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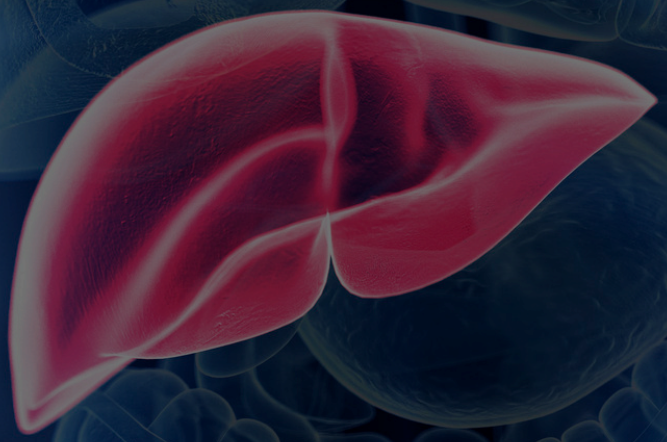

"One Life, One Liver"

HEPATITIS

FOCUS REPORT

With Support by:

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ASSOCIATION OF SOUTHEAST ASIAN NATIONS

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Hepatitis

Introduction

Viral hepatitis poses a significant public health challenge worldwide, with an estimated three (3) million new infections occurring annually. This infectious disease is caused by five different hepatitis viruses (A, B, C, D, and E) and can lead to acute or chronic liver inflammation, resulting in severe health complications. While hepatitis virus B and C are more responsible for chronic progression in liver diseases.[1] While efforts to combat hepatitis have been undertaken globally, substantial progress has been made in reducing its prevalence through massive immunization programs. Vaccination campaigns have played a pivotal role in curbing the spread of hepatitis, particularly for hepatitis B, which has witnessed a decline in new cases. Comprehensive vaccination strategies have contributed to the control of hepatitis, especially in regions with high disease burdens.[2] However, despite this achievement, the decline in prevalence has not been matched by a proportionate decrease in mortality rates, indicating that more targeted approaches are needed to address this persisting issue.[3] This situation has deviated far from the hepatitis eradication target set before.[4]

One region significantly impacted by the burden of viral hepatitis is Southeast Asia (SEA), which reports an alarming 500 thousand new infections each year for both Hepatitis B and C.[5,6] This region's epidemiological situation calls for urgent attention, as the high infection rates can have severe consequences for public health and the region's. socio-economic development.

Understanding the dynamics of hepatitis transmission and identifying specific risk factors are crucial steps in formulating effective prevention and control strategies. In response to the growing global challenge of viral hepatitis, the World Health Organization (WHO) has stepped up its efforts by issuing the Global Health Sector Strategies on HIV, viral hepatitis, and sexually transmitted infections for the period of 2022 to 2030.[7] This strategic initiative aims to reduce the number of new hepatitis infections and associated mortality, while also improving early diagnostics and vaccination access for vulnerable populations.

However, the outbreak of the COVID-19 pandemic in recent times has raised concerns about its potential impact on viral hepatitis control and elimination

efforts. The interplay between these two public health crises creates a complex situation, with potential consequences that must be carefully examined. As healthcare systems grapple with the demands of managing COVID-19 cases, there are concerns about the short-term incidence of chronic hepatitis infections potentially rising. The disruptions in healthcare services and screening programs could lead to late detection of hepatocellular carcinoma, a common complication of chronic hepatitis infections, further compounding the burden of liver-related diseases. Moreover, the transmission of viral hepatitis to future generations remains a significant risk, particularly if prevention and vaccination efforts are hampered during the pandemic.[8]

Method

In this focus report, we delve into viral hepatitis in the SEA region, focusing on case definitions, seroprevalence, disease burden, vaccine coverage, prevention, and treatment updates. Viral hepatitis encompasses illnesses caused by HAV, HBV, HCV, HDV, and HEV viruses. Our study encompasses publications from 2017 to 2023 to ensure currency, employing established guidelines for systematic reviews. Various databases such as PubMed, Embase, and Scopus were searched using specific keywords and MeSH terms like 'viral hepatitis,' 'epidemiology,' 'burden of disease,' 'country-level response,' 'prevention,' and 'treatment.' Additionally, we used the Bluedot platform to gather real-time data from official reports and news articles on viral hepatitis cases in the SEA region, boosting the reliability of our findings. We incorporated studies detailing the prevalence, incidence, risk factors, and outcomes of viral hepatitis, alongside national/regional programs and policies for prevention and treatment. Data extraction included study characteristics, design, sample size, demographics, diagnostics, and key findings. The results, synthesized narratively, spotlight crucial trends, patterns, and gaps. Our comprehensive methodology aims to offer a robust overview of viral hepatitis in the SEA region, emphasizing epidemiology, burden, country-level response, and recent advances in prevention and treatment.

Case Definition

Hepatitis A virus (HAV) is present in the feces of infected persons and is most often transmitted through consumption of contaminated water or food. Certain sex practices can also spread HAV. Infections are in many cases mild, with most people making a full recovery and remaining immune from further HAV infections. However, HAV infections can also be severe and life-threatening. Most people in areas of the world with poor sanitation have been infected with this virus. Safe and effective vaccines are available to prevent HAV.

Hepatitis B virus (HBV) is transmitted through exposure to infective blood, semen, and other body fluids. HBV can be transmitted from infected mothers to infants at the time of birth or from family members to infants in early childhood. Transmission may also occur through transfusions of HBV-contaminated blood and blood products, contaminated injections during medical procedures, and through injection drug use. HBV also poses a risk to healthcare workers who sustain accidental needle stick injuries while caring for infected HBV patients. Safe and effective vaccines are available to prevent HBV. Several indicators are used to measure the stages of Hepatitis B infection: (1) HBsAg or HBV antigen that is detected in early acute phase infection, (2) total HBc antibody is total antibody to HBV core, (3) IgM anti-HBc or IgM antibody towards HBV core, and (4) Anti-HBs or antibody to HBV surface that signify ongoing process for chronic infection.

Hepatitis C virus (HCV) is mostly transmitted through exposure to infective blood. This may happen through transfusions of HCV-contaminated blood and blood products, contaminated injections during medical procedures, and through injection drug use. Sexual transmission is also possible but is much less common. There is no vaccine for HCV.

Hepatitis D virus (HDV) infections occur only in those who are infected with HBV. The dual infection of HDV and HBV can result in a more serious disease and worse outcome. Hepatitis B vaccines provide protection from HDV infection.

Hepatitis E virus (HEV) is mostly transmitted through consumption of contaminated water or food. HEV is a common cause of hepatitis outbreaks in developing parts of the world and is increasingly recognized as an important cause of disease in developed countries. Safe and effective vaccines to prevent HEV infection have been developed but are not widely available.

