*Population and transmission dynamics model to determine WHO targets for eliminating Hepatitis C virus in Thailand*

Abstract

Graphical Abstract

**Introduction**

Hepatitis C Virus (HCV) causes a large health burden in Thailand and transmission relates to population age, which is changing along with other population dynamics in the country. Screening can be used to catch asymptomatic cases and prevent transmission, but screening coverage is low and generally only sought out once symptoms are present, many years – sometimes decades – after infection. Modelling population dynamics can provide a more detailed look at how HCV transmission relates to age and allow for more informed decisions to be made with respect to screening and treatment policies in order to achieve national elimination goals.

**Background**

Hepatitis C is an infectious disease that primarily affects the liver, and most of the global burden exists in Low- and Middle-Income Countries (LMICs) (Graham and Swan, 2015). Transmission is caused by blood contact and certain groups are at higher risk of transmitting HCV. These include individuals with HIV, men who have sex with men (MSM), injecting drug users (IDU) and prisoners (Wasitthankasem et al., 2018a). In recent years, transmission has been relatively low and prevalence in southeast Asia is declining, however the burden in Thailand is still significant, with approximately 790,000 cases in Thailand in 2019 (Posuwan et al., 2019).

Serious disease such as liver fibrosis, liver cirrhosis and hepatocellular carcinoma (HCC) follow as a direct result of HCV infection (Wasitthankasem et al., 2016). These stages of liver failure can take many years to cause symptoms, and in fact only occur later in life, with the respective average ages of Hepatitis C patients with fibrosis and cirrhosis caused by HCV being 36 (Ryder and Group, 2004) and 52 (Sajja et al., 2014). Asymptomatic carriers may spend many years transmitting the disease while unaware of their status. For this reason, screening can be an effective tool for intercepting these asymptomatic cases and supplying treatment much earlier on, halting the transmission chain and reducing the health and economic burdens by preventing further cases.

Prior to 2019, the first-line treatments for Hepatitis C were Pegylated Interferon therapies (PEGs). The current first line treatment in Thailand is oral administration of Direct-Acting Antivirals (DAAs), which have much higher efficacy but are generally only given to symptomatic patients, and there is no targeted screening programme currently in place, despite suggestions that this may be necessary to reach elimination (Posuwan et al., 2020).

Increasing affordability for these treatments is leading researchers to believe that elimination is an attainable goal (Thaineua et al., 2021), and the Ministry of Public Health Thailand has called for elimination by 2030 (Drugs for Neglected Diseases Initiative, 2022). Elimination is defined in the most recent Global Hepatitis Report as a 90% reduction in yearly incidence and a 65% reduction in yearly mortality as compared to the 2015 values (World Health Organization, 2017).

The population structure of Thailand, as with many other MICs, is changing as mortality amongst older age groups decreases rapidly (Sudharsanan and Bloom, 2018), and as such the proportions of older age groups are growing while younger groups diminish. HCV disproportionately affects older age groups (Wasitthankasem et al., 2020), hence it may be useful to consider these heterogeneities within a population when considering the disease’s impact and possible intervention and treatment options.

Previous HCV transmission models in Thailand have not considered age or population dynamics, rather modelling the population homogeneously, assuming all individuals are equally susceptible to infection and different disease stages (Coalition for Global Hepatitis Elimination and World Health Organisation, 2019; Poovorawan et al., 2016). The 2016 model also assumed logistic population growth in Thailand, which is inconsistent with recent population projections (United Nations, 2022, 2019).

The model in this report incorporates changing population structure and dynamic birth and death rates into an HCV transmission model to explore potential screening policy decisions. Aspects of this model could be used in other transmission models in Thailand, and with sufficient data could be applied more broadly to different population projections. Furthermore, with data on other population dynamics on specific groups relevant to disease transmission, this approach could be used to model the targeting of risk groups as well as age groups.

This study employs a novel, age-structured HCV transmission model to investigate the effect of changing population structure on the effectiveness of baseline and targeted screening programmes and explore whether elimination goals outlined by the World Health Organisation are feasible in the timescale suggested.

