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Hepatitis C virus elimination in Indonesia: Epidemiological, cost, and cost-effectiveness modelling to advance advocacy and strategic planning

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Abbreviations:

HCV: Hepatitis C Virus

HCC: Hepatocellular carcinoma

DAAs: Direct acting antivirals

WHO: World Health Organization

anti-HCV: HCV antibodies

PWID: People who inject drugs

PKNI: Persaudaraan Korban Napza Indonesia

CHAI: Clinton Health Access Initiative

MoH: Ministry of Health

IDU: Injecting drug use

CC: Compensated cirrhosis

DC: Decompensated cirrhosis

SVR: Sustained virologic response

95%CI: 95% Confidence Interval

SOF/DAC: Sofosbuvir/Daclatasvir

LMICs: Lower- and middle-income countries

VL: Viral load

ICER: Incremental cost-effectiveness ratio

YLS: Years of life saved

YLL: Years of life lost

GDP: Gross domestic product

DALY: Disability adjusted life year

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Abstract 250/250

Backgrounds and aims:

In Indonesia 1.9 million people are chronically infected with hepatitis C virus (HCV), but a national strategic plan for elimination has not yet been developed, despite the availability of low-cost treatments which could save many lives. We used epidemiological- and cost-modelling to estimate targets and resource requirements of a national elimination program and explore the potential impact and cost-effectiveness.

Methods:

To model the HCV epidemic, we used a dynamic model, parameterised with Indonesia-specific data, accounting for disease progression, injecting drug use, and demographics. Future scale-up scenarios were designed for 2018-2050 to capture possible policy choices. Costs of an initial five-year national strategy and of long-term elimination were estimated for the most feasible scenario, as agreed with government and local partners. Cost savings from reduced drug and diagnostics prices were also estimated. The cost-effectiveness of baseline predictions and those with drug price reductions were compared to the no-treatment scenario.

Results:

Elimination by 2045, considered the most feasible path to scale-up, would prevent 739,000 new infections and avert 158,000 HCV-related deaths. The costs would be $5.6 billion (USD) using baseline prices but could fall to $2.7 billion if price reductions for HCV drugs and diagnostics are secured. With these price reductions, the incremental cost-effectiveness ratio for a 2045 elimination program would be cost-effective at $300 (USD) per year of life saved versus the no-treatment scenario.

Conclusions:

This study has underpinned advocacy efforts to secure Indonesian government commitment to HCV elimination, and provides further inputs for HCV strategic planning efforts.

Keywords: Cirrhosis, Direct Acting Antivirals, epidemiology, ICER, mathematical modelling

Lay Summary:

- Eliminating hepatitis C virus (HCV) in Indonesia by 2045 would prevent 739,000 new infections and avert 158,000 HCV-related deaths.
- With conservative price reductions, the costs of elimination by 2045 are estimated to be around $2.7 billion (USD).
- This would give an incremental cost-effectiveness ratio of $300 (USD) per year of life saved versus a status quo scenario with very low levels of treatment.

Introduction

Globally, 70 million people are chronically infected with Hepatitis C Virus (HCV), a bloodborne virus affecting the liver(1). HCV causes over 400,000 deaths annually from liver complications, including hepatocellular carcinoma (HCC) and cirrhosis(1).

Following the breakthrough of direct acting antivirals (DAAs), which are highly effective cures for HCV(2), the World Health Organization (WHO) set global goals for the elimination of HCV(3). These ambitious goals call for countries to reduce incident HCV infections by 80% and hepatitis-related mortality by 65% by 2030(3, 4). Although there is a growing interest amongst governments to control and eliminate HCV, most countries have yet to launch national HCV programs(5).

In Indonesia, the prevalence of HCV antibodies (anti-HCV) among the general population is estimated at 1.0%(6), while the prevalence among people who inject drugs (PWID) is estimated to be as high as 90%(7). As the fourth most populous country, Indonesia has one of the largest HCV epidemics in the world(8), with an estimated 2.5 million HCV infected people(6). Despite this great burden, in 2017 fewer than 1,000 individuals were treated with DAAs(9, 10). Indonesia's social health insurance scheme continues to only cover pegylated interferon, the pre-DAA standard therapy with vastly lower sustained virologic response (SVR) rates and toxic side effects(2). DAAs are only available at private health facilities and a limited number of public health facilities(5, 10).

One reason for this delayed scale-up of DAA treatment is a paucity of data and strategic information to understand the local burden and potential benefits, and inform strategic planning efforts of policy makers(11). As of 2017, a national HCV seroprevalence study had not been conducted nor had a national hepatitis strategy based on DAAs been developed. Nonetheless, key building blocks to support HCV program scale-up started coming together by 2017. Persaudaraan Korban Napza Indonesia (PKNI), the leading advocacy organization for PWID in Indonesia, expanded its efforts on awareness campaigns and training for healthcare workers. Treatment guidelines were updated to include DAAs for the first time; and the Clinton Health Access Initiative (CHAI) launched the program Quick Start, aiming to put 6,000 patients on treatment in the greater Jakarta area over three years to demonstrate the feasibility of rolling out a treatment program(12).

