ASSESSMENT OF ANTIVIRAL USAGE, BARRIERS, AND STRATEGIES FOR SCALING UP HEPATITIS C TREATMENT IN MALAYSIA: A MIX-METHODOLOGY STUDY

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by

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LIST OF ABBREVIATIONS

Anti-HCV	Hepatitis C virus antibody
APRI	Aspartate aminotransferase-to-platelet ratio index
cAg	Core antigen
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
DAA	Direct-acting antiviral
FGD	Focus group discussion
FIB-4	Fibrosis-4
GHR	Global Hepatitis Report
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
MYR	Malaysian ringgit
NS3/4A	Non-structural 3/4A
NS5A	Non-structural protein 5A
NS5B	Non-structural protein 5B
OR	Odds ratio
rDNA	Recombinant deoxyribonucleic acid
RNA	Ribonucleic acid
SVR	Sustained virologic response
SVR12	Sustained virologic response at week 12 following treatment completion
SPSS	Statistical Package for the Social Sciences
TRIPS	Trade-Related Aspects of Intellectual Property Rights
US$	The United States dollar
WHO	World Health Organization

LIST OF SYMBOLS

>	Greater than
≥	Greater than or equal to
<	Smaller than
+	With
-	Without
±	With or without

PENILAIAN PENGGUNAAN ANTIVIRAL, HALANGAN DAN STRATEGI UNTUK MENINGKATKAN LIPUTAN RAWATAN HEPATITIS C DI MALAYSIA: KAJIAN METODOLOGI BERCAMPUR

ABSTRAK

Malaysia menggunakan tiga strategi utama untuk mencapai matlamat sedunia bagi menghapuskan hepatitis C. Strategi-strategi ini adalah perlaksanaan perlesenan wajib atas agen antivirus yang bertindak secara langsung (DAA), penggunaan regimen rawatan tetap yang terdiri daripada DAA (sofosbuvir dan daclatasvir) dan penyahpusatan rawatan hepatitis C melalui klinik-klinik kesihatan. Kajian tiga fasa ini menggabungkan kaedah kuantitatif dan kualitatif dengan tujuan untuk (i) menilai perubahan liputan rawatan dalam kalangan penghidap hepatitis C dan perbelanjaan atas agen-agen antivirus selepas perlaksanaan perlesenan wajib, (ii) menilai hasil klinikal penerima rawatan dengan rejimen tetap, dan (iii) mengkaji halangan dan strategi berpotensi untuk meningkatkan lagi liputan rawatan farmakologi bawah model penyahpusatan rawatan hepatitis C yang dilaksanakan sekarang. Fasa pertama kajian ini adalah berdasarkan data yang dikumpulkan daripada 177 pusat kesihatan awam. Data ini merangkumi rejimen-rejimen antivirus yang digunakan untuk hepatitis C, bilangan penerima rawatan dan perbelanjaan atas agen-agen antivirus antara tahun 2013 dan 2019. Liputan rawatan dalam kalangan penghidap hepatitis C menunjukkan trend peningkatan yang ketara daripada 0.05% pada tahun 2013 kepada 0.5% pada tahun 2019 (p=0.001). Peningkatan liputan rawatan yang mendadak didapati berlaku dalam dua tahun selepas perlaksanaan perlesenan wajib.

Walau bagaimanapun, perbelanjaan kerajaan atas agen-agen antivirus berbanding dengan perbelanjaan kesihatan awam tahunan adalah dalam lingkungan 0.02%-0.06% dan tidak menunjukkan trend peningkatan yang ketara dalam tempoh yang sama (p=0.053). Reka bentuk kohort retrospektif seterusnya digunakan dalam fasa kedua kajian ini untuk menilai hasil klinikal dalam kalangan 1,797 individu yang dirawat dengan sofosbuvir dan daclatasvir di 16 hospital. Kadar gerak balas virologi berkekalan pada minggu ke-12 selepas tamat rawatan (SVR12) adalah 95.4% (95% selang keyakinan: 94.2%, 96.7%). Pencapaian SVR12 juga didapati tidak dipengaruhi oleh status sirosis penerima rawatan mahupun genotip virus. Kesan sampingan rawatan juga adalah jarang. Perbincangan kumpulan fokus melibatkan 180 individu berkepentingan dalam rawatan hepatitis C pula dijalankan dalam fasa ketiga kajian ini. Enam tema yang telah dikenalpasti adalah akses terhad kepada kemudahan kesihatan, kelemahan dalam penyampaian penjagaan, rawatan percuma tetapi kurang kemampuan untuk mendapat rawatan, penerimaan rawatan yang suboptimum, mengatasi halangan pihak pembekal rawatan dan mengatasi halangan pihak penerima rawatan. Secara keseluruhan, kajian tiga fasa ini mengesahkan kesan perlesanan wajib dalam meningkatkan liputan rawatan dalam kalangan penghidap hepatitis C tanpa membebankan perbelanjaan kesihatan awam. Rejimen rawatan yang dipilih juga didapati telah menghasilkan kadar SVR12 yang tinggi. Kajian ini juga mengenalpasti beberapa kelemahan dalam model penyahpusatan rawatan hepatitis C yang dilaksanakan sekarang dan memberikan cadangan untuk mengatasi kelemahan-kelemahan tersebut.

