Journal of Virus Eradication 6 (2020) 100003

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.viruseradication.com

Review

Towards the elimination of viral hepatitis in Thailand by the year 2030

Nawarat Posuwan [a], Nasamon Wanlapakorn [a,b], Palittiya Sintusek [c], Rujipat Wasitthankasem [d], Kittiyod Poovorawan [e], Sompong Vongpunsawad [a], Yong Poovorawan [a,*]

[a] Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University Bangkok, Thailand
[b] Division of Academic Affairs, Faculty of Medicine, Chulalongkorn University Bangkok, Thailand
[c] STAR (Special Task Force for Activating Research), Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University Bangkok, Thailand
[d] National Biobank of Thailand, National Science and Technology Development Agency, Thailand Science Park, Pathum Thani, Thailand
[e] Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

ARTICLE INFO

Keywords:
Viral hepatitis
HAV
HBV
HCV
Elimination
Thailand

ABSTRACT

Viral hepatitis is a global problem with mortality comparable to HIV, tuberculosis and malaria. The WHO aims to eliminate hepatitis B (HBV) and hepatitis C (HCV) by 2030. Improved socioeconomic status of developing countries such as Thailand has reduced the incidence and morbidity associated with hepatitis A. Since the beginning of hepatitis B vaccination in all Thai newborns in 1992, at least 95% of one-year-olds are currently receiving 3–4 hepatitis B doses. The second vaccination of newborns of carrier mothers at 1 month of age has contributed to an effective reduction in mother-to-child transmission. Universal vaccination, blood donation screening, and decreasing needle sharing have reduced hepatitis B infection. Under the test and treat model, cost-effective screening at the point-of-care (health center or village hospital) is recommended for adults >30 years-old. Following referral to a tertiary healthcare center for a treatment plan in developing disease management plan, its implementation by trained healthcare professionals is preferably administered at the point-of-care. Hepatitis C prevalence is also decreasing as a result of blood-borne pathogen awareness. Current hepatitis C infection is highest for adults >35 years who were born prior to 1983, with screening is recommend once in their lifetime. Treatment strategy recommendation follows that of hepatitis B. The availability of direct antiviral agents with high cure rates is expected to contribute to the reduction in hepatitis C transmission and mortality as set forth by the WHO policy. Thus, ensuring the successful planning of hepatitis elimination in Thailand requires pilot regional assessment prior to national implementation.

Introduction

Hepatitis virus infection causes acute and chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). There are five main strains of the hepatitis virus referred as types A, B,C D, E. Viral hepatitis is a global public health problem with currently estimated 240 million infections for hepatitis B virus (HBV) and 71 million infection for hepatitis C virus (HCV) worldwide.[1,2] Before 1990, viral hepatitis was a major cause of liver disease in Thailand. However, liver cancer remains the first and third most common causes of cancer in Thai men and women, respectively. In 2014, the national surveillance data estimated that there were 2.2 million chronic HBV and 400,000 chronic HCV infections in Thailand.[3,4]

Effective prevention of new HBV and HCV infections, highly efficacious treatment to prevent chronic complications from HBV, and a cure for HCV infection are currently available. The first World Hepatitis Summit 2015 released the Declaration on Hepatitis, which sets the goals and targets towards viral hepatitis elimination by 2030.[5] In 2016, the World Health Assembly adopted the resolution and approved the Global Health Sector Strategy to eliminate primarily HBV and HCV by 2030.[6] The aim coverage targets in 2030 for HBV and HCV are shown in Table 1.

As a middle-income country, Thailand was previously thought to be highly endemic for viral hepatitis.[7,8] Numerous epidemiological data have now demonstrated that prevalence has decreased sharply. Here, we summarize the current situation, which may assist in the future efforts in eliminating viral hepatitis nationwide in the next decade.

* Corresponding author.
E-mail address: Yong.P@chula.ac.th (Y. Poovorawan).

https://doi.org/10.1016/j.jve.2020.100003
Received 17 April 2019; Received in revised form 12 January 2020; Accepted 23 June 2020
Available online 27 June 2020

Table 1
The aim of service coverage targets and impacts, leading to the elimination of HBV and HCV by 2030.