Recognizing that despite these initial steps for developing a national program, Indonesia was still missing a long-term strategic plan to guide elimination efforts, our team of advocates and technicians used epidemiological and cost modelling to: (a) estimate the projected impact and cost-effectiveness of an elimination program to support advocacy efforts for securing national commitment and (b) produce a framework to help establish a timeline, targets, and resource requirements to inform long-term planning of an HCV elimination effort.

Methods

There is a growing body of viral hepatitis investment cases(13-15) that have been used to push for accelerated government and donor action to support and finance national strategies(16). In Indonesia, there was interest among stakeholders (ministry of health [MoH], local advocates, international technical partners) to develop such a tool to secure additional investment.

In the absence of a national strategy, we needed to first develop a high-level intervention framework to guide modelling analyses, based on previous national plans for hepatitis elimination in South Africa, Morocco, and Senegal(13, 17). Table 1 shows the priority areas and main activities of this framework. The full framework is in the supplement. We then applied several elements of an investment case, including disease modelling, cost estimation, and cost-effectiveness analysis to generate evidence to guide advocacy and planning efforts.

Scenario design

To understand the range of possible policy responses, we modelled treatment scale-up scenarios of varying elimination timeframes and scale-up intensity. The WHO definition for elimination is an 80% reduction in HCV incidence and a 65% reduction in HCV-related mortality from 2015 levels.

A "no treatment" scenario was designed to represent the counterfactual of treatment scale-up where no patients would receive treatment from 2018-2050. We then explored four elimination scenarios: elimination by 2036, 2040, 2042, and by 2045. Elimination by 2030, as per the WHO's overall target, was found to be impossible even if all infected people were treated in 2019, due to the existing burden of irreversible liver cirrhosis leading to HCV-related deaths. Elimination by 2036 represented the most aggressive elimination scenario, with other scenarios designed to represent increasingly more gradual paths to scale-up.

Epidemiological model

To simulate the HCV epidemic among the general population and PWID in Indonesia, a dynamic, deterministic HCV transmission model was used, incorporating population growth, age demographics, and HCV progression. The age groups included were: 0-14, 15-34, and ≥35-year olds. Supplementary figure 1 shows how the population was stratified into individuals who had never injected drugs, people who inject drugs currently (henceforth referred to as PWID), and ex-injectors. Initiation of injecting is assumed to occur only among 15-34-year olds. PWID cease injecting at a fixed rate to become ex-injectors.

Individuals enter the model susceptible to infection (except those infected through mother-to-child transmission). HCV transmission occurs at a specific modelled rate among all individuals in the general population due to medical/community risk factors and occurs at an additional modelled rate due to injecting drug use (IDU) among current PWID. Infected individuals either spontaneously clear their infection, and return to the susceptible class, or then develop chronic infection. Chronically infected individuals then gradually progress through different HCV-related disease stages (chronic infection, compensated cirrhosis (CC), and decompensated cirrhosis (DC); supplementary figure 2). Individuals in the DC stages have increased HCV-related mortality. Individuals can also die at age-specific death rates or from drug-related mortality among PWID. After successful DAA treatment (sustained virologic response [SVR]; essentially an effective cure), individuals return to being

susceptible, whilst those not achieving SVR transition back to chronic infection. Those who achieve SVR can become re-infected.

The model is described further in the supplement.

Model parameterization

Information on population sizes, age distributions, and mortality rates were taken from United Nations datasets(18). Anti-HCV prevalence data in the Indonesian general population, 1.0% (95% confidence interval [95%CI]: 0.9%-1.1%), were from a 2013 Indonesian MoH report(6). The proportion of PWID among adults in Indonesia, 0.11% (95%CI: 0.09%-0.13%) and anti-HCV prevalence among PWID, 89.2% (95%CI: 85.8%-92.6%) were taken from a recent systematic review and data from PKNI(19, 20). The supplement gives further parameterization information.

Selecting the most feasible scenario

Stakeholders, including the MoH, were consulted to understand the limitations on program capacity for scale-up. The elimination 2045 scenario was selected as the most feasible option for Indonesia as stakeholders judged the other scenarios to demand too steep a scale-up. Given Indonesia was treating <1,000 patients annually in 2017, the other elimination scenarios would have required over a 100-fold increase in patients treated within five years.

Five-year cost estimation

To inform immediate-term government planning efforts, we estimated the costs of the first five years of an elimination effort under the 2045 scenario, using the aforementioned framework (table 1). Where possible, a unit cost per activity was estimated based on literature review, interviews with key information holders, and a review of MoH and PKNI documents. Table 2 contains key costing assumptions, including a baseline unit cost of $1,314 for a 12-week course of DAAs(21). Full unit costs and sources are listed in the supplement. Unit costs were multiplied by scale factors, based on the coverage output of the epidemiological modelling when relevant, such as for treatment activities, or based on stakeholder consultations and review of plans from other countries(13, 14, 17). Scale factors for the first five years are shown in the strategy framework in the supplement(22). Priority areas of prevention, lab capacity decentralization, monitoring and evaluation, and management and coordination could not be costed based on the limited information available. A 25% mark-up of the costs of the other costed priority areas was used as a benchmark for the costs of these supporting activities, based on reviewing other national strategy costings.

