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Editorial

Lower chronic hepatitis B in South Asia despite all odds: Bucking the trend of other infectious diseases

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Hepatitis B virus (HBV) infection remains a significant global health problem. As per estimates of the World Health Organization (WHO), approximately 2 billion people have been infected worldwide, which represents one-third of the world population. Of these, more than 350 million (5-7% of the world's population) suffer from chronic HBV infection.[1,2] Approximately 15-40% of the infected patients will develop life-threatening liver diseases (cirrhosis, liver failure and hepatocellular carcinoma) resulting in 600,000 to 1.2 million deaths per year due to HBV.[3,4] Epidemiological data on HBV infection is therefore important for strategies to tackle the spread of the disease.

Based on the prevalence of hepatitis B surface antigen (HBsAg), countries are classified as having high (≥8%), intermediate (2-7%) or low (<2%) HBV endemicity. Areas of high endemicity (where ≥8% of the population is HBsAg positive) include South-East Asia, China, most of Africa, most of Pacific Islands, the Amazon basin and parts of the Middle East. The areas of intermediate endemicity (2-7%) include South Asia, Eastern and Southern Europe, Russia and Central and South America. On the other hand areas with low endemicity (<2%) include United States, Western Europe and Australia.[5]

The South Asian countries, a contiguous block of countries which have been classified together as Global Burden of Disease Regions include Afghanistan, Bangladesh, Bhutan, India, Nepal and Pakistan.[6] People in South Asia are at a higher risk of developing infectious diseases due to poverty and its associated problems of unhygienic living conditions, malnutrition, illiteracy, and poor access to clean water, toilet facilities, and quality health care. Spread of HBV infection in many South Asian countries is attributed to unsafe blood supply, reuse of contaminated syringes, lack of maternal screening to prevent perinatal transmission and delay in the introduction of hepatitis B vaccine.[7] However, it is intriguing that bucking the trend of other infectious diseases, the prevalence of HBV in South Asian countries is lower than some of the more affluent neighbors in the South East Asian countries. Re-emphasizing the lower prevalence of HBV in South Asia is an article by Shrestha et al[8] in this issue of Tropical Gastroenterology, which shows that the prevalence of HBV in Nepal is even lower than that in other countries of South Asia.

HBV in India

India is the largest nation in the region and by its sheer population bears the bulk of HBV burden in South Asia and accounts for 10-15% of the entire pool of HBV carriers of the world.[9] It has been estimated that India has over 40 million HBV carriers. Of the 25 million infants born every year in India, it is estimated that over one million run the lifetime risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illnesses related to HBV infection.[10]

The overall rate of HBsAg positivity has been reported to range between 2-4.7%.[11,12] A meta-analysis found the point prevalence of HBV to be 2.4% in non-tribal populations and 15.9% among tribal populations.[13] However, a disproportionately high amount of data is from a select few areas. In a repeat calculation of the prevalence of HBV in India using population-weights, it was estimated that the point-prevalence of hepatitis B among non-tribal and tribal populations was 3.07% (95% CI: 2.5-3.64) and 11.85% (95% CI: 10.76-12.93), respectively and the overall prevalence was 3.70% (95% CI: 3.17-4.24), (corresponding to a chronic carrier rate of 2.96%).[14]

A higher prevalence of HBV infection has been reported in patients with human immunodeficiency virus (HIV) positive intravenous drug users in Manipur in northeast India[15] and in tribals. The point prevalence of HBsAg in the Idu Mishmi tribe of Arunachal Pradesh, which has common ancestral roots with the Lobha tribe of Tibet, was found to be 21.2%.[16] Very high levels of HBsAg positivity have also been reported in the tribes of Andaman and Nicobar Islands (Nicobarese tribe - 23.3%, Shompen tribe - 37.8%, Jarawa tribe - 65%).[17,18] The high endemicity of HBV infection in the tribal populations has been attributed to inbreeding, poor hygienic living conditions, close person-to-person contact and certain socio-culture practices which may facilitate transmission of HBV.[19]

While earlier studies have shown a prevalence of HBsAg positivity of 2.3-6.3% in pregnant women,[20-23] Dwivedi et al[24] have shown a lower prevalence rate of 0.9%. However, unlike most studies showing lower levels of HBeAg positivity in HBV infected pregnant women,[12] Dwivedi et al[24] reported a high replicative rate, with 56.8% of the patients being HBeAg positive.