ASSESSMENT OF ANTIVIRAL USAGE, BARRIERS, AND STRATEGIES FOR SCALING UP HEPATITIS C TREATMENT IN MALAYSIA: A MIX-METHODOLOGY STUDY

ABSTRACT

Malaysia adopted three key strategies to pursue the global goal of hepatitis C elimination, namely applying compulsory licensing on a direct-acting antiviral (DAA), introducing a standard DAA-based treatment regimen (sofosbuvir and daclatasvir) and decentralizing hepatitis C care through primary healthcare centers. This three-phase study adopted both quantitative and qualitative methods, aiming to (i) assess changes in the treatment coverage of individuals with hepatitis C and the government spending on antivirals after applying compulsory licensing, (ii) evaluate clinical outcomes in treatment recipients of the standard regimen, and (iii) explore barriers and potential strategies to further scale up pharmacological treatment under the existing hepatitis C care decentralization model. The first phase of the study used the data gathered from 177 public health settings, covering antiviral regimens used for hepatitis C, the number of treatment recipients and the corresponding expenditure between the years 2013 and 2019. A significant increasing trend in the treatment coverage of individuals with hepatitis C from 0.05% in the year 2013 to 0.5% in the year 2019 was detected ($p=0.001$), and a massive expansion in the treatment coverage in the two years after applying compulsory licensing was observed. Yet, the government spending on antivirals in relation to the public health expenditure did not significantly increase within the same period, narrowly fluctuating between 0.03% and 0.06% ($p=0.053$). A retrospective cohort design was subsequently

applied in the second phase of the study for the clinical outcome evaluation in the 1,797 individuals treated using sofosbuvir and daclatasvir in 16 hospitals. An overall rate of sustained virologic response at week 12 following the treatment completion (SVR12) of 95.4% (95% confidence interval: 94.2%, 96.7%) was recorded. The SVR12 achievement varied across neither cirrhosis status of the treatment recipients nor viral genotypes. Adverse events were also found to be rare. Focus group discussions involving 180 stakeholders in hepatitis C care were performed in the last phase of the study. Six themes were identified: limited access to health facilities, gaps in care delivery, free yet unaffordable treatment, suboptimal acceptability of treatment, addressing supply-side barriers and addressing demand-side barriers. Overall, this three-phase study confirmed the effect of compulsory licensing in expanding the treatment coverage of individuals with hepatitis C without elevating the budgetary pressure, along with the high SVR12 rate achieved with the standard treatment regimen. It also identified gaps in the existing care decentralization model for hepatitis C and offered possible strategies to address them.

CHAPTER 1

INTRODUCTION

1.1 Global burden of hepatitis C

Hepatitis C virus (HCV) was discovered in the late 1980s via the recombinant deoxyribonucleic acid (rDNA) immunoscreening method (Houghton, 2009, 2019). Hepatitis C, characterized by HCV-induced liver inflammation, has since become a global health concern (Brown, MacLachlan, & Cowie, 2017; Bukh, 2016). It is estimated that slightly over 70 million individuals around the world are currently living with hepatitis C, and approximately 400,000 deaths associated with the complications of the disease have been reported annually (Jefferies, Rauff, Rashid, Lam, & Rafiq, 2018; Roudot-Thoraval, 2021). Hepatitis C, together with hepatitis B, has contributed to nearly 90% of the fatalities attributable to viral hepatitis over the years (Jefferies et al., 2018).

The prevalence of hepatitis C varies across continents, ranging between 1.3% in the Americas and 2.9% in Africa. Asia falls near the higher end of the range, recording a prevalence of 2.8% (Petruzziello, Marigliano, Loquercio, Cozzolino, & Cacciapuoti, 2016). Among countries in the Western Asia-Pacific Region, the prevalence of hepatitis C also widely ranges from 0% to 18.8% (World Health Organization, 2019). Individuals with an intravenous drug use history, individuals with immunodeficiency virus (HIV) infection, men who have sex with men, sex workers and prison inmates are among the known key populations who have a high risk of contracting hepatitis C (Martin, Vickerman, Dore, & Hickman, 2015; Mason et al., 2019; Scheibe et al., 2020).

Although hepatitis C is likely to be self-limiting in its acute phase, the majority (60-85%) of the individuals with hepatitis C would still develop into the chronic phase of the disease (Saito & Ueno, 2013). Without early interventions, chronic hepatitis C could eventually cause highly fatal complications, particularly cirrhosis and hepatocellular carcinoma (Zamor, deLemos, & Russo, 2017). These two conditions affect approximately 28.5% and 3% of the individuals with hepatitis C, respectively (El-Serag, 2002; Gordon et al., 2015).

1.2 Virology of HCV

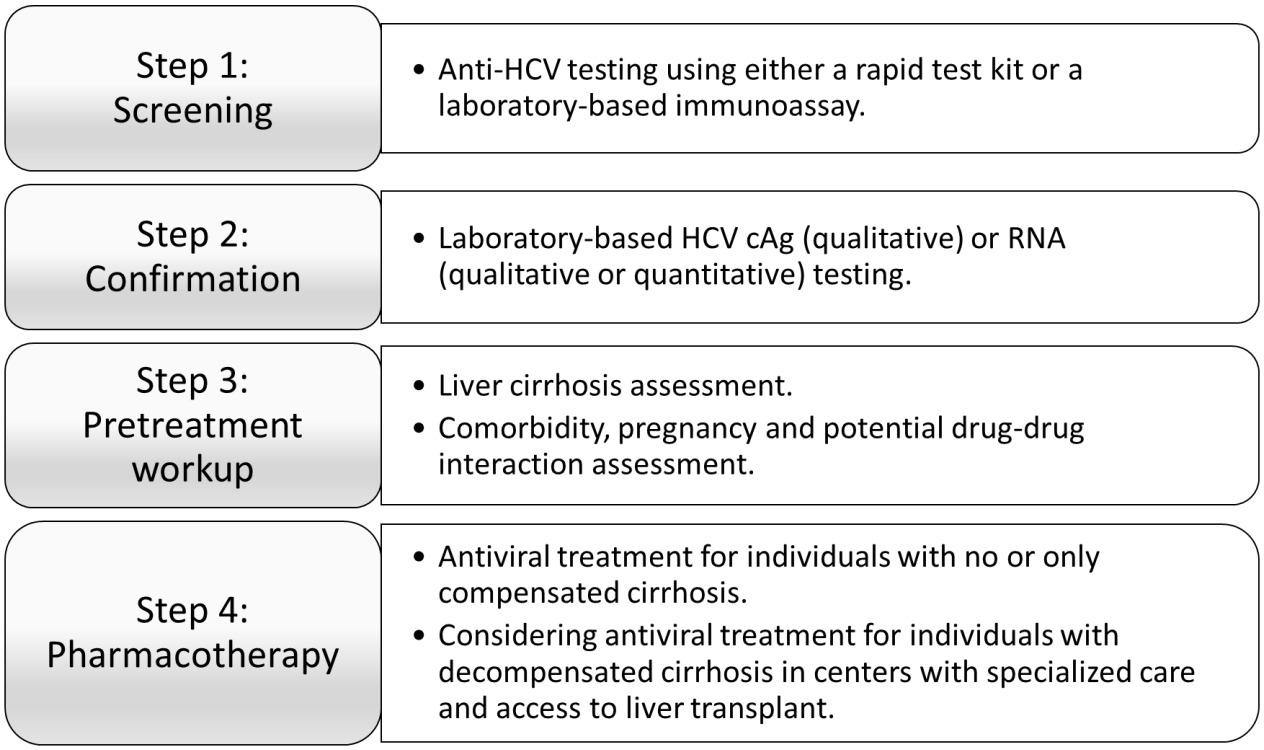
Until the world is hard-hit by Coronavirus Disease 2019 (COVID-19), HIV, hepatitis B virus (HBV) and HCV were among the most common and pathogenic blood-borne pathogens globally (Chigbu, Loonawat, Sehgal, Patel, & Jain, 2019; Pirozzolo & LeMay, 2007). HCV is transmissible through a blood-blood contact or vertically from mother to child (Moosavy et al., 2017). It appears as a single-stranded, enveloped ribonucleic acid (RNA) virus, taxonomically placed under the *Flaviviridae* family and the *Hepacivirus* genus (Li & Lo, 2015). With the variations in the nucleotide sequence up to 50%, the viruses circulate in an infected host as a genetically heterogeneous and yet closely related population (Kim & Chang, 2013; Li & Lo, 2015). The genetic variability of the viruses, in addition to their adaptability and high mutation rate, often enables their evasion from immune responses of infected hosts. This could explain the high tendency of hepatitis C to advance into the chronic phase and the inherent difficulty of producing either a vaccine or a pan-genotypic antiviral against HCV (Bartenschlager et al., 2018;