**Methods**

All data used (in raw and modified formats) can be found in Supplementary File A and are publicly available via the links provided. Further descriptions of all methods can be found in Supplementary File B.

*Population Demographic Data*

United Nations demographic data were used for the years 2004 to 2021 to visualise the population dynamics of Thailand and to calibrate the model. Population structure, birth and death rates (per person per year) were recorded, and UN projections were considered (United Nations, 2019). Figure 1 shows the proportion of each age group in Thailand. Supplementary Figure S1 shows total population and birth rate data and projections (United Nations, 2022).

Chart, bar chart, histogram

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Figure 1: Population structure of Thailand by age group from 2004 to 2021. Note the clear aging of the population: age groups below 44 are declining while those above 50 are growing.

*Epidemiological Data*

Epidemiological data on HCV in Thailand are very scarce, especially by age. Sources report both the prevalence of anti-HCV and HCV in the Thai population (Wasitthankasem et al., 2018a, 2018b). Throughout this investigation, data on anti-HCV carriers were used for prevalence calculations, in line with previous HCV transmission modelling work (Poovorawan et al., 2016). The work of Wasitthankasem et al., 2016 was used to calibrate the model as the study includes relatively complete national prevalence data stratified by age groups for 2004 and 2014. The 2004 values were used to initialize the model and the 2014 values were used for model calibration. These data and calculations can be found in Supplementary File A: *prevalence\_data\_by\_age*, with more information in Supplementary File B.

*Sexual Contact Matrix*

The contact matrix was derived from data on sexual partners and sexual contact between age groups from a study on Human papillomavirus infection (HPV) in Laos (Chanthavilay et al., 2016). Although more complete contact matrices exist describing other types of contact between age groups (Prem et al., 2017), very limited data are available on the particular type of contact that transmits HCV; namely sexual and blood contact. Although not specific to HCV and Thailand, the contact matrix for a sexually transmitted disease in a Southeast Asian setting was deemed the most appropriate for the purposes of this model. Supplementary Figure S2 shows a heat map of the transmission matrix *beta*.

*Transmission model*

An age-structured compartmental model was used to model progression through the transmission cycle that also accounted for population dynamics, with screening and treatment programmes represented in the model. The HCV transmission portion was adapted from the work of Poovorawan et al., 2016 and the age structure from an otherwise unrelated disease transmission model (Pan-Ngum et al., 2017). Figure 2 shows the general structure of the transmission and age compartments of the model. A full list of equations, compartments and parameters can be found in Supplementary File B, with the full model code available at *https://github.com/astleyjennie/HCVinThailand*. More details about the methods involved in the model setup can be found in Supplementary File B.

Diagram

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Figure 2: Compartment diagram showing the HCV transmission cycle modelled as well as the embedded age structure. Individuals travel through both simultaneously. 21 5-year age groups were modelled, from 0 – 4 to 100+.

The current first-line treatment – Direct-Acting Antivirals – was modelled to begin in 2019, with the previous standard treatment being Pegylated Interferon therapies. The target population for the treatment intervention was any individual in the liver fibrosis (F0-F3) and cirrhosis (C1 for PEGs, C1-C4 for DAAs) compartments i.e., anyone with active HCV infection that had not yet progressed to HCC, in line with the original HCV model. Parameters relating to HCV transmission and treatment from the work of Poovorawan et al., 2016 were used. The screening intervention was modelled at different age group targets and coverages depending on the strategy explored. Prevalence (%) was defined as 100 times the total number of cases (F, C and HCC) over total individuals in that age group or population, while incidence was defined as the total number of new cases of HCV in the given year. The elimination targets outlined in the Global Hepatitis Report (World Health Organization, 2017) – a 90% reduction in new cases and a 65% reduction in HCV related death compared to 2015 baseline – refer only to global values, and no Thailand specific values were given for the 2015 baseline. The 2015 values of the model were used to calculate 2030 incidence and mortality elimination targets due to lack of data.