Seroprevalence in The ASEAN Region

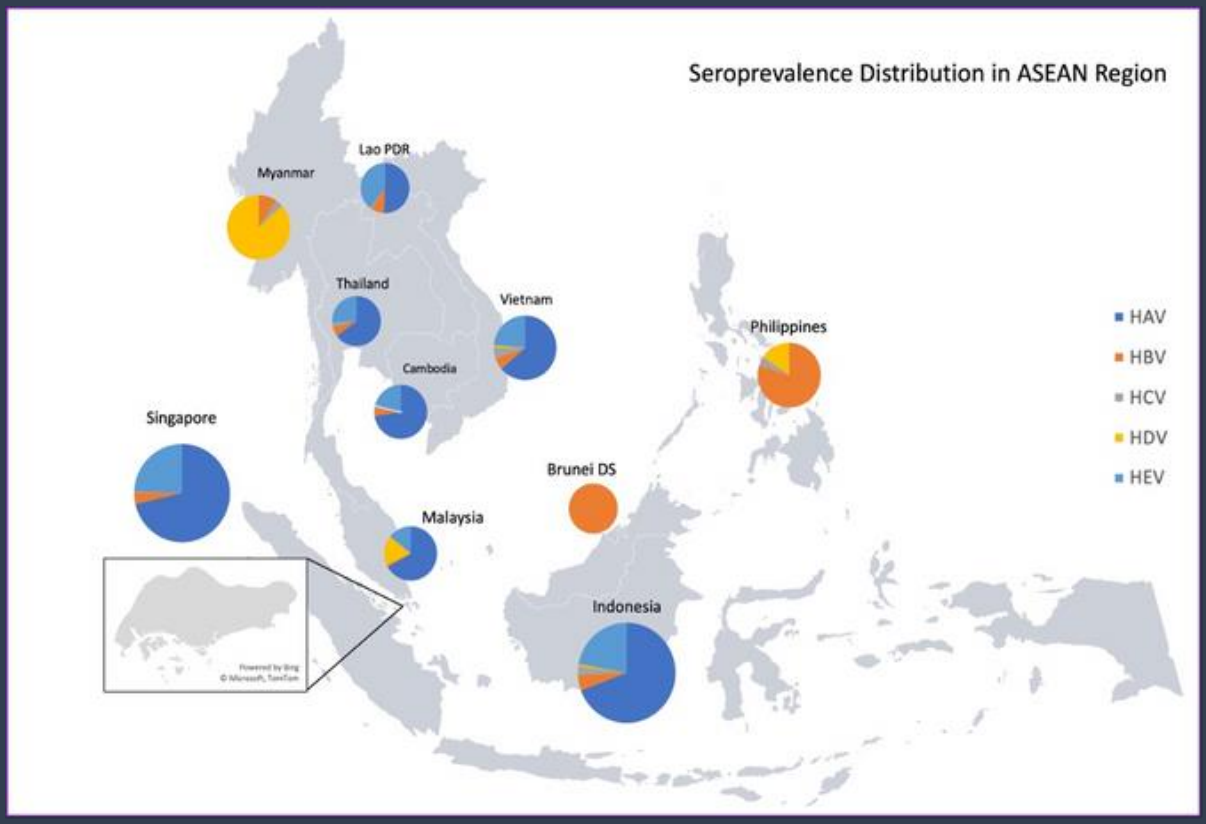


Figure 1 Seroprevalence of Viral Hepatitis Type in ASEAN Region

Seroprevalence surveys encompassed sample sizes ranging from 100 to 4,260 individuals, with the endemicity level of HAV determined through serological surveys assessing HAV antibodies in the blood. These surveys offer reliable insights into disease burden within populations, as evidenced by the scores of the reviewed studies, ranking between low and medium risk. Most studies exhibited strong internal validity.

From 1990 to 2019, seroprevalence rates for all age groups and those <5 years old displayed a decline. However, in 2019, HBV seroprevalence rates for all ages in Cambodia, Lao PDR, the Philippines, and Vietnam exceeded the global rate. Moreover, the 2019 HBV seroprevalence rates among <5 years old in Lao PDR and the Philippines surpassed global prevalence rates. Notably, Thailand achieved the regional hepatitis B control target with a national HBsAg seroprevalence ≤1% among children aged ≥5 years, as confirmed by the South-East Asia Regional Expert Panel (SEA REP) in 2019.

HCV prevalence in Asia ranged from 0.37% (Singapore) to 6.1% (Vietnam) based on a 2013 systematic review. Although volunteer blood donors might not represent the general population, the most reliable estimates were

derived from a substantial seroepidemiological study of healthy individuals in Thailand and World Health Organization data for Vietnam.

Information on HDV in the ASEAN region is limited, primarily stemming from 2010 data:

- Indonesia: HDV prevalence was < 0.5% among HBsAg carriers in Surabaya (2003).
- Malaysia: Various prevalence rates were recorded among different populations, including cases of acute hepatitis B, homosexual individuals, drug abusers positive for HBsAg, and jaundiced patients.
- Thailand: Studies revealed varying HDV prevalence rates among HBsAg-positive individuals, chronic hepatitis patients, and cirrhotic patients in different years.
- Philippines: In 1990, a study estimated a 1.6% HDV prevalence among acute viral hepatitis patients, with 40.6% having HBV.
- Vietnam: In a 2007 cross-sectional study in Thai Binh Province, 1.3% of HBsAg-positive samples were also positive for HDV.

A 2023 meta-analysis by Raji et al. examined HEV seroprevalence in the SEA region. The study covered 32 publications from 1995 to 2019,

Burden of Hepatitis

Hepatitis A

Findings of a systematic review of literature published in 2021 on HAV incidence and seroprevalence in select countries in the SEA region over the last 20 years, point to a very low HAV endemicity profile in Thailand and Singapore and evidence of a shift towards low HAV endemicity in Indonesia, Lao People's Democratic Republic, Malaysia, the Philippines, and Vietnam. Only Singapore, Thailand, Malaysia, and the Philippines have existing HAV disease surveillance and have reported incidence rates below 1 per 100,000. Several outbreaks with varying magnitude documented in the region provide insights into the evolving epidemiology of HAV in the region.[9]

Burden of Hepatitis A in the ASEAN Region

Hepatitis A seroprevalence in the SEA region in 2005 was categorized as low. In 2010, the World Health Organization (WHO) modified this from low to low/medium endemicity, pointing out that these estimates were based on limited evidence. [10] Findings of a systematic review of the literature published in 2021 on HAV incidence and seroprevalence in select countries in the Southeast Asian region over the last 20 years, points to a very low HAV endemicity profile in Thailand and Singapore and evidence of a shift towards low HAV endemicity in Indonesia, Lao People's Democratic Republic, Malaysia, the Philippines, and Vietnam. Only Singapore, Thailand, Malaysia, and the Philippines have existing HAV disease surveillance and have reported incidence rates below 1 per 100,000. Several outbreaks with varying magnitude documented in the region provide insights into the evolving epidemiology of HAV in the region. [10]

1. HAV Seroprevalence

Seroprevalence surveys had sample sizes ranging between 100 and 4,260 individuals. The endemicity level (i.e. circulation) of HAV within a given region or population is readily estimated through serological surveys (measurement of HAV antibodies in the blood) and are reliable estimate of the burden of disease in a population. Scores of all seroprevalence papers included in this review ranked between low and medium risk, highlighting the reliability of the results included in the analysis. Most of the studies performed well in the internal validity items.