Burke & Cox, 2010; Pavio & Lai, 2003; Preciado et al., 2014; Stoll-Keller, Barth, Fafi-Kremer, Zeisel, & Baumert, 2009). Despite the growing understanding of HCV, hepatitis C is still not a vaccine-preventable disease at this point (Duncan, Urbanowicz, Tarr, & Ball, 2020).

To date, six major genotypes of HCV (HCV-1, HCV-2, HCV-3, HCV-4, HCV-5 and HCV-6), in addition to two rare genotypes (HCV-7 and HCV-8) and more than 84 subtypes, were discovered (Borgia et al., 2018; Simmonds et al., 1993; Smith et al., 2014; Spengler, 2018). HCV-1 and HCV-3 account for nearly 80% of the hepatitis C cases, while the rest are relatively uncommon and responsible for less than 10% of the hepatitis C cases each (Basyte-Bacevice & Kupcinskas, 2020; Messina et al., 2015). The viruses of different genotypes differ in their infectivity, pathogenicity and responses to antiviral treatment, and so do the subtypes (Irshad et al., 2010; Li & Lo, 2015). The two subtypes of HCV-1 (HCV-1a and HCV-1b), for instance, were reported to have different resistance profiles for antivirals (McCown, Rajyaguru, Kular, Cammack, & Nájera, 2009; Pellicelli et al., 2012). Furthermore, HCV genotypes demonstrate a unique geographical distribution. For example, HCV-1 is more common in North America, while HCV-3 is predominant over other genotypes in Southeast and Central Asia (A. Chan, Patel, & Naggie, 2017; Gordon et al., 2019; Messina et al., 2015; Yu & Chiang, 2010). Although confirming the HCV genotype at an individual level has become relatively unimportant after the emergence of broad-spectrum antivirals, it could still be useful in guiding the antiviral selection, setting the treatment duration and predicting the treatment response, especially in places where the accessibility of pan-genotypic treatment regimens is limited (Li & Lo, 2015).

1.3 Diagnosis of hepatitis C and pretreatment assessment

Hepatitis C is typically asymptomatic before its chronic complications transpire. Nonetheless, it occasionally manifests as fatigue, malaise, arthralgia and myalgia in the early phase (Dhingra, Ward, & Thung, 2016; Modi & Liang, 2008). Given the nonspecific symptoms of hepatitis C, a thorough examination is required to rule out other liver diseases (Figure 1.1) (World Health Organization, 2018a). In clinical settings worldwide, hepatitis C screening is usually performed by using either a rapid test kit or a laboratory-based immunoassay, with an active infection suggested by the detection of HCV antibody (anti-HCV) in the blood. Laboratory-based, confirmatory testing of hepatitis C is subsequently performed on individuals who have a positive test result for anti-HCV to ascertain the presence of HCV core antigen (c-Ag) or RNA. Alternatively, hepatitis C could also be quantitatively diagnosed by measuring the level of HCV RNA in the blood via a nuclei acid amplification test (E. Gupta, Bajpai, & Choudhary, 2014; Mane et al., 2019; World Health Organization, 2018a).



Reference: World Health Organization, 2018a.
Anti-HCV, hepatitis C virus antibody; cAg, core antigen; HCV, hepatitis C virus; RNA, ribonucleic acid.

Figure 1.1 Steps for hepatitis C diagnosis and pretreatment assessment recommended by the World Health Organization

If the diagnosis of hepatitis C is confirmed, the assessment of hepatic fibrosis, which indicates the extent of liver scarring due to the chronic injury (Fallowfield & Hayes, 2011), is required to guide the prognostic judgment and treatment decision-making. Liver biopsy is the gold standard to detect the presence of hepatic fibrosis and cirrhosis, the late-stage hepatic fibrosis. However, the use of non-invasive measures, including transient elastography, Fibrosis-4 (FIB-4) index and aspartate aminotransferase-to-platelet ratio index (APRI), in the assessment of hepatic fibrosis is also getting more common in recent years (Toosi, 2015). In the case that cirrhosis is present, the Child-Turcotte-Pugh (CTP) scoring system could then be adopted to judge whether it is clinically well compensated (Class A) or decompensated (Class B and C) (Sharma & Nagalli, 2021). Pharmacological treatment is recommended mainly for individuals with hepatitis C who have no or only compensated cirrhosis. Nevertheless, pharmacological treatment could still be considered for those who have decompensated cirrhosis, especially if they have access to specialized care and liver transplant (World Health Organization, 2018a).