*Model Calibration: Population Demographics*

Four population scenarios were compared to explore potential patterns of population growth in order to investigate the effect of population structure on HCV transmission, elimination and screening strategy success. The mean historic natural death rates (deaths per person per year) from 2004 – 2021 were further decreased by 2% per year for ages 0-49 and 3% per year for ages 50+ from 2022 onwards in order to be consistent with Thailand’s aging population trend, while historic and projected birth rate values (births per person per year) were multiplied by a single value in order to approximate the overall projected trend in the Thai population (United Nations, 2022, 2019). This was taken as baseline and used for the main result. Three other modifications on age-specific mortality rates and birth rates were explored. More details about the population scenarios can be found in Supplementary File B.

Figures 3 and 4 show the model output for total and age-group populations with historic and projected values. The baseline scenario does not adequately capture the data; however, sensitivity analyses were performed to investigate the effect of population trends on other epidemiological quantities of interest and did not significantly affect any results. These results can be found in Supplementary File C.

Chart

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Figure 3: The model output of the total population of Thailand for each of the four population structure scenarios. The narrow ribbons show the 95% confidence interval based on the uncertainty in baseline coverage. The points show the United Nations data and projection for Thailand’s population.

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Figure 4: The model output of population by age group for each of the four population scenarios overlaid with United Nations data and projections.

*Model Calibration: Epidemiological Data*

Thai HCV prevalence data from 2004 and 2014 were used to calculate initial conditions and to check the fit of the HCV transmission aspect of the model. Prevalence data in Thailand are very limited, especially prevalence by age, so the baseline coverage between 2004 and the start of proposed screening programmes was estimated in order to fit the data available. The baseline screening coverage was assumed to be uniform across age groups, and the results of the fit using *optim* was a baseline screening coverage of 6.18% ± 1.22%. Although coverage is not expected to be uniform, insufficient data are available to assume otherwise. The upper and lower 95% levels were calculated to give an upper and lower estimate of all population and epidemiological quantities. The model showed a sufficient representation of the prevalence data available, as shown in Figure 5. More details about model calibration methods can be found in Supplementary File B.

Four target age groups at four yearly screening coverages including the current baseline were compared to investigate whether the national elimination goals appeared to be achievable in the desired time frame. Low (15%), medium (25%) and high (50%) values were chosen for yearly coverage, targeting individuals aged 30+, 40+, 50+ and 60+, starting in 2023 at a duration of 7 years to reflect the 2030 elimination target.

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Figure 5: Model output compared with 2004 and 2014 prevalence data by age group. Data error bars were calculated using sample and population size from the 2004 data (Wasitthankasem et al., 2018b). The 95% confidence interval ribbons were based on uncertainty in baseline screening coverage. Note the total prevalence in 2004 is slightly higher due to differences in total population value between the data source used for prevalence and population. Also note the difference in fit across age groups due to the assumption that baseline screening is uniform. 2022 prevalence data was available for total population only.

*Model Assumptions*

Inherent in the use of a compartmental transmission model is the assumption that all individuals in a single compartment are identical. Stratification of the previous model into age groups has mitigated this assumption somewhat, but there are still limitations to the conclusions that can be drawn from such a model. The model assumes spatial homogeneity across Thailand, whereas prevalence is in fact concentrated in certain endemic regions (Wasitthankasem et al., 2020).

The limited data available were used to initialise the model in the year 2004, and assumptions were made about younger age groups being constrained to the earlier stages of disease (see Supplementary File B). Little to no reliable data was available on distribution of age groups across the stages of fibrosis, cirrhosis and HCC, so an early initialisation (2004) compared to present day (2022), along with calibration to 2014 data was imposed to mitigate this assumption: transition rates between liver stages over a period of 18 years was assumed to stabilise results enough to make the necessary conclusions about 2023 onwards, however further data on this distribution could improve the accuracy of the model.

The model assumed that an individual in a disease compartment will be treated if they are targeted by the screening programme coverage, and that all individuals requiring treatment will receive it. Due to Thailand’s universal healthcare system this assumption is reasonable, however it is noted that not all those who need treatment receive it.

*Technology*

R Studio® version 2021.09.0 Build 351 was used to run the model. R packages used were: pacman, tictoc, Hmisc, viridis, deSolve, tidyverse, doParallel, manipulate, readxl, gridExtra, grid, scales. Microsoft® Excel® 2019 MSO (16.0.10387.20023) 64-bit was used to store and manipulate data, initial conditions, results and scenarios.