Prevention	
Coverage of three-doses of HBV vaccine for infants	90%
Mother-to-child transmission prevention	90%
Blood safety, donations screened with quality assurance	100%
Harm reduction (sterile set distributed per person per year for IVDU)	300
Treatment	
Diagnosis of HBV and HCV (coverage %)	90%
Treatment HBV and HCV (coverage %)	80% Eligible treated
Impact leading to elimination	
Reduction incidence of chronic HBV and HCV infection	90%
Reduction mortality from chronic HBV and HCV infection	65%

Hepatitis B virus (HBV); hepatitis C virus (HCV) and Intravenous drug user (IVDU)

Hepatitis A

Prior to the 1980's, hepatitis A virus (HAV) infection was the most common cause of acute viral hepatitis, especially in children younger than 6 years of age.[9,10] It has shifted from high to low endemicity as a result of Thailand's improving sanitation, socioeconomic status, and education.[11,12] Thailand achieved low to very low endemicity for hepatitis A. The lack of prior HAV exposure and immunity is a significant concern for potential outbreaks and symptomatic infection in adolescents, and those with advanced age and weakened immune system.[11] Either an inactivated or a live-attenuated HAV vaccine provides very good efficacy with lasting induced immunity.[13,14] However, the relatively high cost of the HAV vaccine limits its use and is not included in the Expanded Program on Immunization (EPI). Although a previous study in 2002[15] failed to show the cost-benefit of a two-dose inactivated vaccine when administered to the Thai population, future research into vaccine safety, efficacy and cost-effectiveness in Thailand is needed to provide a strong incentive for its addition to the EPI.

Epidemiology and burden of the disease

Overall, improving sanitation and socio-economic status has decreased the risk of HAV infection in Thailand. HAV seroprevalence rates in Thailand has declined from 86.4% in 1972 to 27.35% in 2004.[9,16,17] A 2014 study involving 4260 individuals showed that by the age of 42 years, more than 50% of the populations were HAV seropositive. This was a significant improvement from the early 1970s, when 50% of the Thai populations were seropositive by the age of 4.5 years. The study also suggests significant HAV susceptibility among middle-aged individuals with no prior HAV exposure, which is exemplified by the reported HAV outbreak associated with ice in Bueng Kan province in northeastern Thailand.[7] At the time, three waves of acute HAV infection were detected in this outbreak and up to 495 patients were hospitalized. Using molecular diagnostics and post-exposure vaccination, rapid response from the health authorities could have prevented subsequent outbreaks and manage to control the infection from spreading.

The strategic plan for incidence reduction

HAV eradication for any country must rely on increasing vaccine coverage implemented as depending on incidence and vaccine costs. To further eliminate HAV infection in Thailand, universal immunization with HAV vaccine either with two doses of inactivated vaccine or a single dose of live-attenuated one may need to be considered depending on incidence and vaccine costs.[15] In a study conducted in a cohort of medical students, those who received the optional HAV vaccination showed higher prevalence of acquired HAV immunity (63.1%).[12] Better education, improved sanitation and hygiene, and maintaining outbreak preparedness through ring vaccination are also important to limit transmission. HAV immunization of high-risk groups such as healthcare workers in hospitals, men who have sex with men,[18] persons who inject drugs, restaurants, military camps, childcare facilities[19] and chronic liver diseases[20] may also provide an alternative strategy to a universal vaccination. Meanwhile, documentation of HAV immunity among migrant workers and foreign travelers prior to entering the country may also contribute to limiting HAV infection. These strategies combined will diminish sporadic infection and may eventually lead to HAV elimination.

Hepatitis B (HBV)

Before 1990, the country had endemic HBV with 6–8% carrier rate in the population.[21] Transmission was frequently through vertical transmission. Most of the chronic HBV infections began with infection during infancy. HBV carriers may develop chronic hepatitis, cirrhosis and HCC later in life, which often leads to significant morbidity and mortality.[22]

Hepatitis B vaccine

HBV vaccine represents the first vaccine shown to be effective in preventing chronic liver disease, including HCC.[23] In 1986, we studied the immunogenicity and efficacy of the recombinant HBV vaccine.[24] We observed high efficacy in preventing vertical transmission in the absence of HBV immunoglobulin therapy (HBIg). We also found that the first dose given within 12 h after birth effectively prevented vertical transmission, which also correlated with long-term protection from infection.[25] The duration of protection after a full course of HBV vaccine doses in newborns and infants was examined after a long-term follow-up of 20 years.[26–29] We found that one-fourth of adolescents still retained detectable antibodies.[30] Although some individuals had undetectable or low antibody titer, none had evidence of HBV infection as defined by negative anti-HBc and HBsAg. The booster effect or anamnestic response with high antibody titers after the challenge dose of HBV vaccine was found in more than 90% among vaccinees.[30] Since HBV infection has a long incubation period (1–6 months) and the secondary response to the antigen is adequate to protect individuals from infection (4 weeks for an anamnestic response),[26] HBV screening and booster HBV vaccination can decrease the risk of infection in high-risk individuals.