1.4 Pharmacotherapy of hepatitis C

The primary aim of pharmacotherapy for hepatitis C is to eradicate HCV in infected individuals (González-Grande, Jiménez-Pérez, González Arjona, & Mostazo Torres, 2016). The key indicator of viral eradication widely used in hepatitis C treatment is the sustained virologic response (SVR), indicated by an undetectable HCV RNA level in the blood at a specific time point (either 12 or 24 weeks) after the completion of antiviral treatment (Smith-Palmer, Cerri, & Valentine, 2015). Achieving an SVR, particularly at

week 12 after the treatment completion (SVR12), was proven to provide great durability of HCV seroclearance (Lin et al., 2021). In addition to improving quality of life, the existing literature also often associates the SVR achievement with the reduction in mortality, liver morbidity and the corresponding medical expenditure among individuals with hepatitis C (Backus, Belperio, Shahoumian, & Mole, 2018; Juanbeltz et al., 2018; Nuño Solinís, Arratibel Ugarte, Rojo, & Sanchez Gonzalez, 2016). Treatment recipients who achieve an SVR are deemed to be cured of hepatitis C (Smith-Palmer et al., 2015), even though post-treatment follow-ups are still required to monitor the regression of hepatic fibrosis, as well as the development of other liver-related complications (Serfaty, 2016).

A two-drug treatment regimen consisting of interferon-α and ribavirin used to be the cornerstone of hepatitis C treatment globally (Buti & Esteban, 2011; Karbasi-Afshar, 2014). Interferon-α and its pegylated form are both available in the market as self-injectable formulations (Hartwell & Shepherd, 2009), while ribavirin is formulated as film-coated tablets for oral administration (Naik & Tyagi, 2012). Pharmacologically, interferon-α suppresses various stages of the HCV replication by inducing interferon-stimulated genes, and the addition of ribavirin potentiates its antiviral activity through the up-regulation of the genes (Te, Randall, & Jensen, 2007; E. Thomas et al., 2011). Over almost two decades, individuals infected with HCV-1 from all around the world received 48-week treatment using interferon-α and ribavirin, and the treatment duration was halved for HCV-2 and HCV- 3 infections (Palumbo, 2011). Nonetheless, such a combination only yielded an SVR rate of approximately 65% for both HCV-2 and HCV-3 infections, and 30% for HCV-1 infection (C. H. Chen & Yu, 2010; Niederau et al., 2014). While the

usefulness and optimal treatment duration of the interferon-α-ribavirin combination for infections caused by other HCV genotypes remained debatable, the SVR rates reported were also inconsistent, widely ranging from 31.2 to 88% (Al Ashgar et al., 2009; Al Naamani, Al Sinani, & Deschênes, 2013). Moreover, poor medication adherence and premature treatment discontinuation emerged as the major challenges of interferon-α-based treatment, mainly due to intolerable adverse events. Besides cutaneous reactions at injection sites (Mistry, Shapero, & Crawford, 2009), the use of interferon-α was often linked to the events of neutropenia, thrombocytopenia, asthenia, flu-like syndrome, sleep alteration and depression (Larrey, Ripault, & Pageaux, 2014). Ribavirin-induced hemolytic anemia also occurred in up to 30% of the treatment recipients (Sung, Chang, & Saab, 2011).

Since the last decade, the advent of orally administered, direct-acting antivirals (DAAs) has transformed the landscape of pharmacological treatment for hepatitis C (Lam, Jeffers, Younoszai, Fazel, & Younossi, 2015). DAAs, by definition, directly interrupt different stages of the viral replication (Gaetano, 2014). They act pharmacologically as either a non-structural 3/4A (NS3/4A) protease, non-structural protein 5A (NS5A) or non-structural protein 5B (NS5B) inhibitor (Table 1.1) (Spengler, 2018). Boceprevir and telaprevir, both NS3/4A protease inhibitors, were launched in the year 2011 as the first-generation DAAs. However, their use was limited as an add-on to interferon-α and ribavirin. Both of them were withdrawn from the market in the mid-2010s due to the overwhelming competition from newer DAAs, which generally had a wider HCV genotype coverage and a better efficacy profile (Mangia et al., 2017; Tungol, Rademacher, & Schafer, 2011). Following the emergence of all-oral, DAA-based regimens, interferon-

α was also phased out as the mainstay of hepatitis C treatment (Basar, Dailey, Dailey, Tahan, & Daglilar, 2021). On the contrary, ribavirin continues to be recommended as an adjunct to DAAs, especially in harder-to-treat cases, in order to elevate the likelihood of SVR achievement (Lu et al., 2019).

Table 1.1 Types of direct-acting antivirals commonly used in pharmacological treatment for hepatitis C

Pharmacological classes	Examples
NS3/4A protease inhibitors	Simeprevir Paritaprevir Grazoprevir Glecaprevir Voxilaprevir Boceprevir (withdrawn in the mid-2010s) Telaprevir (withdrawn in the mid-2010s)
NS5A inhibitors	Daclatasvir Ledipasvir Ombitasvir Velpatasvir Elbasvir Pibrentasvir
NS5B inhibitors	Sofosbuvir (nucleotide) Dasabuvir (non-nucleotide)

Reference: Spengler, 2018.

NS3/4A, non-structural 3/4A; NS5A, non-structural protein 5A; NS5B, non-structural protein 5B.