**Results**

The success of each screening strategy with respect to elimination target years did not vary significantly between population growth scenarios, in both HCV incidence and HCV related death. In all four population scenarios, the current baseline screening strategy with mean estimate of coverage (6.18% across all age groups) did not reach incidence elimination until 2039 or beyond the simulation (after 2040). The mortality elimination goal was not reached until after the end of the simulation for all screening strategies and population scenarios. At the baseline screening strategy, the total number of deaths increased in the plateau and growth population scenarios, with 541 and 231 more deaths than baseline population.

At baseline population scenario, increasing coverage from 15% to 50% for individuals age 30+ brought forward the year of incidence elimination by 4, from 2038 to 2034, while incidence elimination was not reached until beyond the simulation for 50+ and 60+ groups at all coverages. The difference in incidence elimination years between baseline and the most extreme screening strategy (individuals age 30+ at 50%) was at least 6 years (beyond simulation to 2034). This strategy led to the highest number of cases and deaths averted (11,049 cases and 10,558 deaths averted). This involved the highest level of excess screening, at 300,790 individuals over the 7-year period.

Yearly incidence (total new cases per year) and mortality (HCV-related deaths per year) for the baseline and most extreme screening strategies are shown in Figure 6. Results of the baseline population strategy are shown in Table 1. Full results of all scenarios and strategies can be found in Supplementary File C.

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Figure 6: Model output for incidence and deaths compared with the WHO elimination goals for baseline and maximum screening programmes. The ribbons show 95% interval as given by the uncertainty in the baseline screening coverage.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Screening Strategy** | **Incidence** Difference to Target (95% CI) | **Deaths** Different to Target (95% CI) | **Cases** Averted Compared to Baseline (95% CI) | **Deaths** Averted Compared to Baseline (95% CI) | Extra Screened Compared to Baseline (95% CI) | Year **Incidence Elimination Target** Reached (95% CI) | Year **Mortality Elimination Target** Reached (95% CI) |
| **Baseline** | 2,431 (1,564, 4,540) | 4,655 (3,430, 6,837) | 0 | 0 | 0 | **Beyond simulation (2038, Beyond simulation)** | **Beyond simulation** |
| 30+ at 15% | 1,657 (824, 3,031) | 3,755 (2,759, 5,122) | 3,765 (-11,066, 13,855) | 3,680 (-7,973, 12,545) | 134,542 (49,152, 248,206) | **2038 (2035, Beyond simulation)** | **Beyond simulation** |
| 30+ at 25% | 1,141 (462, 2,296) | 3,151 (2,324, 4,282) | 6,769 (-6,823, 15,983) | 6,565 (-3,995, 14,643) | 219,742 (109,586, 368,447) | **2036 (2033, Beyond simulation)** | **Beyond simulation** |
| 30+ at 50% | 607 (90, 1,528) | 2,517 (1,869, 3,396) | 11049 (-769, 19,010) | 10,558 (1,510, 17,547) | 300,790 (166,898, 483,245) | **2034 (2031, 2039)** | **Beyond simulation** |
| 40+ at 15% | 2,039 (1,006, 3,774) | 3,873 (2,816, 5,347) | 1,918 (-14,549, 12,947) | 3,259 (-8,761, 12,336) | 103,747 (34,510, 188,073) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |
| 40+ at 25% | 1,771 (819, 3,390) | 3,348 (2,439, 4617) | 3466 (-12,358, 14,040) | 5,818 (-5,236, 14,200) | 170,830 (81,979, 283,014) | **2039 (2035, Beyond simulation)** | **Beyond simulation** |
| 40+ at 50% | 1,480 (618, 2,967) | 2,797 (2,044, 3,847) | 5,714 (-9,168, 15,626) | 9,371 (-343, 16,787) | 237,727 (129,098, 378,191) | **2038 (2034, Beyond simulation)** | **Beyond simulation** |
| 50+ at 15% | 2,275 (1,119, 4,235) | 4,046 (2,901, 5,678) | 766 (-16,724, 12,380) | 2,582 (-10,019, 11,998) | 69,572 (18,252, 121,370) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |
| 50+ at 25% | 2,168 (1,044, 4,080) | 3,636 (2,606, 5,107) | 1,389 (-15,842, 12,820) | 4,618 (-7,218, 13,482) | 115,670 (50,801, 186,783) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |
| 50+ at 50% | 2,047 (961, 3,904) | 3,203 (2,296, 4,499) | 2,304 (-14,541, 13,466) | 7,463 (-3,302, 15,557) | 164,238 (84,890, 256,163) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |
| 60+ at 15% | 2,383 (1,170, 4,446) | 4,265 (3,008, 6,094) | 239 (-17,718, 12,121) | 1,674 (-11,698, 11,542) | 34,554 (1,499, 53,380) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |
| 60+ at 25% | 2,349 (1,147, 4,397) | 3,999 (2,817, 5,722) | 437 (-17,437, 12,261) | 3,005 (-9,867, 12,513) | 55,788 (16,658, 83,176) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |
| 60+ at 50% | 2,309 (1,119, 4,337) | 3,709 (2,611, 5,313) | 734 (-17,014, 12,470) | 4,891 (-7,272, 13,889) | 74,002 (29,684, 108,703) | **Beyond simulation (2036, Beyond simulation)** | **Beyond simulation** |