EPI program in Thailand

The Thai Ministry of Public Health began implementing HBV vaccination into the EPI in 1988 with the monovalent vaccine within 24 h after birth and at 2, 6 months simultaneously with the DTP vaccine.[31] A field trial in the province of Chiang Rai compared the use of combined diphtheria/tetanus/whole-cell pertussis (DTPw)-HB vaccine with separate administration of DTPw and monovalent HBV vaccines (simultaneously) at 2, 4 and 6 months after the first dose of monovalent HBV vaccine at birth. Vaccination with the combined DTPw-HB vaccine demonstrated comparable protective efficacy,[32] therefore DTPw-HBV vaccine was added to the EPI thereafter. The current immunization strategy now includes HBV monovalent vaccine given within 24 h after birth and the combined DTPw-HB vaccine given at 2, 4 and 6 months of age. Additionally, in HBsAg-positive mothers, an extra dose of HBV monovalent vaccine given to infants at 1 month of age reduced the risk of infection by three-fold.[33]

Beginning in 1988, the Advisory Committee on Immunization Practices recommended that all women undergo HBsAg screening when they become pregnant to identify HBV infection and, if necessary, their infants given post-exposure prophylaxis with HBV immunoglobulin (HBIg).[34] Over the past 20 years, universal screening of HBsAg, but not HBeAg, during pregnancy has been performed in Thailand according to the recommendations of the Ministry of Public Health. Unfortunately, even if individuals requiring HBIg were identified, HBIg treatment is often not available outside large cities due to cost and limited supply. Nevertheless,

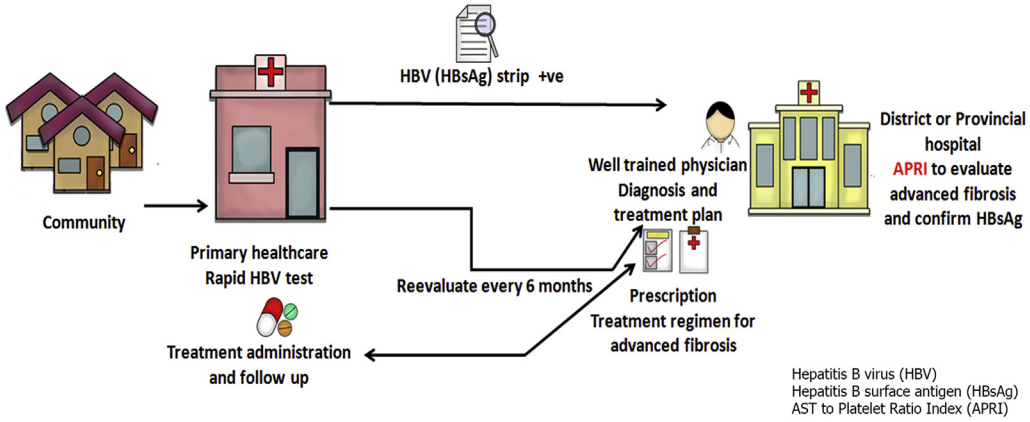

Fig. 1. Treatment strategy of HBV infection in Thailand.

Poovorawan et al. *1989*[24] reported that newborns from HBV carrier mothers who had received the recombinant DNA vaccine alone without HBIg were significantly less likely to be infected.

The importance of HBV vaccination at birth and timely second HBV vaccination dose

Previous studies in Thailand with monovalent HBV vaccine given within 12 h after birth and either 2 doses (at 1 and 6 months) or 3 doses (at 1, 2, and 12 months) thereafter showed equally high efficacy to prevent HBV vertical transmission in babies born to HBeAg-positive mothers.[22,24] As part of the EPI, The Ministry of Public Health therefore adopted the strategy to give the first HBV vaccine dose within 24 h after birth. A subsequent impact study conducted in 1999 showed a high preventative rate whereby there was low incidence HBV infection in children who were born after the vaccine was integrated into the EPI.[35] Delaying the second dose significantly increased the risk of chronic HBV infection later in life.[33] Therefore, a second dose of vaccine at 1 month is extremely important, and the EPI has incorporated it into the vaccine regimen.