Currently, combinations of at least two DAAs from different pharmacological classes are widely used in the real world for their synergistic effects in eradicating HCV (Table 1.2) (European Association for the Study of the Liver, 2020; Ministry of Health Malaysia, 2019a; Pomeroy, Drusano, Rodriquez, & Brown, 2017). DAAs have been shown to be more effective than interferon-α, rendering hepatitis C highly curable with an 8- to 24-week course of treatment (Asselah et al., 2018; Kish, Aziz, & Sorio, 2017). Aside from individuals with hepatitis C who are naïve to antiviral treatment, DAA-based treatment is recommended for those who were previously treated with interferon-α-based regimen (treatment failure or reinfection) and those who have cirrhosis (European Association for the Study of the Liver, 2020; Ministry of Health Malaysia, 2019a). One of the DAAs regularly paired with its counterparts from other classes to form an interferon-α-free regimen is sofosbuvir, an NS5B inhibitor (Welzel, Dultz, & Zeuzem, 2014). For example, the sofosbuvir-ledipasvir combination, used either with or without ribavirin, could yield an SVR rate above 95% for HCV-1 infection (Lawitz et al., 2014). An SVR rate in the range between 90.8% and 94.5% for HCV-2 and HCV-3 infections is also achievable when sofosbuvir is used in conjunction with daclatasvir or velpatasvir (Belperio, Shahoumian, Loomis, Mole, & Backus, 2019). Although pharmacotherapy for HCV-4, HCV-5 and HCV-6 infections was less studied due to their relatively low prevalence (M. H. Nguyen & Keeffe, 2005), a comparable SVR rate is still attainable with the use of DAAs (Baumert, Berg, Lim, & Nelson, 2019; Di Biagio, Taramasso, & Cenderello, 2018; Horsley-Silva & Vargas, 2017). Besides showing excellent efficacy, DAAs also generally have a better safety profile in comparison with the interferon-α-ribavirin combination, with only mild and tolerable fatigue, gastrointestinal symptoms and headache reported as common adverse events (Gonzales Zamora, 2018).

Table 1.2 Direct-acting antiviral combinations recommended for different viral genotypes and cirrhosis status

Genotypes	Cirrhosis status	Treatment experience [a]	Direct-acting antiviral combinations					
			SOF-DAC	SOF-LDV	SOF-VEL	GLE-PIB	EBR-GZR	OrPD
HCV-1a	No	Naïve	12w	8w/ 12w	12w	8w	12w	12w+R
		Experienced	12w+R/ 24w	12w	12w	8w	12w	12w+R
	Compensated	Naïve	12w	12w	12w	12w	12w	-
		Experienced	24w	12w+R	12w	12w	12w	-
	Decompensated	-	12w ± R	12w/ 24w	12w+R/ 24w	-	-	-
HCV-1b	No	Naïve	12w	8w/ 12w	12w	8w	12w	8w/ 12w
		Experienced	12w	12w	12w	8w	12w	12w
	Compensated	Naïve	12w	12w	12w	12w	12w	12w
		Experienced	12w	12w	12w	12w	12w	12w
	Decompensated	-	12w±R	12w/ 24w	12w+R/ 24w	-	-	-
HCV-2	No	Naïve	12w	-	12w	8w	-	-
		Experienced	12w	-	12w	8w	-	-
	Compensated	Naïve	12w	-	12w	12w	-	-
		Experienced	12w/ 16w/ 24w	-	12w	12w	-	-
	Decompensated	-	12w±R	-	12w+R/ 24w	-	-	-
HCV-3	No	Naïve	12w	-	12w	8w	-	-
		Experienced	24w	-	12w	12w/ 16w	-	-
	Compensated	Naïve	24w+R	-	12w	12w	-	-
		Experienced	24w+R	-	12w+R	16w	-	-
	Decompensated	-	12w±R/ 24w±R	-	12w+R/ 24w	-	-	-

Table 1.2 Continued

Genotype	Cirrhosis status	Treatment experience [a]	Direct-acting antiviral combination					
			SOF-DAC	SOF-LDV	SOF-VEL	GLE-PIB	EBR-GZR	OrPD
HCV-4	**No**	**Naïve**	12w	12w	12w	8w	12w	-
		Experienced	24w	12w	12w	8w	12w	-
	Compensated	**Naïve**	12w	12w	12w	12w	12w	-
		Experienced	24w	12w+R	12w	12w	12w	-
	Decompensated	-	12w±R	12w/ 24w	12w+R/ 24w	-	-	-
HCV-5	**No**	**Naïve**	12w	12w	12w	8w	-	-
		Experienced	24w	12w	12w	8w	-	-
	Compensated	**Naïve**	12w	12w	12w	12w	-	-
		Experienced	24w	-	12w	12w	-	-
	Decompensated	-	12w±R	-	-	-	-	-
HCV-6	**No**	**Naïve**	12w	12w	12w	8w	-	-
		Experienced	24w	12w	12w	8w	-	-
	Compensated	**Naïve**	12w	12w	12w	12w	-	-
		Experienced	24w	-	12w	12w	-	-
	Decompensated	-	12w±R	-	12w+R/ 24w	-	-	-

Reference: Ministry of Health Malaysia, 2019a.

GLE/PIB, glecaprevir/ pibrentasvir; GZV/EBR, grazoprevir/ elbasvir; OrPD, ombitasvir/ ritonavir/ paritaprevir/ dasabuvir; R: ribavirin; SOF/DAC, sofosbuvir/ daclatasvir; SOF/LDV, sofosbuvir/ ledipasvir; SOF/VEL, sofosbuvir/ velpatasvir; w, week; +, with; ± with or without.

[a] Treatment experience is defined as a history of receiving interferon-α and ribavirin.

