patients.196

Extrahepatic manifestations of HCV such as cryoglobulinaemia, membranoproliferative glomerulonephritis, porphyria cutanea tarda, sicca syndrome, lichen planus, etc. have been reported infrequently from India. Agarwal et al. failed to detect cryo-
Hepatitis C virus

- Prevalence of anti-HCV antibody in India is around 1% which is similar to that in western countries and Japan.
- 15%-20% of chronic liver disease and HCC in India are caused by HCV.
- 80% of post-transfusion hepatitis in India is due to HCV.
- Transfusion and use of unsterile glass syringes are the dominant mode of transmission of HCV in India.
- Genotypes 3 and 2 are more prevalent in India.
- Therapeutic response among Indian patients with chronic hepatitis C seems to be excellent.

TABLE XI. Prevalence rates (%) of hepatitis D virus antibody among patients with liver disease, healthcare workers (HCW) and patients with chronic renal failure (CRF) in India

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Viral hepatitis</th>
<th>CLD</th>
<th>HCC</th>
<th>Liver failure</th>
<th>HBV carrier</th>
<th>HCW</th>
<th>CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Chronic</td>
<td>Acute</td>
<td>Subacute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kochhar et al. (1989)&lt;sup&gt;206&lt;/sup&gt;</td>
<td>15</td>
<td>33</td>
<td>0</td>
<td>26</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>Jain et al. (1994)&lt;sup&gt;204&lt;/sup&gt;</td>
<td>4.7</td>
<td>43</td>
<td>nr</td>
<td>13</td>
<td>28.5</td>
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<td>Narang et al. (1996)&lt;sup&gt;205&lt;/sup&gt;</td>
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<td>nr</td>
<td>36</td>
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<td>Tandon et al. (1987)&lt;sup&gt;206&lt;/sup&gt;</td>
<td>23.5</td>
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<td>Amarapurkar et al. (1992)&lt;sup&gt;201&lt;/sup&gt;</td>
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<td>Arankalle et al. (1992)&lt;sup&gt;206&lt;/sup&gt;</td>
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<td>nr</td>
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<td>nr</td>
<td>6</td>
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<td>9</td>
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<tr>
<td>Jaiswal et al. (1999)&lt;sup&gt;209&lt;/sup&gt;</td>
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HBV hepatitis B virus: nr not reported. CLD: chronic liver disease. HCC: hepatocellular cancer.

Hepatitis D Virus (HDV)

HDV is a small RNA virus, 36 nm in diameter, which shares several properties with defective plant RNA viruses, including viroids and satellite RNAs. The HDV genome encodes for a protein, the hepatitis D antigen (HDAg), which together with the viral RNA requires encapsidation with the HBsAg. Therefore, HBV infection is mandatory for the existence of a replicative HDV infection.

HDV infection is common in Italy and Eastern Europe, South America, the Amazon basin and in the Mediterranean region; about 15 million persons are infected with HDV globally. The infection is transmitted among HBV-infected persons by the parenteral route. HDV co-infection (simultaneous infection of HBV and HDV) and HDV superinfection (HDV infection superimposed on pre-existing chronic HBV infection) are both associated with progressive and severe liver disease. During HDV infection, IgM anti-HDV, IgG anti-HDV and HDV RNA can be detected in serum, and HDAg can be detected in the liver tissue. HDV co-infection and superinfection are diagnosed based on the presence and absence, respectively, of IgM anti-HBc in the presence of one of the HDV markers. HDV infection is common in India though at a relatively low rate, and may be the cause of severe liver disease in a subset of patients.

OTHER RARE HEPATITIS VIRUSES

Hepatitis G virus (HGV), Sen virus and TT virus (TTV) are candidate hepatitis viruses. Although these agents are transmitted through blood transfusion, there is little evidence to associate these with liver disease.

In India, Kar et al. showed HGV RNA in 4% of 50 healthy controls and 47% of 46 healthy commercial blood donors. Panigrahi et al. reported HGV viraemia in 39.7% of multi-transfused thalassaemic children; sequence analysis of 11 of their
HGV isolates showed 81.3%–94.5% homology to isolates from the rest of the world. Kapoor et al.\textsuperscript{213} could detect HGV RNA in 5/35 (14.3%) patients with acute viral hepatitis and in 4/15 (26.6%) patients with ALF; however, its relation to disease was doubtful, because HGV RNA persisted even 6 months after full clinical and biochemical recovery.