Evaluating universal HBV vaccination

The impact of universal HBV vaccination in Thailand was assessed in 1999, 2004, and 2014, which showed a high effectiveness in preventing transmission among children who were born after the HBV vaccine was integrated into the EPI.[3,35,36] The last national HBV serological surveillance conducted in 2014 showed that the rates of HBV carriers born after universal HBV vaccination were markedly reduced. The carrier rates in age groups <5, 5–10, 11–20, 21–30, 31–40, 41–50 and > 50 years old were 0.1, 0.3, 0.7, 3.1, 3.8, 4.7 and 6.0%, respectively. HBV infection as evaluated by anti-HBc also declined in younger age groups.[3]

Preventing vertical HBV transmission with antiviral drugs

In endemic countries, HBV transmission primarily occurs through vertical transmission, which leads to chronic disease as adults.[37] Prevention is the key to minimize HBV transmission and long-term disease burden. In addition to universal immunization starting at birth, further reduction in the risk of vertical transmission can be achieved by treating infants at risk with HBIg.[38] Despite HBV vaccination and immunoglobulins, infection remains possible in infants born to mothers who have a high viral load (>200,000 IU per milliliter) or who are HBeAg--positive.[39,40] Antiviral drugs have been shown to suppress HBV replication and reduce the risk of progression to advanced liver complications.[41] Significant reduction in vertical HBV transmission with the use of tenofovir disoproxil fumarate, lamivudine and telbivudine has been reported.[42–45] Tenofovir disoproxil fumarate given to HBeAg-positive mothers together with HBIg and HBV vaccine in infants has been shown in a study to not significantly lower the rate of transmission (0% vs. 2%, $p = 0.12$), likely as a result of the relatively small study size and the very early first vaccination.[46] Since the reduction of the burden of HBV infection primarily relies on immunization, prevention of vertical HBV transmission in Thailand is not supported by the use of anti-viral drugs due to limited data.

HBV screening in blood donations

National blood centers began screening for HBsAg in 1984. Thereafter, all blood components underwent screening beginning in 1986. Nucleic acid testing (NAT) in pooled bloods of 6 donors was introduced in 2006, and individual screening began in 2016.[47] HBV transmission from blood or blood products has now been eliminated.

Low incidence of HBV in intravenous drug users

Awareness of blood-borne pathogens has significantly increased due to the emergence of the human immunodeficiency virus, which led to decreased intravenous illicit drug use in the last 30 years.[48] This in turn has reduced new HBV infections in Thailand.

Strategic plan to reduce HBV-related diseases

With HBV vaccination in place for nearly 30 years, the reduction of HBV-related liver diseases now focuses on the proposed program to treat HBV carriers through screening of all individuals older than 30 years and in high-risk groups once in a lifetime. This could be done effectively, reliably, and economically at primary health centers. A national survey has shown that 6% of individuals aged 35-64-years-old are HBsAg seropositive.[3] The HBeAg positive rate among women of childbearing age in the clinical trial of HBV maternal to child prevention was 40%, with a majority with high viral load.[46] There is no current data on how many who have antibody-HBe and high HBV DNA viral load are HBeAg-negative (active phase), but unpublished data suggest that 15% of those who are HBe-antibody-positive or HBeAg-negative between the ages of 35 and 64 years old have HBV DNA >10,000 IU/ml, most of whom are in the HBeAg inactive phase. Therefore, HBeAg-seronegative individuals with high viral load should receive treatment. From a practical point of view, evaluating HBV viral load (and therefore active infection) in all individuals is not currently feasible. Determining HBV chronic infection for advanced disease by estimating the fibrotic status with a simple method such as Aspartate to Platelet Ratio Index (APRI) and long-term treatment with effective anti-viral drugs to reduce complications (cirrhosis, HCC) could be possible (Fig. 1). Such strategy should accelerate HBV elimination proposed by the WHO by the year