1.5 Global agenda to eliminate hepatitis C

Riding the wave of rapidly evolving DAAs, the World Health Organization (WHO), through the World Health Assembly held in the year 2016, decided to adopt the Global Health Sector Strategy and set a goal to eliminate hepatitis C by the year 2030 (Sun, Cheng, Hassan, Chan, & Piedagnel, 2021; Waheed, Siddiq, Jamil, & Najmi, 2018). To make hepatitis C less a public health threat, the WHO aimed to reduce the global incidence and mortality of the disease by 80% and 65%, respectively, from the baseline recorded in the year 2015 (Heffernan, Cooke, Nayagam, Thursz, & Hallett, 2019; World Health Organization, 2016). Such a target is only achievable by diagnosing at least 90% of individuals with hepatitis C and treating at least 80% of them by the year 2030 (Waheed et al., 2018; World Health Organization, 2016). All countries are also required to develop a national strategic plan to provide a framework for responses to hepatitis C (World Health Organization, 2015). The three key strategies recommended by the WHO to pursue the hepatitis C elimination at the country level are (i) enhancing the availability of DAAs to ensure universal access to pharmacological treatment, (ii) selecting right treatment regimens for individuals at different stages of hepatitis C, and (iii) offering highly accessible hepatitis C care through decentralized screening services and treatment (World Health Organization, 2017b; World Health Organization, 2018a).

To date, regardless of the efforts made on a global scale, only one-fifth of individuals with hepatitis C were diagnosed, and approximately 13% of them had received pharmacological treatment (World Health Organization, 2021b). Even though curative treatment has the potential to alleviate the financial burden caused by the complications of the disease, the overall cost saving is still not assured due to the exorbitant prices of

branded DAAs (Zhuo et al., 2020). In fact, the limited access to DAAs among individuals with hepatitis C remains a global issue, as a course of a sofosbuvir-based regimen is highly priced in the range between US$ 34,381 and US$ 67,430 (Barber, Gotham, Khwairakpam, & Hill, 2020). While interferon-α-free regimens are highly recommended by international guidelines to be used for hepatitis C treatment, a mismatch between the production costs and list prices of DAAs has also prompted grievances against the pharmaceutical industry (Dennis, Naji, Jajarmi, Ahmed, & Kim, 2021). Nearly 75% of individuals with hepatitis C are from low- and middle-income countries (World Health Organization, 2017c), and therefore the fact that the prices of DAAs are not adjusted according to the income levels and disease burden of these countries hampers the progress of hepatitis C elimination (Barber et al., 2020). Apart from high drug costs, the poor access to healthcare, inadequate knowledge, disease-related stigma, concerns for confidentiality, late presentation for care, poor medication adherence and multiple life struggles continue to become obstacles to the scale-up of pharmacological treatment for hepatitis C worldwide (Crowley et al., 2018; Younossi et al., 2016).

1.6 The management of hepatitis C burden in Malaysia

It its estimated that the prevalence of hepatitis C in Malaysia ranged between 0.3% and 2.5% (97,800 to 815,000 people of a 32.6 million population) (Department of Statistics Malaysia, 2021; McDonald et al., 2015; Md Said et al., 2020; Muhamad et al., 2020). The accumulative number of deaths related to hepatitis C in Malaysia is projected to constantly grow, potentially reaching 63,900 by the year 2039 (McDonald et al., 2015;

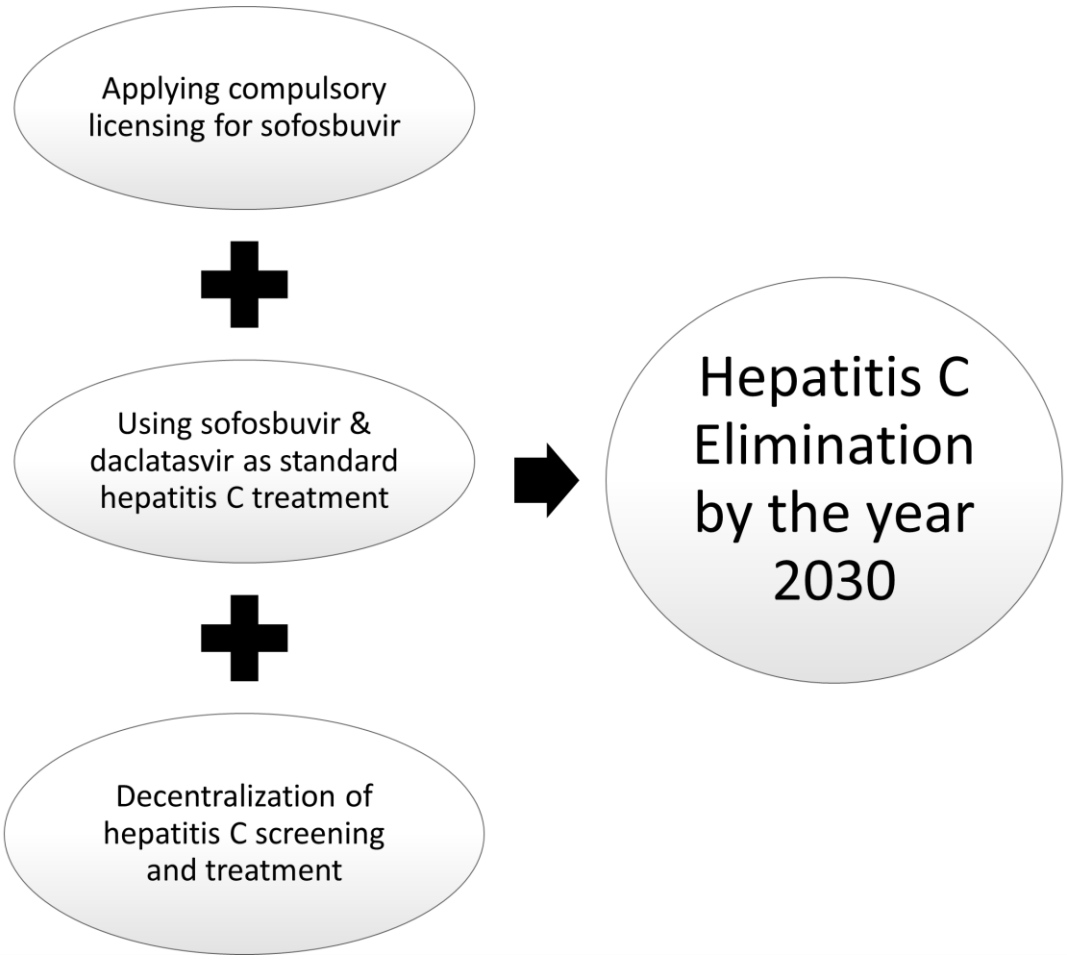
Raihan, 2016). HCV-3 (61.9-73%) and HCV-1 (27-35.9%) predominate over other genotypes in causing hepatitis C in Malaysia (Mohamed, Zainol Rashid, Wong, Abdullah, & Rahman, 2013). The mounting evidence to support the effectiveness of DAAs against these two viral genotypes suggests that individuals with hepatitis C in Malaysia are highly curable (Chan et al., 2017; Forde & Bhattacharya, 2017). Nevertheless, the limited accessibility of DAAs due to their prohibitively high acquisition costs, along with the absence of a strategic plan at the national level, was once the major challenge restricting the scale-up of pharmacological treatment for hepatitis C in Malaysia (Raihan, Mohamed, Abu Hassan, & Md Said, 2017).