**VIRAL HEPATITIS AND HEPATOCELLULAR CANCER**  
Globally, hepatocellular cancer (HCC) is the fourth most common cause of cancer-associated deaths.\textsuperscript{214} About 80% of these liver cancers as well as mortality related to the disease occurs in Asia and Africa.\textsuperscript{215} Five-year survival among patients with symptomatic HCC is less than 5%.\textsuperscript{216} About 60%–80% of HCC throughout the world are associated with chronic HBV or HCV infections and a similar proportion have underlying cirrhosis.\textsuperscript{218}

Information on HCC in India is scarce and comes from three main sources:\textsuperscript{216} (i) autopsy data, (ii) cancer registry data, and (iii) published reports. Autopsy studies have reported the prevalence of HCC to be 0.2%–1.6%,\textsuperscript{216} being higher in southern India (1%–2%) than in other parts of India (<0.2%).\textsuperscript{216} However, in contrast to autopsy studies, cancer registry data revealed similar prevalence of HCC throughout the country, which is lower than that for China, Southeast Asia and Japan but higher than that for the USA, UK and Europe.\textsuperscript{216} Based on the population registry data, the mean incidence of HCC per 100 000 population was reported to be 2.77 and 1.28 for men and women, respectively.\textsuperscript{216} The incidence among the immigrant populations in Singapore and Australia, as documented in cancer registries in these countries, also indicate that Indians are less prone to develop HCC than Chinese or Malays (Table XII).

However, there is a dearth of cohort studies among Indian patients who are at a high risk to develop HCC, such as those with HBV- and HCV-induced cirrhosis. In an ongoing study (unpublished), 9 of 194 cirrhotics during a 3-year follow up period developed HCC—an annual incidence of 1.63 among these cirrhotics.\textsuperscript{216}

Globally, HBV and HCV are the major aetiological agents associated with HCC.\textsuperscript{215} In India, 36%–74% of HCC were associated with HBV and about 30% with HCV infection.\textsuperscript{216} In a recent large series of 215 patients with HCC from India,\textsuperscript{216} 55% patients had HBV infection, 9% had HCV infection and 6% were alcoholics. More than one aetiological factor was present in 10% of patients, whereas in 26% no underlying cause was found. Only 69 (32%) of these 215 patients could be provided curative (surgery, radiofrequency ablation or percutaneous acetic acid injection) or palliative (transarterial chemoembolization or radioisotope embolization) therapy. The remaining patients had advanced disease with portal vein thrombosis or extrahepatic spread.

Therefore, the incidence of HCC in India seems to be lower than that in other Asian and African countries. The reason for this remains unclear but may be related either to host factors (genetic predisposition) or to viral factors (HBV genotype, viral load, etc.). In India, genotypes A and D of HBV and genotypes 2 and 3 of HCV are prevalent. These prevalent genotypes presumably are less virulent than the genotypes B and C of HBV or genotypes 1 and 4 of HCV, which are more prevalent in countries with a higher incidence of HCC such as Japan, Taiwan and China. Control of HBV and HCV infections should lead to a reduced incidence of HCC.

**SUMMARY**

Viral hepatitis is a major public health problem in India, which is hyperendemic for HAV and HEV. Seroprevalence studies reveal that 90%–100% of the population acquires anti-HAV antibody and becomes immune by adolescence. Many epidemics of HEV have been reported from India. HAV related liver disease is uncommon in India and occurs mainly in children. HEV is also the major cause of sporadic adult acute viral hepatitis and ALF. Pregnant women and patients with CLD constitute the high risk groups to contract HEV infection, and HEV-induced mortality among them is substantial, which underlines the need for preventive measures for such groups. Children with HAV and HEV infection are prone to develop ALF.

India has intermediate HBV endemicity, with a carrier frequency of 2%–4%. HBV is the major cause of CLD and HCC. Chronic HBV infection in India is acquired in childhood, presumably before 5 years of age, through horizontal transmission. Vertical transmission of HBV in India is considered to be infrequent. Inclusion of HBV vaccination in the expanded programme of immunization is essential to reduce the HBV carrier frequency and disease burden. HBV genotypes A and D are prevalent in India, which are similar to the HBV genotypes in the West. HCV infection in India has a population prevalence of around 1%, and occurs predominantly through transfusion and the use of unsterile glass syringes. HCV genotypes 3 and 2 are prevalent in 60%–80% of the population and they respond well to a combination of interferon and ribavirin. About 10%–15% of CLD and HCC are associated with HCV infection in India. HCV infection is also a major cause of post-transfusion hepatitis. HDV infection is infrequent in India and is present about 5%–10% of patients with HBV-related liver disease.

HCC appears to be less common in India than would be expected from the prevalence rates of HBV and HCV.

The high disease burden of viral hepatitis and related CLD in India, calls for the setting up of a hepatitis registry and formulation of government-supported prevention and control strategies.

**REFERENCES**


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