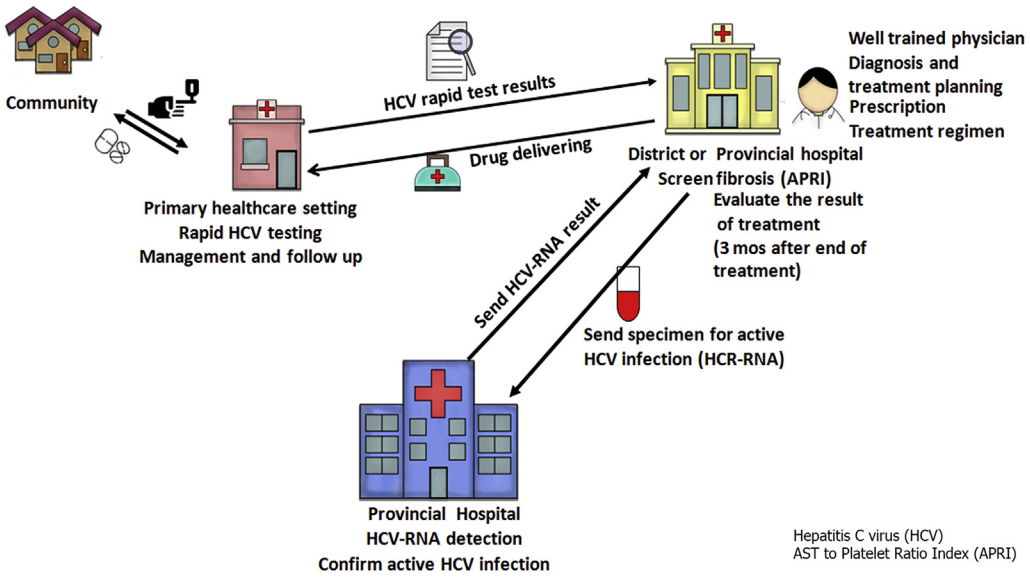

Fig. 2. Treatment strategy of HCV infection in Thailand.

2030.

The cost-effective method to enroll HBV carrier for treatment

Our ongoing work aims to evaluate cost-effective methods involving the use of low-cost rapid HBsAg screening with a strip test. This point-of-care testing can be done at the village or primary care centers. Patients initially testing positive could later be referred to the district or provincial hospital for confirmation and evaluation of treatment for appropriate treatment. Some investigations (e.g., HBV DNA, viral load, fibrotic assessment, etc.) could be performed at the regional health centers or tertiary care centers, with results sent to the district or provincial hospital for management and treatment plan. After a complete evaluation, the patient could receive antiviral drugs and advice from the primary health center as HBV treatment ideally requires long-term follow up and evaluation. The follow-up blood testing every 6–12 months for HBV status can be managed by the secondary health center (Fig. 1). The national health security office (NHSO) should adopt guidelines for the treatment of HBV carriers to reduce the long-term complications by more than 65% by 2030. If implemented in Thailand, such strategy will complement universal vaccination, screening, and inclusion of individuals aged >30 years for treatment, and thus contribute to the elimination and the eventual eradication of HBV.

Hepatitis C

Hepatitis C virus infection is also a major public health problem worldwide and should be targeted after the reduction of HBV infection from a mass vaccination program. Similar to HBV, HCV can cause chronic hepatitis, cirrhosis, and HCC.

HCV infection in Thailand

To evaluate the ongoing burden of HCV infection in Thailand, serological screening was initially undertaken by the National Blood Center using enzyme immunoassay (EIA) in 1991 with a positive rate of approximately 2%.[47] Since 1996, screening uses a chemiluminescent microparticle immunoassay (CMIA) platform. NAT was incorporated in parallel with the serological assay since 2006. After implementation of the mandatory screening program, HCV infection has declined to less than 0.5% among new blood donors.[47] The national survey, based on sampling from different geographical regions, confirmed the declining HCV prevalence.[4,49] Between 2004 and 2014, the seropositive rate decreased from 2.15% to 0.96%, which correlated with a 50% decline in HCV viremia.[4] This decrease was consistent with the mathematical modeling estimation and will continue to the lowest level after 2040.[50] The reduction in HCV infections may be associated with several factors, including changes in intravenous-to-oral illicit methamphetamine use, increase awareness of HIV infection, significant improvement in healthcare and clinical practice, and precautionary measures against blood-borne pathogens.[50]

HCV infection in Phetchabun province, the model for “test and treat”

Our HCV epidemiological study in the two provinces of Phetchabun and Khon Kaen was undertaken to assess disease burden, target population screening, and establish a diagnostic strategy. We found that a higher HCV seroprevalence was significantly associated with intravenous drug use and tattoo (15.5% and 3.6% in Phetchabun and Khon Kaen, respectively).[51] Comparable proportions of advanced liver disease patients were found in both areas, although Phetchabun had substantially more such patients.[52] To determine the population target for HCV screening, the birth-cohort analysis demonstrated that people who were born on or before 1982 (therefore aged 35 years or older) had disproportionately high HCV seroprevalence, which accounted for 71.4–100.0% of all seropositive individuals (evaluated from epidemiological studies in 2014).[53] It would therefore be ideal to include this age group in the initial phase of HCV mass screening.