Despite the possible drug expenditure expansion following a massive scale-up of pharmacological treatment, Malaysia, as a member state of the WHO, still pledged to eliminate hepatitis C by the end of 2030s (Wait et al., 2016). To achieve this goal, the Malaysian government has been playing a crucial role in providing financial support and putting a national strategic plan in place (Hiebert et al., 2019; McDonald et al., 2018). Pharmacological treatment forms one of the key components of hepatitis C care in the strategic plan, given the same importance as screening, diagnosis and post-treatment monitoring and evaluation (Ministry of Health Malaysia, 2019c). In line with the recommendations of the WHO, Malaysia, under the lead of the Ministry of Health, has adopted the following three key strategies over the last few years to upscale pharmacological treatment for hepatitis C (Figure 1.2) (Abu Hassan & Chan, 2020; Ministry of Health Malaysia, 2019c):

(i) Enhancing the availability of DAAs in the country by issuing a compulsory license to enable the import of generic sofosbuvir;

(ii) Introducing the sofosbuvir-daclatasvir combination to be used in public hospitals with specialized gastroenterology services as the standard treatment regimen for hepatitis C; and

(iii) Decentralizing hepatitis C care by offering screening services and DAA-based treatment (sofosbuvir and daclatasvir) in primary healthcare centers under the Ministry of Health.



References: (i) Abu Hassan & Chan, 2020, and (ii) World Health Organization, 2018c.

Figure 1.2 Three key strategies adopted by Malaysia to pursue the hepatitis C elimination goal

1.7 Problem statement

It is important to note that the WHO has only set a goal to eliminate hepatitis C as a public health threat by the year 2030 and made general recommendations as outlined in the previous section. All countries are expected to devise their own strategies to meet the goal. Malaysia is one of the countries taking initiative to implement three key strategies in line with the WHO's recommendations (Abu Hassan & Chan, 2020; Ministry of Health Malaysia, 2019c). However, as the strategies to tackle hepatitis C are highly country-specific, it is unlikely to design studies from which findings are generalizable on a global scale.

To date, the impact of compulsory licensing applied by Malaysia to enhance the availability of DAAs on the treatment coverage of individuals with hepatitis C and the public health expenditure remains unclear. Moreover, it is uncertain if such an initiative has resulted in the transition of hepatitis C treatment from the interferon-α-based regimen to DAAs in Malaysia. Due to limited options for DAAs, Malaysia has also adopted a "one-size-fits-all" approach and treated all individuals with hepatitis C using a fixed, two-DAA regimen regardless of viral genotypes and their cirrhosis status. However, the clinical outcomes of treatment recipients are yet to be determined. While Malaysia pins its hope on the care decentralization for hepatitis C to massively upscale pharmacological treatment, the challenges faced at the level of primary healthcare centers were also not extensively explored.

With only about a decade left to meet the goal set by the WHO, the Ministry of Health has scheduled a revision of its national strategic planning for hepatitis C to take

place in the year 2023. Hence, Malaysia is in dire need of the aforementioned information to confirm that the country is on the right track toward meeting the hepatitis C elimination goal and to guide the subsequent actions of the government. Through the engagement with policymakers and key stakeholders in hepatitis C care, this study is expected to provide evidence to inform the national strategic planning for hepatitis C and be translated into public health policy in Malaysia.

1.8 Study objectives

The general objective of this three-phase study was to assess the antiviral usage, barriers and strategies for scaling up hepatitis C treatment in Malaysia. The three specific objectives of the study were as follows:

(i) To assess the changes in the treatment coverage of individuals with hepatitis C, the government spending and the utilization patterns of antivirals in Malaysia between the years 2013 and 2019, particularly after the application of compulsory licensing on sofosbuvir.

(ii) To evaluate the clinical outcomes including the treatment completion rate, SVR achievement and adverse events in individuals with hepatitis C, who received a course of standard treatment with sofosbuvir and daclatasvir in Malaysia.

(iii) To explore the barriers and potential strategies to further scale up pharmacological treatment in individuals with hepatitis C under the existing care decentralization model in Malaysia.

1.9 Conceptual framework

As illustrated in the conceptual framework (Figure 1.3), this study started with the assessment of the impact of the compulsory licensing applied on sofosbuvir, which was intended to enhance the availability of DAAs in Malaysia. Aside from the changes in the treatment coverage of individuals with hepatitis C, the assessment was extended to the changes in the government spending on antivirals over time to provide insight into the financial impact of this approach. Additionally, the findings on the changes in drug use patterns over the years were expected to show if granting a compulsory license to sofosbuvir successfully accelerated the replacement of interferon-α-based regimen with DAAs as the mainstay of pharmacological treatment for hepatitis C in Malaysia. This study continued with the evaluation of clinical outcomes in treatment recipients of sofosbuvir and daclatasvir. The three aspects of clinical outcomes evaluated were the treatment completion rate, SVR achievement and adverse events. While the WHO advocates the selection of the right DAA regimens for hepatitis C treatment, this phase of the study was expected to determine if the "one-size-fits-all" approach of using only a fixed treatment regimen could eliminate the disease in Malaysia. In the last phase of the study, the focus was placed on the exploration of ways to further scale up pharmacological treatment after hepatitis C care was decentralized through primary healthcare centers in Malaysia. Through the direct involvement of policymakers from the Ministry of Health, the findings of this study were expected to provide evidence to guide the revision of the strategic planning for the disease in the year 2023 and eventually eliminate the disease as a public health threat by the year 2030.