Table 1: Results of all screening strategies at baseline population scenario including 95% CI based on uncertainty in baseline screening coverage

**Discussion**

The results showed that the four population structure projections modelled do not appear to significantly affect the elimination year of any of the screening strategies modelled: a screening strategy reaches incidence elimination target values at roughly the same time regardless of changing population demographics, and epidemiological quantities of interest (incidence, mortality and prevalence in 2030) also remain largely unchanged between scenarios (see Supplementary Figures S3, S4 and S5). This is likely because the strategies were based on a percentage coverage, so as the number of older individuals increased, so did the amount of excess screening. However, the aging population scenarios (growth and plateau) lead to a higher number of deaths and cases overall, due to HCV disproportionately affecting older individuals. If the population projection of Thailand changes due to fertility campaigns or further decreasing mortality, or indeed in other countries where population structure is volatile and changing rapidly, consideration of population dynamics and structure may not be necessary when proposing screening programmes and policies. However, more HCV-related deaths and cases could be expected in an aging population.

The model showed that yearly screening coverage may impact elimination results less than the age group targeted, and in fact even radical screening strategies may only bring incidence elimination forward by a few years. The most effective group to target appeared to be individuals aged 30+ (the largest group targeted), but even at a high coverage of 50% per year this strategy did not achieve the WHO 2030 target in the model. Note that the model underestimated the prevalence of HCV in the 20 – 29- and 40 – 49-year age group due to the assumption that baseline coverage was uniformly distributed across all ages, so in reality the most effective age group to target may in fact be different. Additional age-stratified epidemiological data could substantiate this. Supplementary Figures S6 and S7 show incidence and mortality results for all screening strategies at baseline population scenario.

The screening strategies modelled would undoubtedly require a great deal of resources to achieve such coverages of a large population due to the high cost of screening, which may not be feasible within government budgets and resource allocation. The screening strategies with the highest success (cases and deaths averted, year of incidence elimination) require a large amount of excess screening. Further in-depth economic evaluation would be required to investigate the impact of such screening strategies compared to the current baseline.

The work in this study could also be built upon by applying the age stratified transmission structure and changing population demographics to other populations. Better fitting of the model could be performed if more data become available. The model could be modified to focus on risk groups that are disproportionately affected by HCV as well as older age groups, such as MSM (Men who have Sex with Men), prisoners and IDU (Injecting Drug Users).

Data surrounding age stratification of HCV cases and deaths in Thailand are significantly lacking, leading to a large amount of uncertainty in the results, and this limitation is recognised. Mortality decreased around 2020 both in data and in another HCV-related deaths model (Coalition for Global Hepatitis Elimination and World Health Organisation, 2019) (see Supplementary Figure 8) as expected due to the new treatment programme implemented in 2019. However, the model in this report underestimated the number of deaths caused by HCV compared to the 2019 model, and mortality elimination targets were still not met in the timescale simulated. This underestimation is likely due to the assumption that all individuals requiring treatment receive it, when many do not receive treatment until the fatal stages of liver failure by which point treatment is ineffective. Few robust conclusions can be drawn about efficacy of screening programmes on mortality based on the results of this study, however it appears that the WHO mortality goal may not be reached by 2030 in Thailand.