Table 1 HAV Seroprevalence in the ASEAN Region [10]

ASEAN Member States	Year and Survey/ Study Description	HAV Endemicity
Cambodia	2011-2017 survey among immigrant women in Korea (N=58)	100% HAV Seropositivity by 20-29 years of age
Indonesia	1993 survey in Yogyakarta, Indonesia	50% at around 25 years of age
Lao PDR	2017 cross sectional study -	50% among individuals 20 years of age
Philippines	2009 WHO Report	57.1%-100% among individuals aged 20-39 years
	2011-2017 survey among immigrant women in Korea (N=58)	78% by 20-29 years of age and 72% by 30-40 years of age
Singapore	1993 population-based survey	50% by 35 years of age
Thailand	3 surveys conducted: National 1999-2014; Bangkok 1998-2007, Across Different Provinces 2004	≤ 20% in <2years of age to more than 90% in those ≥60 years of age 50% at 42 years of age in 2014 compared to 50% at 36 years of age in 2004
Vietnam	1994 surveys (2)	Almost complete seroconversion by 10 years of age
	2011-2017 survey among immigrant women in Korea (N=42)	60% by 20-29 years of age and 80% by 30-40 years of age

2. Incidence of Hepatitis A

Reports on the incidence of hepatitis A were found for four countries in the SEA including Malaysia, Singapore, Thailand, and the Philippines, where hepatitis A is a notifiable waterborne disease.[10]

Table 2 Incidence of Hepatitis A in Selected ASEAN Member States[10]

ASEAN Member States (notifable Disease since)	**Incidence or Number of New Cases (Year)**				**Estimated Crude Annual Incidence**
Malaysia (1980)	9/100,000 (1991)	2.2/100,000 (2004)	0.14/100,000 (2007)	1/100,000 (2018)	1/100,000
Philippines (2010)	440 new cases (2010)	563 new cases (2015)	443 new cases (2016)	462 new cases (2017)	0.4-0.6 /100,000
Singapore (1999)	146 new cases (2006)	48 new cases (2016)	75 new cases (2018)	66 new cases (2019)	1/100,000
Thailand (2003)	<1/100.000 (2003)	4/100,000 (2005)	3/100,000 (2012)	0.65/100,000 (2019)	0.65/ 100,000

3. Outbreaks in the ASEAN Region

Several outbreaks with varying magnitude have been documented in the region and provide insights into the evolving epidemiology of HAV in the region. Outbreak information was reported for Indonesia, Malaysia, Singapore, and Thailand. No information on outbreaks occurring in the Philippines was published.[10] However, HAV subgenotypes IA and IIIA have been detected in environmental water in the Philippines in a study conducted in 2012-2013, posing a risk of HAV infection/ outbreak.[12]

Table 3 HAV Outbreaks in the ASEAN Region[10]

ASEAN Member States	**Year**	**Description**
Indonesia	2015	Setting – 2 junior High Schoold in urban Surabaya N=59
Malaysia	2000	Source – Mixed sources/ person to person spread N=334
	2002	Source – Contamined rivers for recreational purposes and human sewage N=51
	2012	Source – Contamined alcoholic beverage N=78
Singapore	2002	Source – Raw shellfish N=159
Thailand	2019	Setting – Prison N=61

Hepatitis B

Hepatitis B may be a life-threatening liver disease. It is the most common blood-borne infectious disease and continues to be a global public health concern. In 2017, there were an estimated 145 million new cases of AHB. According to WHO estimates, 3.5% of the world's population was living with chronic HBV infection in 2017. The prevalence of HBV infection is the highest in the Western Pacific and Africa regions, accounting for 6.2% and 6.1% of the adult population, respectively, compared to 0.7% in the American region. Although AHB resolves on its own, CHB may develop from AHB. AHB is prevalent in males; however, female patients tend to exhibit more severe cases of overt AHB. Further, HBV transmits via sexual contact, drug injection in medical institutions, contact with HBV-infected blood with shared needles, and mother-to-child transmissions.[13]

Acute Hepatitis B in the ASEAN Region

HBsAg Seroprevalence

Seroprevalence rates, for all ages and <5 years decreased from 1990 to 2019. However, the 2019 HBV seroprevalence rates, for all ages, of Cambodia, Lao PDR, the Philippines, and Vietnam were higher than the global seroprevalence rate, and the 2019 HBV seroprevalence rate among < 5 years old of Lao PDR and the Philippines higher than the global prevalence rates. (Table 4) [14] In addition, Thailand achieved the regional hepatitis B control target of a national HBsAg seroprevalence ≤1% among children aged ≥5 years, as verified by the South-East Asia Regional Expert Panel (SEA REP) in 2019.[15]

HBV-Related Mortality

HBV-related death rates varied widely across regions, with the highest all-age death rates in the Western Pacific region (10.7 per 100,000), and SEA region (8.4 per 100,000). (1) Except for Brunei and the Philippines, all other AMS have death rates higher than the global death rate of 7.2 per 100,000. Thailand reported the highest death rate at 18.9 per 100,000 in 2019. (Table 4)

Table 4 HBsAg seroprevalence and HBV deaths in the ASEAN Region by age*[14]

	HbsAg Seroprevalence, all ages			HbsAg Seroprevalence, < 5 years			Death counts, all ages			Death rate per 100,000 all ages		
	1990	2005	2019	1990	2005	2019	1990	2005	2019	1990	2005	2019
Global	6.0	4.4	4.1	4.4	1.2	1.0	524,000	540,000	555,000	9.8	7.3	7.2
Western Pacific	10.8	7.7	7.1	8.3	1.0	0.5	266,000	192,000	206,000	17.0	10.1	10.7
Southeast Asia	4.0	3.2	3.1	2.4	0.6	0.5	110,000	172,000	169,000	8.5	8.9	8.4
Brunei Darussalam	4.7	2.5	2.1	0.5	0.2	0.2	15.5	27.6	31.2	6.0	6.6	7.1
Cambodia	9.7	7.4	6.6	6.2	0.7	0.5	1,870	2,300	2,450	18.0	14.7	14.7
Indonesia	4.7	3.8	3.6	2.7	0.9	0.6	18,300	20,900	22,600	9.9	8.3	8.7
Lao PDR	11.7	9.4	8.7	9.0	2.5	2.1	526	519	519	12.7	7.6	7.3
Malaysia	2.0	1.4	1.3	0.4	0.1	0.09	1,260	2,670	3,000	7.2	8.9	9.6
Myanmar	3.2	2.6	2.4	2.2	0.8	0.6	6,120	6,590	6,640	14.9	12.5	12.2
Philippines	14.1	9.6	8.2	8.8	4.3	1.2	4,960	5,700	6,060	7.8	5.4	5.4
Singapore	3.9	2.6	2.7	0.4	0.1	0.1	240	444	502	7.9	8.0	8.9
Thailand	6.8	5.0	4.8	3.0	0.4	0.4	6,980	12,000	13,200	12.3	17.2	18.9
Vietnam	11.4	7.2	6.6	7.6	0.8	0.7	7,440	6,790	7,600	11.0	7.3	7.9

HBV-Related DALYs

Notably, 70% of DALYs attributed to HBV were concentrated in ten countries including Indonesia, Thailand, and Myanmar.[14]

Hepatitis C

HCV infection is a major and growing public health concern worldwide. There is no vaccine available for HCV to date. In 2015, 71 million people were living with HCV infection globally, accounting for 1% of the population. In 2017, an estimated 5 million new cases of AHC were reported. The current records show that the prevalence of HCV infection is the highest in the Eastern Mediterranean (2.3%) regions, whereas it is the lowest (0.5%) in the SEA region. In industrialized countries, the main route of HCV transmission is injection drug use, whereas it is iatrogenic, blood transfusions, and medical procedures in resource-limited countries. An increase in HCV infection is usually accompanied by a growing opioid epidemic and injection drug use. AHC rarely develops into fulminant hepatic failure.[15]

Globally, an estimated 3% of the world's population equating to 170–180 million persons are living with hepatitis C virus (HCV) infection. Approximately, 70%–80% of acute HCV-infected individuals will develop chronic liver disease and, within 10–30 years, approximately 20% of them will experience cirrhosis and its complications, of which 1%–5% are HCC each year.[16]

I. Acute Hepatitis C in the ASEAN Region HCV Prevalence

From a systematic review of hepatitis C in Asia in 2013, HCV prevalence ranged from 0.37 (Singapore) to 6.1% (Vietnam). Volunteer blood donors, however, may not be representative of the general population. A large sero- epidemiological study of healthy individuals in Thailand and data compiled by the WHO in Vietnam presented the best estimates. (Table 5) [17].