The common genotypes reported from most parts of India are genotype A followed by D.[25-31] However, gentotype C has also been reported besides genotypes A and D from eastern India and the northeastern Indian state of Arunachal Pradesh.[12,32,33] There are isolated reports of genotype E, F and G from India.[32,34,35]

HBV in Nepal

Shrestha et al[8] in this issue of Tropical Gastroenterology report that the prevalence of HBV in Nepal is 0.9%. The low prevalence of HBV in Nepal has also been earlier noted in 1987 by Nakashima et al.[36] However, like India, Nepal has its own share of higher prevalence communities. The high prevalence of HBV in the migrant Tibetan population has been attributed to their Tibetan ancestory.[8] Chiba et al[37] have however shown low prevalence of HBV in Sherpas despite their Tibetan ancestry. Besides, nucleotide sequencing of the PreS1, PreS2 and S genes among Sherpas was similar to that prevalent in Nepalese but rare in native Tibetans, suggesting transmission within Nepal rather than association with ancestral migration from Tibet, as the origin.

The HBsAg prevalence among pregnant women in Nepal is low (0.5%) and limited data has shown no evidence of replication.[8] The commonest HBV genotypes in Nepal are D (69%) followed by genotype A (22%); while mixed infections (4.4%) and genotype C (4.4%) occur rarely.[8]

HBV in Bangladesh

The prevalence of HBV in Bangladesh has been reported to vary from 3 to 7.5%.[38-44] HBV prevalence in the healthy adult population in Bangladesh appears to be on the decline since earlier reports of 7.2-7.5%[43,44] to 5.5% in recent data.[39] The prevalence of HBsAg positivity in pregnant women has been reported to be 0.4% in the rural population[45] and 3.5% in urban regions.[46] The subgenotype C2, which has been isolated in China and South-East Asia has also been detected in Bangladesh.[47]

HBV in Bhutan

There is limited data available from the other mountain kingdom, Bhutan, located to the northeast of India. HBsAg was found in 5.9% of the samples from the general population (5.2% in children, 5.6% in young people and 6.3% in adults) and in 5.4% of pregnant women. Of the HBsAg-positive pregnant women, 29.1% were HBeAg negative and HBV DNA positive.[48] Surprisingly the HBsAg carrier rate was found to be low (0.9%) in Bhutanese refugees residing in Nepal.[49]

HBV in Pakistan

Reviews of published literature have estimated that there are 7-9 million carriers of HBV with a carrier rate of 2.6-5% in Pakistan.[50,51] A prevalence survey on hepatitis B infections to obtain national estimates showed a HBsAg positivity of 2.5%.[52] A prevalence of 5-7% HBsAg positivity has been reported from Sindh.[53,54] A high HBsAg positivity of 9.8% has been detected in Balochistan.[55] Armed conflicts and political

instability in Afghanistan have lead to a huge influx of refugees into the neighboring provinces of Pakistan. Hepatitis B is highly endemic among these Afghan refugees.[56,57]

Studies on pregnant women in Pakistan showed HBV infection rates of 2.9% (range 1.8—12.6%).[58] HBeAg positivity has been shown to be 22.9% in HBsAg-positive mothers.[59]

Genotype D has been reported as the most prevalent genotype in Pakistan.[60] A summary of reports from Pakistan show the average prevalence of HBV genotypes as, D (62%), A (14%), C (6%), other genotypes, including B (4%), and recombinants (10%). The genotypes E and F are unusual in the Pakistani population.[61] However, Awan et al[62] in patients from four different geographical provinces of Pakistan, found contradictory results, with Genotype C as the most prevalent genotype.

HBV in Afghanistan

The country has been ravaged by prolonged armed conflicts resulting in poverty, increasing illiteracy, breakdown of social structure and increase in high-risk behavior of intravenous drug abuse. There has been paucity of community based epidemiologic data about the actual prevalence rate of HBV from Afghanistan. The limited data available from Afghanistan shows a HBV prevalence of 1.9%.[63] Prevalence of HBV in IV drug users has been reported as 5.8-6.5%.[64-65]

Evaluation of genotypes from Afghanistan showed that genotype D (35.67%) was the predominant genotype followed by genotype C (32.16%), genotype A (19.30%), and genotype B (7.02%).[66]

Interpreting the epidemiology of HBV in south Asia

The epidemiology of HBV in South Asia is depicted in **Table 1**.