The strategic plan for enrollment of HCV-infected individuals for treatment

Patients with HCV infection experience a high cure rate with an oral drug regimen of directed acting antivirals (DAAs). Nevertheless, treatment costs have been high during the last few years and thus have precluded mass treatment. There are pan-genotypic DAAs available without HCV genotype testing. Since August 2017, Gilead has allowed voluntary licensing in Thailand, which will ultimately increase access to affordable, effective drugs for HCV treatment. However, the majority of HCV-infected individuals in the population are asymptomatic. Therefore an effective strategic plan with low-cost HCV screening is needed to identify

and recruit all patients towards curative treatment. Eventually, the elimination of HCV would therefore be possible.

Plan for viral hepatitis elimination in Thailand

To achieve viral hepatitis elimination in 2030, the diagnosis rate should be increased by implementing mass HBV and HCV testing, especially in high endemic area. We therefore suggest a pilot plan to test and treat in Phetchabun province as a model for micro elimination where HBV and HCV prevalence are high in adults over 35 years old.[3,4,53] Diagnostic screening will be performed by the local clinical nurse or other healthcare personnel at primary health centers using a simple and affordable HBsAg and anti-HCV rapid strip tests. Any positive results will then be confirmed for active infection at the district or provincial hospital. Individuals who are HBsAg-positive will be evaluated for advance fibrosis by APRI and given treatment priority with HBV antiviral drugs. In parallel, the diagnostic assay for HCV RNA to identify active HCV infection could be performed at the regional hospital or tertiary care center (Fig. 2). Results sent back to the secondary care hospitals will assist in treatment evaluation with pan-genotypic DAAs. Treatment decisions and medicine are then delivered at the primary health center where local healthcare staff will be responsible for managing treatment and patient follow-ups. Three months after the end of treatment, qualitative HCV-RNA testing could be performed. The cost-effectiveness of the whole process could later be evaluated and treatment strategy will be delivered to the NHSO considered for implementation expansion. This information will be crucial for public health policy decisions towards a nationwide HCV elimination by the year 2030. Such elimination model could be adapted for applicability in other middle-income countries.

Acknowledgments

This study was supported by the Research Chair Grant from the National Science and Technology Development Agency (P-15-50004), The Center of Excellence in Clinical Virology in the Faculty of Medicine of Chulalongkorn University and Hospital. Charoen Pokphand Group, MK Restaurants Group. The Rachadapisek Sompote Fund of Chulalongkorn University for awarding a postdoctoral fellowship to Nawarat Posuwan.