II. Burden in Special Risk Groups

Co-infections play an important role in increasing the burden of HBV and HCV in developing and resource-limited countries.[16]

Table 5 Prevalence of Hepatitis C in the SEA region[17]

ASEAN Member States	Population	N	Prevelance (%)	Reference	Year
Cambodia	Healthy adult volunteers	1,431	2.3	Akkarathamrongsin	2011
Indonesia	Blood donors	7,572	2.1	Sulaiman	1995
Lao PDR	Blood donors	13,897	1.1	Jutavijittum	2007
Myanmar	Blood donors	65,240	0.95	Myo-Khin	2010
Philippines	Blood donors	74,180	0.47	Yanase	2007
Singapore	Blood donors	65,208	0.37	Wang	1995
Thailand	Healthy adult volunteers	5,825	2.2	Sunanchaikarn	2007
Vietnam	Meta-analysis	N/A	34	WHO	2011

IIA. Acute Hepatitis C Among Men Who Have Sex with Men (MSM)

A systematic review published in 2021 of HCV prevalence and incidence among the MSM population estimated the prevalence of HCV in MSM to be 5.9% (95% CI: 5.1–6.8), with substantial differences between countries and regions. HCV prevalence in HIV-positive MSM was substantially higher than in HIV-negative MSM (8.1 vs. 2.8%, p < 0.001).[18] Countries with the highest HCV burden among MSM included Malaysia (59.2%, 95% CI: 51.9–66.3), Thailand (41.4%, 95% CI: 4.6–85.3), Indonesia (32.5%, 95% CI: 22.4–43.4). (Table 6) [18].

Table 6 Estimates of anti-HCV prevalence and incidence among MSM in the ASEAN region[18]

Geographic Region/AMS	Prevelance		Incidence	
	Participants	Pooled Prevalence estimates (95% CI)	Follow Up Person Year	Pooled Incidence Estimates/1000 py (95% CI)
Southeast Asia	2,406	2.9 (14.4-4.61)	4,012	12.5 (9.2-18.1)
Indonesia	77	32.5 (22.4-43.4)		
Malaysia	179	59.2 (51.9-55.3)		
Myanmar	177	3.4 (1.1-6.7)		
Singapore			4012	12.5 (9.2-16.1)
Thailand	108	41.4 (4.6-85.3)		
Vietnam	1865	15.1 (0.3-44.5)		

Among HIV-positive, anti-HCV-positive MSM participants, the pooled prevalence of HCV was 8.1% (95% CI, 6.8–9.4) (I^2 = 97%). Indonesia (100.0%, 95% CI: 30.3–100.0), and Vietnam (84.1%, 95% CI:77.7–89.7) had high prevalence rates. Among HIV- negative, anti-HCV-positive MSM participants, the pooled prevalence was 2.8% (95% CI: 1.9–4.0), lower than that of HIV-positive patients (p<0.001). Indonesia (30.7%, 95% CI: 20.7–41.6), and Vietnam (19.9%, 95% CI: 17.9–22.1) still had high prevalence. (Table 7) [18] High rates of

drug use that strikingly increased the risk for HCV transmission have been reported among MSM from multiple Southeast Asian countries [18].

Table 7 Estimates of anti-HCV prevalence by HIV status in the ASEAN region[18]

Geographic Region/AMS	HIV (+) MSM		HIV (-) MSM	
	Participants	Pooled Prevalence estimates (95% CI)	Follow Up Person Year	Pooled Incidence Estimates/1000 py (95% CI)
Southeast Asia	366	44.9 (0.0-98.8)	1.450	24.0 (14.4-35.1)
Indonesia	2	100 (30.3-100.0)	75	30.7 (20.7-41.6)
Myanmar	177	3.4 (1.1-6.7)		
Thailand	145	19.0 (8.4-32.5)		
Vietnam	1865	15.1 (0.3-44.5)	1375	19.9 (17.9-22.1)

IIB. Acute Hepatitis B and Hepatitis C Among People with HIV (PWH)

In 2015, chronic HBV infection was estimated to be in 3.5% of the world population.[14] People with HIV (PWH) had a higher estimated prevalence rate of 7.4%. Similarly, the global hepatitis C prevalence in 2015 was 1.0%, while 6.2% was the reported HCV prevalence among PWH. However, there is a heterogeneity of risk HCV infection among PWH populations: 82.4% of PWH who inject drugs, 6.4% of MSM living with HIV, and only 2.4% of PWH from the general population.[19] Around 5–10% of newly diagnosed PWH in Bangkok had hepatitis B viral infection after years of universal vaccination. Anti-HCV positivity was found in 4–5% of PWH who were men who have sex with men (MSM) and transgender women (TGW).

IIC. Acute Hepatitis B and Hepatitis C Among People Who Inject Drugs (IDU)

The first global systematic review of HCV and HBV infection among people who inject drugs in 2011 estimated that 10.0 million (range 6.0–15.2M) IDUs might be anti-HCV positive and that 1.2 million (0.3–2.7M) might be HBsAg positive worldwide. The largest HCV-positive IDU populations were estimated to be living in Eastern Europe (2.3 million; range 1.2–3.9 million) and East and South- East Asia (2.6 million; range 1.8– 3.6 million). The largest HBsAg positive IDU populations by region were estimated to be East and SEA (0.3 million; range 0.1– 0.7 million) and Eastern Europe (0.3 million; range 0.1–0.5 million) [20].

III. Chronic Hepatitis B and Hepatitis C

Globally in 2019, an estimated 316 million people had chronic HBV infection. The global all-age chronic HBV prevalence was 4.1% in 2019, a 31.3% decrease from 1990 with the introduction of the HepB3 vaccine. The chronic HBV all-age and among <5 years old prevalence rates decreased across countries from 1990 to 2019 [14]. HBV-related diseases resulted in an estimated 555,000 deaths in 2019, accounting for 48.8% of all hepatitis-related deaths. Hepatitis B was the leading etiology of liver cancer deaths (39.5%) and the third largest contributor to deaths from cirrhosis (22.5%). HBV-related cirrhosis was responsible for 331,000 global deaths, liver cancer was responsible for 192,000 global deaths, and acute hepatitis was responsible for 32,500 global deaths. The absolute number of HBV-related deaths in 2019 increased by 5.9% from 1990 [14]. The burden of disease and the death rate associated with HCV is expected to double over the next 2 decades as the large cohort of

HCV- positive patients progresses to cirrhosis, cancer, and liver failure. In resource-limited countries, HCV infection, chronic hepatitis, cirrhosis, and HCC have serious economic consequences that include the direct health-care expenditures in caring for the disease and indirect costs in terms of loss of productivity or absence from work because of chronic hepatitis C infection, cirrhosis, and HCC [16].