The data on prevalence of HBV from South Asia is sketchy with scarcity of large nation-wide epidemiological studies. As more data becomes available it may not be surprising to find a higher prevalence in some countries like Afghanistan where the available data shows only 1.9% prevalence of HBV. In comparison to these prevalence rates of HBV in South Asia, the South-East Asian countries in general have a higher prevalence with the highest rates in Taiwan (>10%) and Thailand (>8%).[67]

Looking at the prevalence of HBV in South Asia, two questions arise in one's mind. First, how is it that the prevalence of HBV is lower in South Asia as compared to South-East Asia despite the lower socio-economic status, illiteracy, low immunization rates, regional conflict and high-risk tribal populations? Second, how does one explain the lower prevalence of HBV in Nepal as reported in this issue by Shrestha et al?[8]

This lower transmission of HBV in South Asia, despite all odds, is due to the fact that unlike the vertical transmission of HBV in South-East Asia, the predominant mode of transmission is horizontal in South Asia as shown by Gupta et al[68] from North India and Shrestha et al[8] from Nepal. The precise mode of horizontal transmission is unknown but it may be due to contact of non-intact skin or mucous membranes with tears, saliva or blood containing secretions or through sharing of toothbrushes. The age of acquisition of HBV is an important determinant of outcome; the earlier the age, the higher the likelihood of chronicity. The risk of chronicity in HBV infection acquired at different ages ranges from >90% in newborns, 30% in children aged 2-5 years and <5% in adults. Neonates with vertically acquired HBV infection have a higher chance of chronicity and serve as a reservoir of the infection. On the other hand, infection acquired in adulthood is more likely to present as acute hepatitis B and contribute less to the burden

Table 1: Epidemiology of Chronic hepatitis B in South Asia

	Overall prevalence of HBV	High prevalence regions	Prevalence of HBV in pregnancy	Genotypes
Afghanistan*	1.9%			D>C>A>B
Bangladesh*	5.5%		Rural: 0.4%, Urban: 3.5%	
Bhutan	5.9%		5.4% (HBsAg +ve: 29.1%)	- C2
India	2.96%	- Tribals (Arunachal Pradesh, Andaman & Nicobar) - IVDU# Manipur	0.9-6.3 % (HBeAg +ve: 12 - 57%)	- D >A - Eastern India: C - Isolated reports: E, F, G
Nepal	0.9%	- Tibetan community	0.5% (HBeAg +ve:0 %)	- D >A-Rare: C
Pakistan	2.5%	- Balochistan - Afghan Refugees	2.9% (range 1.8-12.6%) (HBeAg +ve:22.9 %)	- D >A>C (?Commonest genotype C) - Rare: E, F

** Limited data*

 # IVDU- Intravenous drug users

of chronic HBV.

The differences in HBV transmission in South-East Asia and South Asia may be related to differences in genotype distribution and mutations in the HBV genome. Genotypes B and C are most prevalent in highly endemic areas where vertical transmission is the primary mode of transmission. In contrast, HBV genotypes A, D, E, F and G are detected in areas where horizontal or sexual transmission is more common. Pockets of high prevalence of genotype C in Arunachal Pradesh have a high prevalence of HBV. Infection with HBV genotype A is associated with increased replication and high concentration of HBV DNA in body fluids of HBV carriers, which lead to an increased risk of horizontal transmission.[69,70] Different genotypes may be preferentially transmitted by different modes.[71] HBV genomic heterogeneity may also play an important role in HBV intrauterine infection and certain mutations in preS1 region, preS2 region and S region might infect fetuses more readily.[72]

The second question that one needs to address is how we interpret the lower prevalence of HBV in Nepal as compared to the rest of South Asia. In Nepal the transmission may be occurring at an older age as postulated by Shrestha et al.[8] The mountain kingdom of Nepal has remained relatively insulated to the spread of HBV as compared to its neighbors. The other South Asian countries, have their own peculiar issues like armed conflicts and terrorism resulting in injuries, transfusions and refugees, high-risk tribal populations, blood donation by paid donors, etc. Besides, reports of genotype C in pockets of the other South Asian countries may have a role in transmission of the virus. Based on the distribution of hepatitis B markers in different age groups in Nepal, Shrestha et al[8] have postulated that the mode of transmission in Nepal is horizontal transmission acquired in the adolescent period. However, they have not offered any explanation for the same based on any socio-cultural behavior patterns in Nepal. The prevalence of HBeAg in HBsAg-positive pregnant Nepalese women was found to be zero. This however is an extreme figure, which would require validation by larger studies.

Conclusion

The burden of vertical and horizontal transmission has been debated to determine the importance of the birth dose in immunization programs. While it is stated that the transmission of HBV in South Asia is horizontal, the contribution by vertical transmission may be underestimated if we look at the high prevalence of replicative markers in HBsAg-positive pregnant women as reported by Dwivedi et al.[24]

As a result of vaccination, carrier rates of hepatitis B surface antigen in children plummeted from 9.8% to 0.7% in Taiwan.[73] South Asia with its large burden of HBV is still far from universal immunization. Despite lower prevalence of HBV, due to its large population, South Asia contributes significantly to the global burden of chronic HBV. It is time for South Asia to take note and consolidate the advantage of lower prevalence of HBV in the area by targeting transmission of the virus to further control the morbidity and mortality related to HBV.

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