References

1. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012;30:2212–2219.
2. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2:161–176.
3. Posuwan N, Wanlapakorn N, Sa-Nguanmoo P, et al. The success of a universal hepatitis B immunization program as part of Thailand's EPI after 22 Years' implementation. *PloS One*. 2016;11, e0150499.
4. Wasitthankasem R, Posuwan N, Vichaiwattana P, et al. Decreasing hepatitis C virus infection in Thailand in the past decade: evidence from the 2014 national survey. *PloS One*. 2016;11, e0149362.
5. hepatitis report WHO. Global. Available at http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1; 2017. accessed July 2018.
6. WHO. Combating hepatitis B and C to reach elimination by 2030. Available at https://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf;jsessionid=E95DAA3D99E0645F1F35A03FF4C6ED09?sequence=1; 2016. accessed March 20019.
7. Poovorawan K, Chattakul P, Chattakul S, et al. The important role of early diagnosis and preventive management during a large-scale outbreak of hepatitis A in Thailand. *Pathog Glob Health*. 2013;107:367–372.
8. Poovorawan Y, Chongsrisawat V, Tangkijvanich P. Problems and prevention of viral hepatitis in Thailand. *J Med Assoc Thai*. 2001;84(Suppl 1):S18–S25.
9. Burke DS, Snitbhan R, Johnson DE, Scott RM. Age-specific prevalence of hepatitis A virus antibody in Thailand. *Am J Epidemiol*. 1981;113:245–249.
10. Poovorawan Y, Theamboonlers A, Chumdermpadetsuk S. Changing seroepidemiology of hepatitis A virus infection in Thailand. *Southeast Asian J Trop Med Publ Health*. 1993;24:250–254.
11. Sa-nguanmoo P, Posuwan N, Vichaiwattana P, et al. Declining trend of hepatitis A seroepidemiology in association with improved public health and economic status of Thailand. *PloS One*. 2016;11, e0151304.
12. Sintusek P, Sa-Nguanmoo P, Posuwan N, Jaroonvanichkul V, Vorayingyong A, Poovorawan Y. Changes in hepatitis A virus (HAV) seroprevalence in medical students in Bangkok, Thailand, from 1981 to 2016. *BMC Res Notes*. 2018;11:640.
13. López EL, Contrini MM, Mistchenko A, et al. Modeling the long-term persistence of hepatitis A antibody after a two-dose vaccination schedule in Argentinean children. *Pediatr Infect Dis J*. 2015;34:417–425.
14. Chen Y, Zhou CL, Zhang XJ, et al. Immune memory at 17-years of follow-up of a single dose of live attenuated hepatitis A vaccine. *Vaccine*. 2018;36:114–121.
15. Teppakdee A, Tangwitoon A, Khemasuwan D, et al. Cost-benefit analysis of hepatitis A vaccination in Thailand. *Southeast Asian J Trop Med Publ Health*. 2002;33:118–127.
16. Poovorawan Y, Paiboonkasemsuthi S, Theamboonlers A, Kamolratanakul P, Chumdermpadetsuk S. Seroepidemiology of antibody to hepatitis A in the rural eastern part of Thailand. *Southeast Asian J Trop Med Publ Health*. 1991;22:35–38.
17. Chatproedprai S, Chongsrisawat V, Chatchatee P, et al. Declining trend in the seroprevalence of infection with hepatitis A virus in Thailand. *Ann Trop Med Parasitol*. 2007;101:61–68.
18. Colby DJ, Posuwan N, Kroon E, et al. SEARCH010/RV254 Study Team. Reply to Chen et al. *J Infect Dis*. 2018;218:505–507.
19. Poovorawan Y, Theamboonlers A, Chongsrisawat V, Jantaradsamee P, Chutsirimongkol S, Tangkijvanich P. Clinical features and molecular characterization of hepatitis A virus outbreak in a child care center in Thailand. *J Clin Virol*. 2005;32:24–28.
20. Pramoolsinsap C, Poovorawan Y, Hirsch P, Busagorn N, Attamasirikul K. Acute, hepatitis-A super-infection in HBV carriers, or chronic liver disease related to HBV or HCV. *Ann Trop Med Parasitol*. 1999;93:745–751.
21. Edmunds WJ, Medley GF, Nokes DJ, O'Callaghan CJ, Whittle HC, Hall AJ. Epidemiological patterns of hepatitis B virus (HBV) in highly endemic areas. *Epidemiol Infect*. 1996;117:313–325.
22. WHO. Department of communicable diseases surveillance and response. *Hepatitis B*; 2002. Available at http://www.who.int/csr/disease/hepatitis/HepatitisB_ who cdscsrlyo2002_2.pdf. accessed February 2013.
23. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in taiwan and the incidence of hepatocellular carcinoma in children. Taiwan childhood hepatoma study group. *N Engl J Med*. 1997;336:1855–1859.
24. Poovorawan Y, Sanpavat S, Pongpunlert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. *J Am Med Assoc*. 1989;261:3278–3281.
25. Poovorawan Y, Sanpavat S, Pongpunglert W, et al. Long term efficacy of hepatitis B vaccine in infants born to hepatitis B e antigen-positive mothers. *Pediatr Infect Dis J*. 1992;11:816–821.
26. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Crasta PD, Messier M, Hardt K. Long-term anti-HBs antibody persistence following infant vaccination against hepatitis B and evaluation of anamnestic response: a 20-year follow-up study in Thailand. *Hum Vaccines Immunother*. 2013;9:1679–1684.
27. Poovorawan Y, Chongsrisawat V, Theamboonlers A, et al. Evidence of protection against clinical and chronic hepatitis B infection 20 years after infant vaccination in a high endemicity region. *J Viral Hepat*. 2011;18:369–375.
28. Poovorawan Y, Chongsrisawat V, Theamboonlers A, et al. Long-term benefit of hepatitis B vaccination among children in Thailand with transient hepatitis B virus infection who were born to hepatitis B surface antigen-positive mothers. *J Infect Dis*. 2009;200:33–38.
29. Chinchai T, Chirathaworn C, Praianantathavorn K, et al. Long-term humoral and cellular immune response to hepatitis B vaccine in high-risk children 18-20 years after neonatal immunization. *Viral Immunol*. 2009;22:125–130.
30. Posuwan N, Vorayingyong A, Jaroonvanichkul V, et al. Implementation of hepatitis B vaccine in high-risk young adults with waning immunity. *PloS One*. 2018;13, e0202637.
31. Chunsuttiwat S, Biggs BA, Maynard J, et al. Integration of hepatitis B vaccination into the expanded programme on immunization in Chonburi and Chiangmai provinces, Thailand. *Vaccine*. 1997;15:769–774.
32. Chunsuttiwat S, Biggs BA, Maynard JE, Thammapormpilas P, O-Prasertsawat M. Comparative evaluation of a combined DTP-HB vaccine in the EPI in Chiangrai Province, Thailand. *Vaccine*. 2002;21:188–193.
33. Tharmaphornpilas P, Rasdjarmrearnsook AO, Plianpanich S, Sa-nguanmoo P, Poovorawan Y. Increased risk of developing chronic HBV infection in infants born to chronically HBV infected mothers as a result of delayed second dose of hepatitis B vaccination. *Vaccine*. 2009;27:6110–6115.
34. Centers for Disease Control (CDC). Prevention of perinatal transmission of hepatitis B virus: prenatal screening of all pregnant women for hepatitis B surface antigen. *MMWR Morb Mortal Wkly Rep*. 1988;37(22):341–346, 351.
35. Poovorawan Y, Theamboonlers A, Vimolket T, et al. Impact of hepatitis B immunisation as part of the EPI. *Vaccine*. 2000;19:943–949.
36. Chongsrisawat V, Yoocharoen P, Theamboonlers A, et al. Hepatitis B seroprevalence in Thailand: 12 years after hepatitis B vaccine integration into the national expanded programme on immunization. *Trop Med Int Health*. 2006;11:1496–1502.
37. Merican I, Guan R, Amarapuka D, et al. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol*. 2000;15:1356–1361.
38. Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. *BMJ*. 2006;332:328–336.
39. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat*. 2009;16:94–103.
40. Wen WH, Chang MH, Zhao LL, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. *J Hepatol*. 2013;59:24–30.

41. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovirdisoproxilfumarate in interrupting mother-to-infant transmission of hepatitis B virus. *Hepatology*. 2015; 62:375–386.
42. Han GR, Jiang HX, Yue X, et al. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. *J Viral Hepat*. 2015;22:754–762.
43. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med*. 2016;374:2324–2334.
44. Wu Q, Huang H, Sun X, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. *Clin Gastroenterol Hepatol*. 2015;13:1170–1176.
45. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology*. 2014;60:468–476.
46. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med*. 2018;378:911–923.
47. Chimparlee N, Oota S, Phikulsod S, Tangkijvanich P, Poovorawan Y. Hepatitis B and hepatitis C virus in Thai blood donors. *Southeast Asian J Trop Med Publ Health*. 2011; 42:609–615.
48. Phanuphak P, Locharernkul C, Panmuong W, Wilde H. A report of three cases of AIDS in Thailand. *Asian Pac J Allergy Immunol*. 1985;3:195–199.
49. Sunanchaikarn S, Theamboonlers A, Chongsrisawat V, et al. Seroepidemiology and genotypes of hepatitis C virus in Thailand. *Asian Pac J Allergy Immunol*. 2007;25: 175–182.
50. Poovorawan K, Pan-Ngum W, White LJ, et al. Estimating the impact of expanding treatment coverage and allocation strategies for chronic hepatitis C in a direct antiviral agent era. *PloS One*. 2016;11, e0163095.
51. Wasitthankasem R, Vichaiwattana P, Siripon N, et al. Assessment of hepatitis C virus infection in two adjacent Thai provinces with drastically different seroprevalence. *PloS One*. 2017;12, e0177022.
52. Wasitthankasem R, Vichaiwattana P, Siripon N, et al. Liver disease burden and required treatment expenditures for hepatitis C virus (HCV) infection in Thailand: implications for HCV elimination in the new therapeutic era, a population-based study. *PloS One*. 2018;13, e0196301.
53. Wasitthankasem R, Vichaiwattana P, Siripon N, et al. Birth-cohort HCV screening target in Thailand to expand and optimize the national HCV screening for public health policy. *PloS One*. 2018;13, e0202991.