IIIA. Cirrhosis

A systematic review including 520 publications from 86 countries or territories, representing 87% of the world population (and reporting on 1,376,503 patients with cirrhosis) was published in 2022. Globally, among patients with cirrhosis, 42% had HBV infection and 21% had HCV infection. In the SEA region, HBV prevalence was 25% and HCV prevalence was 29% among patients with cirrhosis and the HBV/HCV ratio was 0.9. Table 8 shows HBV and HCV prevalence among patients with cirrhosis in the ASEAN Region.[21]

Table 8 HBV and HCV Prevalence among Patients with Cirrhosis in the ASEAN region

ASEAN Member States	**Study Years**	**Ages** (mean)	**Men** (%)	**Number of Patients** (n)	**HBV Prevalence (95% CI)**	**HCV Prevalence (95% CI)**
Cambodia	1990-1991			53	45% (33-59)	34% (23-47)
Indonesia	1992	53	62%	164	24% (17-31)	54% (47-62)
Malaysia	2015-2020	64	66%	75	25% (15-36)	20% (11-30)
Myanmar	1998-2000			81	27% (19-38)	41% (31-52)
Singapore	2002-2017	52	60%	663	35% (23-47)	18% (10-28)
Thailand	1997-2019	56	64%	617	29% (25-33)	28% (21-34)
Vietnam	1998-2020	56	64%	250	35% (24-48)	24% (14-35)

IIIB. Hepatocellular Carcinoma (HCC)

The lifetime risk of progression to HCC is 9.6% and 60.2% in HBV carriers with positive HBsAg and with double positivity of HBsAg and HBeAg, respectively. The risk of progression to HCC is estimated to be 2%–6% each year for HCV-related cirrhosis patients [22]. Rosmawati (2004) presented available HBV-related HCC incidence rates in some AMS. (Table 9)

Table 9 HBV related HCC Incidence[23]

ASEAN Member States	Age-stardardized HBV Related HCC Incidence Rate
Malaysia	54.5(Malay), 301.4 (Chinese), 28.5 (Indian) per 100,000 hospital admissions (Ranjeev et al, 1999)
Philippines	16.8 per 100,000 population 25.6 (male), 9 (female) (Asia Pacific Expert Committee on Hepatitis B Management Meeting 2002)
Singapore	19.4 (male) and 5.6 (female) per 100,000 per year (Chia et al 2000)
Thailand	40.5 (male), 16.3 (female per 100,000 population (DOH-Viral Hepatitis Surveillance in HK 2002)
Vietnam	37.5/100,000 population (Asia Pacific Expert Committee on Hepatitis B Management Meeting 2002)

HBV and HCV are still the leading risk factors of HCC with a slight decline in most Asian countries, which is mainly attributed to HBV vaccination of newborns, prevention of HCV horizontal transmission, and treatment of chronic hepatitis [22]. In 2019, the incidence of Liver Cancer owing to Hepatitis B was 3.81/100,000 and to Hepatitis C as 2.17/100,000.[24] Approximately 39.57% of liver cancer-related mortalities in both sexes were attributed to HBV and 29.26% were attributed to HCV.[25] Table 10 shows the 2020 age-standardized rate of incidence and mortality of liver cancer in Asia where proportions of HBV and HCV may be estimated.

Table 10 Age-standardized Rate of Incidence and Mortality of Liver Cancer in Asia between 2018 and 2020 based on GLOBOCAN. Presented as incidence and mortality per 100,000.[25]

ASEAN Member States	Incidence (ASR, per 100,000)	Mortality (ASR, per 100,000)
	2020	2020
Brunei Darussalam	10.5	8.8
Cambodia	24.3	22.9
Indonesia	7.9	7.7
Lao PDR	24.4	22.9
Malaysia	6.4	6.1
Myanmar	10	9.7
Philipiines	11.4	10.8
Singapore	12.2	10.8
Thailand	22.6	21.9
Vietnam	23.0	21.9

Hepatitis D

Hepatitis delta virus (also known as hepatitis D virus [HDV]) is a defective subvirus that requires HBV surface antigens (HBsAgs) to propagate. HDV has been largely neglected over the past decades since its discovery in the 70's [27]. Approximately 5% of individuals infected with hepatitis B virus (HBV) are coinfected with hepatitis D virus (HDV). Chronic HBV/HDV coinfection is associated with an unfavorable outcome, with many patients developing liver cirrhosis, liver failure, and eventually hepatocellular carcinoma within 5–10 years. (2) At least 12 million individuals infected with the hepatitis B virus (HBV) are coinfected with the hepatitis D virus (HDV) and have a high risk of developing liver cirrhosis and hepatocellular carcinoma within a few years [28].

Hepatitis D in the ASEAN Region

There is limited information from recent years on HDV in the ASEAN region. Available data from 2010 reported the following from the ASEAN region.

ASEAN Member States	HDV Case Reported since 2010
Indonesia	In 2003, the HDV prevalence was found to be < 0.5% in the HBsAg carriers of Surabaya.[29]
Malaysia	In Malaysia, hepatitis D was first described in 1986 in some population groups. The HDV prevalence was found to be 12.5% in cases of acute hepatitis B, 6.7% in homosexual individuals, and 17.8% in drug abusers who were positive for HBsAg. In 1989, the HDV prevalence was found to be 4.9%. In 1996, 0.9% of the 923 jaundiced patients were found to be positive for anti-HDV. In 1985, surveillance results for the detection of anti-HDV in IVDAs showed an absence of anti-HDV. However, in 1986, a prevalence of 17.8% was observed in the same group. The prevalence increased to 20% in 1989 and in 1994, 34% of the drug addicts tested positive for anti-HDV.[29]
Philippines	A study in 1990 estimated the prevalence of HDV among 64 patients with acute viral hepatitis. 1.6% tested positive for HDV. HBV was present in 40.6% of the acute viral hepatitis patients.[29]

Thailand	A study conducted in 1988 tested 84 HBsAg- positive IVDAs, of which, 65.48% showed anti-HDV positivity. The HDV prevalence in 20 chronic hepatitis patients was 11.11% and 8.33% in 12 cirrhotic patients. A study in 2002 tested 55 HBsAg-positive sera of IVDAs, among which, 12 (21.8%) tested positive for anti-HDV. Among these anti-HDV positive sera, eight (66%) tested positive for HDV RNA, and all had genotype virus 1 virus. [29]
Vietnam	Vietnam is considered to be highly endemic for hepatitis B. A cross-sectional seroprevalence study to estimate the prevalence of HBV and HDV was conducted in Thai Binh Province in 2007. Nineteen percent of the samples were HBsAg- positive, out of which, 1.3% were positive for HDV. [29]

Hepatitis E

Acute hepatitis E (AHE) is found globally, and there are an estimated 19 to 20 million HEV infections worldwide each year. Previously, HEV was thought to be limited to certain developing countries. On the contrary, HEV is endemic in most high-income countries, and it manifests as locally acquired zoonotic infections where the pig acts as the true primary host. Genotypes 1 and 2 of HEV are obligate pathogens that spread by the fecal-oral route via contaminated water, and they are often linked to large outbreaks and epidemics in developing countries. In comparison, HEV genotypes 3 and 4 infect humans, pigs, and other animal species, and they are responsible for sporadic cases of the disease. AHE is a self- limiting disease that allows individuals to recover, and it is usually associated with a low mortality rate. However, for pregnant women infected by HEV, the mortality rate can increase by up to 15– 20%. In well-developed, economically advanced countries, HEV may be considered a cause of chronic, progressive liver disease in individuals with compromised immunity. In 2019, the age-standardized incidence rate was 271.2 (221.3–326.4) per 100,000 person-years for males, while it was 263.4 (215.2–316.8) per 100,000 person-years for females [15].

