

## World Hepatitis Day 2019 – Bringing Medical Advances to Every Man

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The World Health Organization (WHO) estimates that 257 million people worldwide have chronic hepatitis B virus (HBV) infection and another 71 million people have chronic hepatitis C virus (HCV) infection.<sup>1</sup> In 2015, both infections accounted for 1.34 million deaths worldwide and this worked out to 2.5 deaths every minute from 1 of the hepatitis viruses. Such diseases of the liver have vexed physicians for centuries and was described by Virchow as “catarrhal jaundice” about 100 years ago.<sup>2</sup> Realising that the condition was probably infectious owing to clustered outbreaks, the term “serum vs infectious hepatitis” was subsequently coined. It was not until 1965 when the late physician, Baruch Samuel Blumberg, discovered HBV in the blood of an Australian aborigine as one of the main culprits of “serum hepatitis”.<sup>3</sup>

Conversely, the predominant cause of “infectious hepatitis” (transmitted via the oral-faecal route), the hepatitis A virus, was isolated in the 1970s. Recognising that there were still many patients who had blood transfusion-related liver disease despite having tested negative for hepatitis A and B, HCV was finally identified in 1989. Since then, 3 other hepatitis viruses—D, E and G—have been discovered but, fortunately, to date only HBV and HCV cause chronic infection in the general population.<sup>4</sup> Chronic hepatitis D virus infections occur only in individuals who are already afflicted with chronic hepatitis B infection.

Asia has one of the highest endemicity for chronic hepatitis B infection with vertical transmission being the primary mode of infection.<sup>5</sup> The introduction of hepatitis B vaccination in the 1980s was a breakthrough in public health intervention and substantially reduced worldwide HBV infection rate in children <5 years old from 4.7% to 1.3%.<sup>1</sup>

In Singapore, the universal neonatal vaccination programme was launched in 1987 and a catchup programme was implemented between 2001 and 2004. Community studies showed that chronic hepatitis B age-standardised prevalence has dropped from 4.0% in 1999 to 2.8% in 2005. In the age group that would have been vaccinated, the presence of hepatitis B surface antibody increased from 27.9% in 1999 to 41.7% in 2005.<sup>6</sup> The implication of this is huge since chronic hepatitis B is the most common cause

of hepatocellular carcinoma (HCC) in Asia. Prospective longitudinal data from Asia has shown convincingly that this anticancer vaccine significantly reduced the incidence of HCC and mortality by >80%.<sup>7</sup>

For those who are already infected, there are now various treatment options that are highly effective for the control of hepatitis B.<sup>8</sup> In addition to pegylated interferon, first-line oral antivirals such as entecavir and tenofovir are highly potent medications that have minimal risks of virological resistance. They have been shown to suppress HBV replication, liver inflammation and reverse fibrosis and to reduce the incidence of liver decompensation and incidence of HCC. However, as HBV integrates into the genome, eradication of HBV covalently closed circular deoxyribonucleic acid remains elusive and most patients still require lifelong treatment to keep the virus in check.

Although hepatitis C is endemic in many parts of South-east Asia, fortunately for Singapore there is a low prevalence of HCV infection in the community and chronic infection is concentrated in a small group of intravenous drug users.<sup>9</sup> For many years, the only therapy available to treat chronic hepatitis C was interferon and ribavirin. These regimens carry significant side effects and they challenge even the most experienced hepatologists. The success rate for viral eradication can also be as low as 40%.<sup>10</sup> The treatment strategy then involved stringent selection of patients who could be treated based on their risk factors, viral genotype, genetic polymorphism, comorbidities and, frequently, severity of liver fibrosis on liver biopsy.

The advent of oral antivirals in the 21<sup>st</sup> century has completely revolutionised HCV therapy. Oral antiviral regimens have achieved a success rate of 99% in resolving hepatitis C with minimal side effects.<sup>11</sup> Simplified pan-genotypic regimens such as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir have shortened therapy and no longer require complex pretreatment evaluation for genotype or even liver fibrosis assessment.<sup>11</sup> Indeed, the success story of HCV drug development is a classic showcase of how advances in molecular biology can be brought to bear on an unmet clinical need.

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Unfortunately, the brilliant strides made by pharmaceutical companies also heralded an era of high-cost drugs. Upon introduction to the market, HCV regimen cost up to US\$90,000 for each treatment course and it gave rise to the infamous “US\$1000 per tablet” label.<sup>12</sup> Unsurprisingly, hepatitis C therapy became the most expensive item in the national health budget of many countries and it created issues of political lobbying, social outcry for patient advocacy and cost manipulation.

It may appear perplexing to many that despite these highly effective prevention and treatment strategies, we seem to be losing the war against viral hepatitis.<sup>1</sup> Since the year 2000, morbidity and mortality from viral hepatitis have risen by 22% worldwide. Despite the universal adoption of neonatal vaccination programmes, the percentage of neonates who received even 1 dose of the vaccine remains abysmal at 39%.<sup>1</sup> The Global Health Sector Strategy on viral hepatitis has bravely called for its elimination as a public health threat by 2030 and aims to reduce new infections by 90% and mortality by 65%.<sup>13</sup> To achieve its aims, significant challenges abound.

While patients are being treated and cured, WHO estimates that more new infections are diagnosed than those who are being treated. Lack of clean needles and syringes, ignorance of hygiene practices in rural healthcare facilities and poor public knowledge and awareness remain major challenges. Since viral hepatitis is a silent disease, an estimated 80% of chronically infected patients remain undiagnosed until they present with advanced disease.<sup>1</sup>

To create a significant impact on population health, strong and sustained government-backed initiatives are needed to provide universal health access, education and screening programmes. More importantly, medication must be made affordable to ensure as many patients as possible get treated. This can only be done through penetration of care into the community and the development of point-of-care diagnostic tests and simplified treatment protocols. To solve the problem of cost affordability, a combination of efforts that include licensing of generic drugs, cost subsidies by the state to offset out-of-pocket payment and philanthropic drives to augment screen-and-treat programmes must be intensified.

With so much to do, World Hepatitis Day remains even more relevant today than when it was first endorsed by WHO in 2010. To coincide with the birthday of the late physician Baruch Samuel Blumberg, World Hepatitis Day is observed on 28 July every year to raise awareness of the global challenge posed by hepatitis and to influence real change in the world. On this day, WHO hopes that it will “provide an opportunity for education and greater understanding of viral hepatitis as a global public health problem, and to stimulate the strengthening of preventive and control measures of this disease in Member States”.<sup>14</sup>

More than any other disease, viral hepatitis has demonstrated the promise of scientific advances to rewrite the story of mankind with HCV becoming the first chronic disease to be cured with designer synthetic drugs. The many exciting chapters of this story have spanned issues of social equality, rights to universal healthcare, politics and healthcare affordability. The last mile to attain the lofty goal of virus elimination by WHO can only be bridged by getting these drugs into the hands of those who need it, not just those who can afford it. If we succeed, it will be one of the biggest triumphs of human civilisation over viruses and the many social challenges that besiege humanity.

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