This model suggested that the elimination of HCV (defined by WHO as a 90% reduction in new cases and 65% reduction in HCV related death from 2015 baseline) can be achieved in Thailand, and with the introduction of screening programmes could be brought forward by several years. However, none of the simulations run here resulted in an elimination year of 2030 or earlier. This result held for a variety of realistic population projections, and as such the consideration of variations in population structure may not be high priority when making screening policy decisions.

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Supplementary Materials

*Graphics*

S1 [Supplementary Figure S1.png] – *Birth Rate and Population*

Figure showing birth rate and population data and projection from United Nations data

S2 [Supplementary Figure S2.png] – *Beta Matrix: Derived from Sexual Contact and HPV in Laos*

Heat map of the beta transmission matrix derived from sexual contact data from a study on HPV in Laos

S3 [Supplementary Figure S3.png] – *Sensitivity Analysis: Effect of Population Scenario on 2030 Incidence*

Bar chart showing the difference in 2030 incidence for each population scenario, screening coverage and targeted age group

S4 [Supplementary Figure S4.png] – *Sensitivity Analysis: Effect of Population Scenario on 2030 Mortality*

Bar chart showing the difference in 2030 mortality for each population scenario, screening coverage and targeted age group

S5 [Supplementary Figure S5.png] – *Sensitivity Analysis: Effect of Population Scenario on 2030 Prevalence*

Bar chart showing the difference in 2030 prevalence across all age groups for baseline and most extreme screening strategies between population scenarios

S6 [Supplementary Figure S6.png] – *Yearly HCV Incidence by Target Age Group and Screening Coverage*

Model output of incidence compared to WHO 2030 goals for all screening coverages and target age groups at baseline population scenario

S7 [Supplementary Figure S7.png] – *Yearly HCV-Related Mortality by Target Age Group and Screening Coverage*

Model output of mortality compared to WHO 2030 goals for all screening coverages and target age groups at baseline population scenario

S8 [Supplementary Figure S8.png] – *Yearly HCV-Related Mortality by Population Scenario*

Model output of mortality at baseline screening coverage for all four populations scenarios compared with 2030 WHO goals and model output from Coalition for Global Hepatitis Elimination and World Health Organisation, 2019

*Files*

Supplementary File A [Supplementary File A.xlsx] – HCV Model Data

Excel file containing all data (raw and manipulated), scenarios, simulations and results.

Supplementary File B [Supplementary File B.docx] – Supplementary Methods

* Complete list of all Ordinary Differential Equations specifying the transmission model.
* Complete list of all compartments in the transmission model.
* Complete list of all parameters in model with description, parameter name (in model code), value and source.
* Further detail on methods used in all aspects of the work done to produce these results.

Supplementary File C [Supplementary File C.docx] – Supplementary Results

Further detail on results obtained from this model that are additional to main results.

*Data*

Data Availability Statement

All data used were publicly available and can be found using the following links (also provided in Supplementary File A):

Birth rate data:

*https://www.macrotrends.net/countries/THA/thailand/birth-rate*

Mortality rate data:

*https://population.un.org/wpp/Download/Standard/Mortality/*

Population structure data (UN):

*https://www.populationpyramid.net/thailand/2004/*

Sexual contact data (HPV in Laos):

*https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-016-1662-5#Sec15*

Prevalence data (National HCV Prevalence Survey):

*https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-022-07074-2*

*https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0149362*

HCV deaths data (WHO data):

*https://www.globalhep.org/country-progress/thailand*

All code and data can be found at:

*https://github.com/astleyjennie/HCVinThailand/*

Code Availability Statement

All code for data cleaning, model setup and analysis associated with the current submission is available publicly at *https://github.com/astleyjennie/HCVinThailand/*. Any updates will also be published on Github.

Declarations of interest: None