Viral Hepattis Outbreaks

Viral hepatitis is a serious infection that affects the liver and can cause severe complications or death. According to our literature search, the first recorded outbreak of viral hepatitis occurred in 1976. Since then, there have been several other outbreaks in different parts of the world. In the ASEAN region, most of the viral hepatitis outbreaks are caused by either hepatitis virus A or E, which are transmitted through contaminated food or water.

Burden of Hepatitis E Infection

In 2005, it was estimated that HEV genotypes 1 and 2 were responsible for about 20.1 millionincidents of HEV infections, 3.4 million symptomatic cases, 70,000 fatalities, and 3000 stillbirths. In general, HEV causes a self-limiting infection and does not need specific treatment. The mortality rate is low. However, fulminant hepatitis may develop and a high mortality rate (as high as 20%–30%) is reported in the population of pregnant women after infection with genotype 1.[30] Pregnant women with HEV, particularly those in the second and third trimester, are at higher risk of poor maternofoetal outcomes.[31] Evidence of HEV infection endemicity in the SEA is not limited to seroprevalence studies alone. Reports on sporadic cases also exist to underscore the fact that hepatitis E is endemic in the region. [30]

I. Seroprevalence of Hepatitis E in the ASEAN Region

A meta-analysis on seroprevalence of hepatitis E in the SEA region was conducted and published by Raji et al in 2023. This included 32 publications from 1995 to 2019 and evaluated 29,944 individuals of which 6,806 were anti-HEV antibody positive.[32]

The overall HEV seroprevalence in the SEA region was 21% (95% confidence interval [CI]: 17–27) with high heterogeneity. The estimated seroprevalence in this study is higher than the global average of 12.5% and is similar to the average prevalence of 21.76% obtained in Africa. At the country level, Lao PDR has the highest prevalence estimate of 39% (CI: 16–69). Studies that combined urban and rural populations produced the highest prevalence. This phenomenon can also be explained by the increase in rural-urban migration and the possibility of sampling high-density urban areas. Data also revealed a pattern that suggests an association of anti-HEV antibody positivity with increasing age. Prevalence was lowest in the age group of 20–25 years and peaked at 44–49 years age group. Evaluation based on the year of publication showed almost a two-fold increase in HEV seroprevalence rate in 2019 from the 1999 rate.[32]

Table 11 HEV Prevalence in the SEA Region[32]

Variables	No. of Studies	Pooled Prevalence	Heterogeneity		*P* subgroup
		% (95% CI)	Tau^2	(I^2)	2020
ASEAN Member States					
Cambodia	4	29 (15-49)	0.1588	97.9%	0.0662
Indonesia	8	16 (9-26)	0.0966	98.8%	
Lao PDR	2	39 (16-69)	0.2677	97.6%	
Malaysia	3	16 (6-35)	0.2005	85.8%	
Singapore	2	17 (6-4)	0.1060	91.3%	
Thailand	7	20 (12-33)	0.5620	98.9%	
Vietnam	6	26 (15-42)	0.7971	98.4%	
Location					
Urban	21	20 (14.3-27)	0.7456	98.4%	0.0456
Rural	9	23.7 (13.3-38.5)	0.8151	98.9%	
Mixed	2	29 (13.5-61.4)	0.0000	0.0	
Age					
20-25	5	18.2 (8.2-35.5)	0.5178	97.2%	<0.0001
26-31	9	21 (11.6-34.9)	0.8124	98.4%	
32-37	5	23 (9.7-45.5)	0.6748	99.0%	
38-43	4	18.5 (7.1-40.4)	0.4495	96.9%	
44-49	4	43.9 (36.8-51.2)	0.0267	81.4%	
≥50	5	13.4 (6.6-25.3)	0.3539	95.4%	
Year of Publication					
≤1999	6	15.2 (6.1-36.5)	1.0504	99.0%	0.0198
2000-2004	4	17.2 (5.1-44.4)	0.6906	98.0%	
2005-2009	4	15.5 (4.5-41.5)	06888	95.8%	
2010-2014	5	16.4 (7.4-32.7)	0.5154	98.5%	
2015-2019	13	30.9 (24.6-38)	0.2581	97.5%	

Ⅱ. Hepatitis E Outbreaks and Sporadic Infections

HEV infection is a major cause of outbreaks and acute sporadic hepatitis worldwide. HEV infecting humans consists of four different genotypes (genotypes 1–4). HEV genotypes 1 and 2 are found mainly in developing countries. They are transmitted via fecal-oral route through a contaminated water source, exclusively infect humans, and are thus responsible for many water-borne outbreaks. In contrast, HEV genotypes 3 and 4 infect humans and animals. They are found mainly in developed countries andare responsible for sporadic cases seen in the Western world. Brunei, Laos, Myanmar, the Philippines, and Timor-Leste have unknown HEV genotypes (data not available). In Singapore HEV genotypes 1, 3, and 4 are present. Thailand and Vietnam both have HEV genotype 3. HEV genotype 4 is

prevalent in Indonesia and Malaysia. While Cambodia has both HEV genotypes 3 and 4 [33] HEV genotype 3 has been detected in the Philippines from river samples (5) and fecal samples from household-raised pigs in rural areas.[34]

Table 12 HEV Outbreaks in the ASEAN Region[35]

ASEAN Member States	Period	No. of Outbreaks	No. of Cases	References
Indonesia	1987-2004	4	>5,000	World Health Organization, 2005; Sedyaningsih - Mamahit, 2002; Corwin 1995
Myanmar	1976-1989	3	20,510	Gideon Informatics et al,2020
Vietnam	1994	1		Corwin, 1996