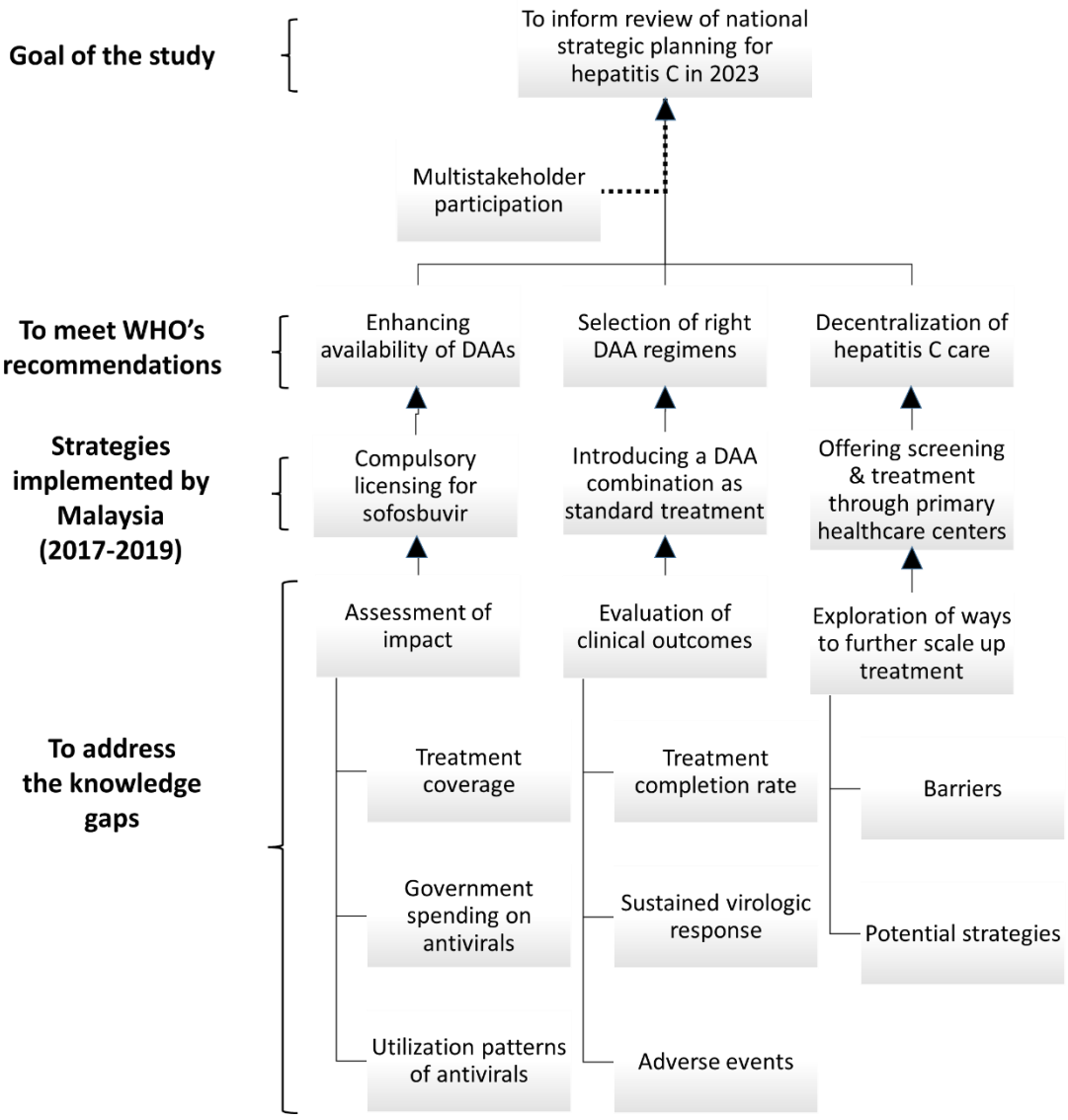


Figure 1.3 Conceptual framework of the study

1.10 Outline of thesis

The current chapter provides background information of hepatitis C and the public health agenda to eliminate it. The subsequent chapters are organized in the following sequence:

(i) Chapter 2 reviews the literature regarding what has been studied or written on the strategies adopted by Malaysia to pursue the hepatitis C elimination goal and the findings in other countries on similar strategies, aiming to provide context and highlight the gaps to be addressed in this study.

(ii) Chapter 3 outlines both the quantitative and qualitative methods applied in the three phases of this study.

(iii) Chapter 4 depicts the findings for each of the three phases of this study.

(iv) Chapter 5 discusses the findings, along with the strengths and limitations of this study.

(v) Chapter 6 summarizes the findings of this study, their impacts and recommendations for future studies.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

In this chapter, a comprehensive review of the existing literatures is offered, aiming to synthesize a summary to provide context for this study (Maggio, Sewell, & Artino, 2016), as well as to underline the knowledge gaps and research needs in pharmacological treatment for hepatitis C in Malaysia (Hempel, Gore, & Belsher, 2019). It focuses on the three key strategies adopted by Malaysia to tackle hepatitis C as outlined in the preceding chapter, ranging from the application of compulsory licensing on a DAA, the use of sofosbuvir and daclatasvir as the standard treatment regimen to the decentralization of screening services and pharmacological treatment through primary healthcare centers across the country.

The literature review for each key strategy starts with the context in which they were selected and implemented in Malaysia. Subsequently, a summary of the findings from previous studies and highlights of review articles on similar strategies applied both internationally and locally is provided. At the end of the literature review for each strategy, the knowledge gaps and research needs are also highlighted.