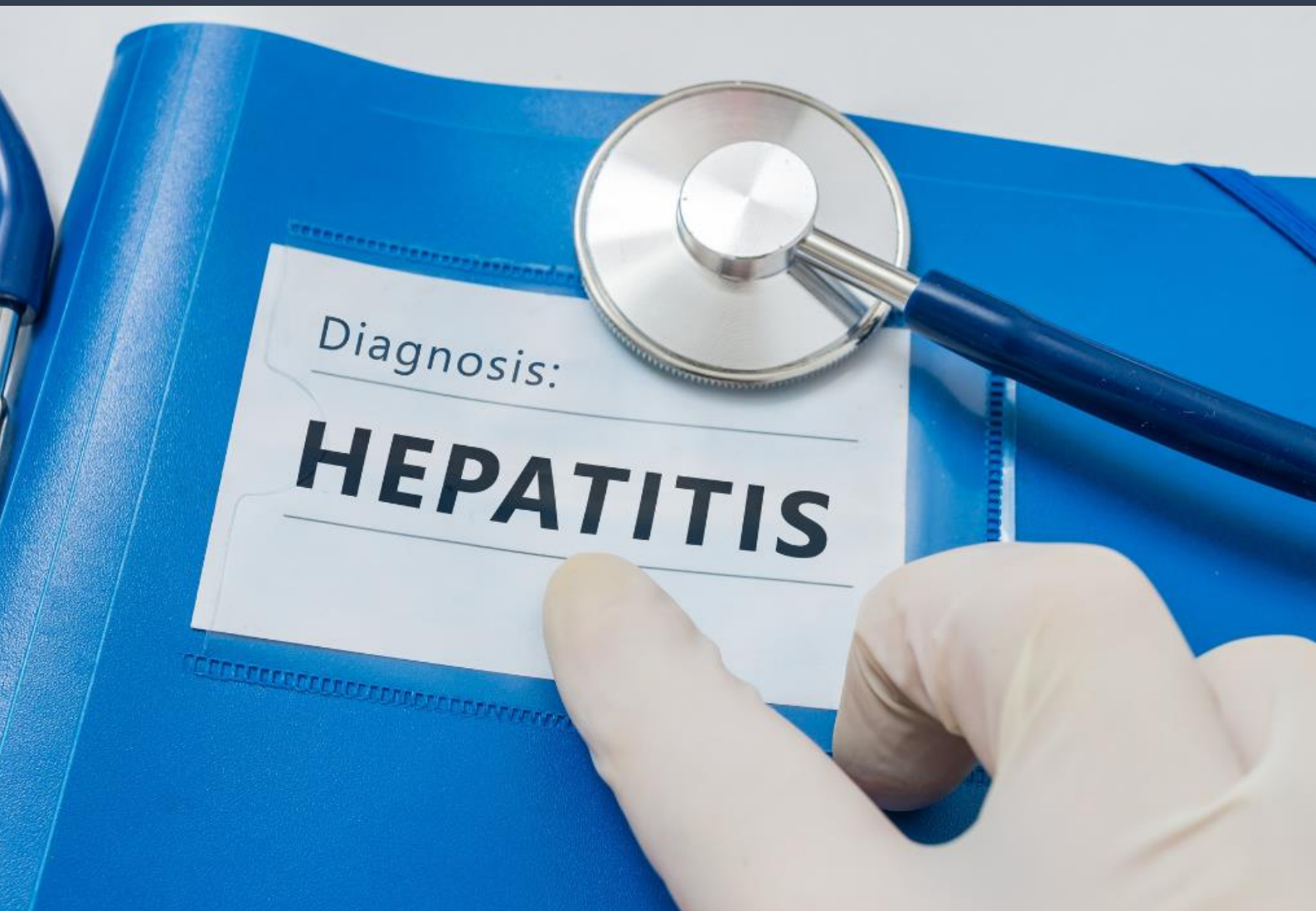
Table 13 Reported Sporadic HEV Infections in the ASEAN Region[33]

ASEAN Member States	Years	Patient Description	Total	HEV (+)	% Seroposi tivty	Reference
Cambodia	2008-2010, 2013	0-59 years old/ Unexplained fever and elevated liver enzymes	825	9	1.1	Nouhan et al, 2015
Indonesia	1997-1998	1-70 yrs old Acute Hepatitis	182	160	88	Sedyaningsih-Mamahit et al., 2002
	2003-2006	12-62 yrs old/ Acute Hepatitis	57	2	3.5	Wibawa et al., 2007
Philipiines	1992	Mean age 31+ 16.62/Viral Hepatitis	65	4	6.15	Gloriani-Barzaga et al., 1997
Singapore	2012-2016	0-65 yrs/Acute Hepatitis	5,080	503	10	Wong et al., 2019
Thailand	1992-1994	16-33 yrs old/Acute Viral Hepatitis	68	5	7.4	Poovorawan et al., 1996
	2008-2009, 2011	1-90 yrs old/ Acute Hepatitis	614	26	4.2	Siripanyaphinyo et al., 2014
Vietnam	1993-1995	1-68 yrs old/Acute Hepatitis	188	60	3.2	Corwin et al., 1996

III. HEV Infections in Pregnancy

A systematic review by Bigna et al in 2020 which included 52 studies (11,663 pregnant women), showed that the seroprevalence was 3.5% (95% confidence interval: 1.4–6.4) in asymptomatic women (most of whom were from high endemic areas). The prevalence in symptomatic women was 49.6% (42.6–56.7) with data only from HEV- high endemic countries. HEV infection was associated with maternal deaths (pooled OR 7.17; 3.32–15.47), low birth weight (OR: 3.23; 1.71–6.10), small for gestational age (OR: 3.63; 1.25–10.49), preterm < 32 weeks (OR: 4.18; 1.23–14.20), and preterm < 37 weeks (OR: 3.45; 2.32–5.13), stillbirth (OR: 2.61; 1.64–4.14), intrauterine deaths (OR: 3.07; 2.13–4.43), and not with miscarriage (OR: 1.74; 0.77–3.90). Data from the same study showed that the prevalence odds ratio in the SEA region was 1.71 (95% CI 1.46–2.00) p< 0.0001.[31]

Hepatitis Prevention Strategies in The ASEAN Region



Viral Hepatitis Prevention Strategies in The ASEAN Region

Strategies	Brunei Darussalam[1]	Cambodia[2]	Lao PDR [3]	Indonesia [4,5]	Malaysia [6]
Prevention	Routine Vaccination, vaccination for at-risk individuals and HCWs	Routine Vaccination, vaccination for at-risk individuals and HCWs	Routine Vaccination, vaccination for at-risk individuals and HCWs	Implementation of Clean&Healthy Lifestyle (PHBS), Routine Vaccination, vaccination for at-risk individuals and HCWs	Routine Vaccination, vaccination for at-risk individuals and HCWs
Screening and Testing	Screening of blood donors helps prevent transfusion-transmitted hepatitis B and C; Mandatory HepB screening in all pregnant women	Screening of blood donors helps prevent transfusion-transmitted hepatitis B and C		• HBV screening-testing in high-risk populations (pregnant women, general population with high risk factors) • HBV screening-testing in high-risk populations (PWID, hemodialysis patient, prisoners, PLHIV) • Active case finding in both community and health-facility-based and their networks • Expanding access to viral load testing for the diagnosis of hepatitis B and C • Data recording-reporting and analysis	Screening mainly executed at hospitals and at central and regional laboratories (except for the screening performed for blood donors and foreign workers)
Public Awareness and Education	Public Awareness Campaigns	Public Awareness Campaigns	Public Awareness Campaigns	Public Awareness Campaigns, multisectoral approach	Public Awareness Campaigns
Capacity Building and Training	Healthcare workforce receive training and capacity building	Departement of Hospital Services assumes responsibility for delivering training, as well as monitoring and evaluating IPC practices		Development of Hepatitis control guidebook, National Medical Service Guidelines (PNPK) for Diagnosis and Treatment of Hepatitis B (in collaboration with professional associations), including training modules for early detection of Hepatitis B	Efforts focused on improving the knowledge and skills of healthcare provides in the prevention and control as well as testing, treatment and care of viral hepatitis
Other Policy Development		• Ministry of Health has officialyy endorsed the national guidelines for infection prevention and control (IPC), with health facilities taking the lead in their coordination and implementation • Standard operating procedure (SOP) for food-borne disease entitled "Intersectoral Outbreak Investigation and Response" was developed	Hepatitis B vaccination was included in the EPI in 2002. Hepatitis B vaccination for newborns was integrated into the EPI in 2004; this gradually expanded from central hospitals to rural areas.	Nationwide HBV immunization has been integrated to National EPI since 1997; "The Guidance of Treatment of Chronic Liver Disease" was issued by the Indonesian Association for the Study of the Liver for treatments of viral hepatitis Ministry of Health launched a programme that focuses on the elimination of vertical transmission from mother to child	Developed National Strategic Plan for Hepatitis B and C (NSPHBC), a comprehensive strategy and plan of action for the planning, implementation, monitoring and evaluation of viral hepatitis programmes and activities in the country

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Strategies	Myanmar [1]	Philippines[2]	Singapore[3]	Thailand[4]	Vietnam[5]
Prevention	Routine Vaccination, vaccination for at-risk individuals and HCWs	Routine Vaccination, vaccination for at-risk individuals and HCWs	Routine Vaccination, vaccination for at-risk individuals and HCWs	Implementation of Clean&Healthy Lifestyle (PHBS), Routine Vaccination, vaccination for at-risk individuals and HCWs	Routine Vaccination, vaccination for at-risk individuals and HCWs
Screening and Testing	Hepatitis B and Hepatitis C screening tests can be done at both National Laboratories and some private facilities; they are compulsory and free for blood donors but are not free of charge for everyone	Screening of blood donors helps prevent transfusion-transmitted hepatitis B and C	Mandatory HepB screening in all pregnant women; Screening of blood donors helps prevent transfusion-transmitted hepatitis B and C	Screening of blood donors helps prevent transfusion-transmitted hepatitis B and C Cost-effective screening at the poiny-of-care (health center of village hospital) under the test and treat model is recommmended for adults over 30 years old	Population-based HBV-HCV screening with the support of a non-profit organization Vietnam Viral Hepatitis Alliance (V-VHA)
Public Awareness and Education	Public Awareness Campaigns	Public Awareness Campaigns	Public Awareness Campaigns	Public Awareness Campaigns,	Public Awareness Campaigns
Capacity Building and Training	Training efforts through the pre-service educational curriculum , on-the-job training, postgraduate training, and continuing medical education activities		Healthcare providers were educated on the proper screening of viral hepatitis, pre- and post- test counselling, and when to refer patients for specialist treatment	Healthcare professionals are trained in developing disease management plan at point-of care or referral	Clinician training for HBV and HCV screening, and linkage to care program
Other Policy Development	National Strategic Plan (NSP) for viral hepatitis and introduced the Five-Year Action Plan of viral hepatitis was developed in 2015	The EPI was revised and expanded in 2010 to cover mumps, rubella, Hepatitis B, and H. influenza type B, through Republic Act No. 10152- the "Mandatory infants and Children Health Immunization of 2011". National Viral Hepatitis Task Force (NVHTF) was organized, a public-private partnership, for vrial hepatitis prevention and control	Singapore revised its National Childhood Immunization Schedule (NCIS) in 2020 to incorporate two new combination vaccines: the hexavelant hepatitis, diphteria, acellular pertussis, tetanus (DTaP), hemophilus influenzae b (Hib), inactivated poliovirus (IPV) (6-in-1), and the quadrivalent measles, mupms, rubella, and varicella (MMRV) vaccines	A national policy led to a pilot project in 19888 to reduce HBV infection by adding the HB vaccine to the Expanded Program on Immunization (EPI)	Ministry of Health developed a national strategic plan for viral hepatitis and released guidelines for the diagnosis and treatment of chronic hepatitis B in 2015

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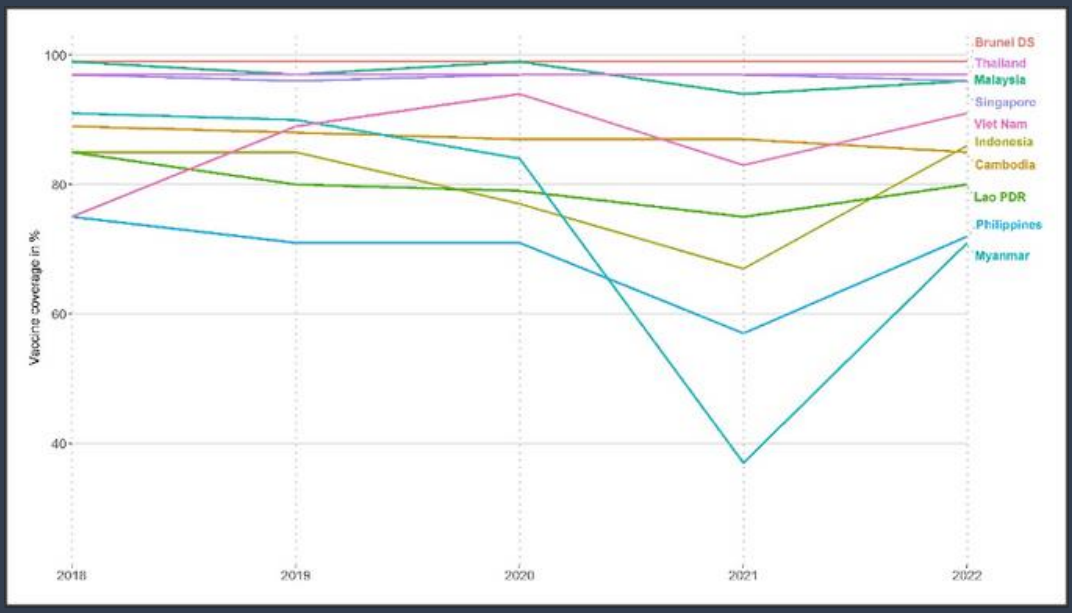

Figure 2 Hepatitis B virus vaccination coverage among children below 1 year in ASEAN Region

Viral Hepatitis Vaccination Coverage in the ASEAN Region

The WHO Global Observatory data on hepatitis B vaccine coverage among children below 1 year old in the ASEAN region reveals a range of coverage percentages spanning from 70% to 99%. This data sheds light on the immunization efforts within the ASEAN countries, showcasing the varying degrees of success in ensuring that the younger population is protected against Hepatitis B.

Within this spectrum, Brunei Darussalam stands out as a leader, boasting the highest vaccine coverage rate of 99%. This remarkable accomplishment reflects the country's robust commitment to public health and immunization initiatives. On the other end of the spectrum, Myanmar struggles with a comparatively lower vaccine coverage rate of 71%, indicating potential challenges in reaching vulnerable populations with adequate healthcare services.

The data also highlights the impressive immunization efforts of other countries in the ASEAN region. Thailand secures the second-highest position with an impressive coverage rate of 97%, closely followed by Malaysia and Singapore at 96% each. These countries showcase substantial achievements in extending healthcare access and promoting vaccination awareness.

The mid-tier performers in this regard include Vietnam with a coverage rate of 91%, Indonesia at 86%, Cambodia with 85%, and Lao PDR with 80%. While not achieving

the highest coverage rates, these countries demonstrate a commendable commitment to immunization, albeit with room for further improvement.

The data reveals that the Philippines and Laos face significant challenges in achieving widespread vaccine coverage. The Philippines reports a coverage rate of 72%, indicating a potential need for enhanced strategies to reach more children with vital immunizations. Laos, with a coverage rate of 80%, showcases the efforts made while emphasizing room for further progress.

However, the emergence of the COVID-19 pandemic has cast a shadow over these achievements. The pandemic's severe impact on National Immunization Programs across the ASEAN region has resulted in a potential plummet in coverage rates to below 50%. This alarming trend poses a serious threat to the prevention of viral hepatitis infections in the years to come. As vaccine delivery and outreach efforts have been disrupted by the pandemic, there is a heightened risk of decreased protection against preventable diseases like hepatitis B.

In conclusion, the WHO Global Observatory data provides a comprehensive overview of hepatitis B vaccine coverage among children below 1 year old in the ASEAN region. The range of coverage percentages underscores the diverse successes and challenges faced by different countries. While some nations have excelled in their immunization efforts, others are grappling with achieving widespread coverage. The COVID-19 pandemic's impact on immunization programs adds an urgent dimension to this issue, emphasizing the need for collective efforts to maintain and enhance vaccine coverage to prevent future health threats.

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