Costs are given in US dollars ($). Future costs were inflation-adjusted at a rate of 2.2%.

Long-term costing estimation

We approximated the long-term costs of elimination for 2018-2050, with details given in the supplement. These costs focused on screening, diagnosis, and treatment since these activities were readily scalable based on treatment coverage targets. Other supporting program activities (awareness, lab strengthening, surveillance, etc.) were costed using the same mark-up of 25% as the five-year costing.

Price reductions

Additional analyses examined how the long-term costs would change over time if key price reductions were secured. The following price reductions were explored:

- 1: DAA price per treatment course drops from $1,314 (baseline) for Sofosbuvir/Daclatasvir (SOF/DAC) to $600 immediately, a price already seen in 2017 in other lower- and middle-income countries (LMICs)(23)
- 2: DAA price per treatment course drops to $150 over first five years, the lowest price for generic SOF/DAC reported in 2017(23)
- 3: Viral load (VL) test price drops from $139 to $40 over the first five years, the lower end for reported VL prices in the public sector where patient payments are required(24)
- 4: A combination of price reductions 2 and 3

Advanced liver disease treatment costs

In addition to the projected costs of a DAA treatment program, the costs of treating advanced liver (CC, DC, and HCC) for treatment-naïve patients were estimated for each scenario. Epidemiological modelling outputs were used for annual CC and DC cases. The ratio of DC cases to cases of HCC of 0.44 from previous modelling work(13) was used to estimate the number of additional HCC cases annually. It was assumed that at baseline 75% of individuals in each disease stage category received treatment annually. Other models have assumed 80% treatment coverage for advanced liver disease(14). The number of cases treated each year was multiplied by an average disease-stage-specific annual cost of treatment. These costs were $403 for CC, $3,050 for DC, and $2,850 for HCC, based on data from local hospitals(25, 26).

Cost-effectiveness analysis

An incremental cost-effectiveness ratio (ICER) was calculated for the 2045 elimination scenario by examining long-term costs and benefits relative to the baseline scenario. The cost-effectiveness analysis was conducted from a societal perspective. Long-term costs included both direct DAA program costs and advanced liver disease treatment costs for DAA-naïve patients from 2018-2050 to capture the total costs of treating hepatitis complications with and without the availability of DAA treatment. Impact was measured in additional years of life saved (YLS), or years of life lost averted (YLL averted). The supplement contains details on how deaths averted were transformed to YLS. The ICER for the 2045 elimination scenario was evaluated for the four price reduction options. ICERs were compared to relevant benchmarks, including the gross domestic product (GDP) per capita and other Indonesia-specific disease programs(27).

Sensitivity analyses

Given the high uncertainty around key epidemiological parameters, we performed a wide range of sensitivity analyses. These included assuming: (a) 50% of infected individuals are treated annually when the numbers of infected individuals is lower than the number of annual treatments available; (b) a stable general population HCV prevalence (rather than decreasing); (c) a lower general population anti-HCV prevalence (0.8%)(11, 28, 29); (d) a lower PWID anti-HCV prevalence (50%); (e) a lower proportion of adults that are PWID (0.02%)(30); (f) a higher viraemic HCV proportion (0.76)(31); (g) a lower (-50%) and higher (+50%) rate of progression from chronic infection to cirrhosis. We investigated selecting PWID for the first 32,000 treatments (total treatments over 2018-2021), for whom infection rates tend to be high(32, 33), selecting people with compensated

cirrhosis for the first 32,000 treatments, and selecting those with decompensated cirrhosis for the first 32,000 treatments (patients with compensated and decompensated cirrhosis have higher mortality(34)). Additionally, given the lack of Indonesia-specific data on screening program yield to date, we examined a range of expected yields from general population screening (+50%, -50%). We also performed sensitivity analyses for higher (+25%) and lower (-25%) assumptions for access to care for advanced liver disease.

Results

Treatment coverage

Figure 1 and supplementary table 1 show the coverage curves for the four scale-up scenarios. The 2036 elimination scenario, the most aggressive option, peaks at 1 million annual treatments in 2020. The 2040 elimination scenario would treat over 200,000 persons annually by 2022, with a peak of 550,000 annual treatments in 2025. The 2042 elimination is more conservative but still reaches over 100,000 treatments in 2022, peaking at 370,000 treatments from 2027-2029. The 2045 scenario is the most conservative in the first five years, with only 40,000 treatments in 2022, and has the lowest overall peak of 250,000 treatments from 2028-2031. The 2045 scenario hits 100,000 annual treatments 3-5 years after the other scenarios, allowing more time for capacity building and resource mobilization.

Disease impact

Each scale-up scenario eventually achieves both the WHO elimination incidence and mortality targets. The 2036 elimination scenario would have the greatest impact on deaths and new infections averted due to treating more individuals earlier on and preventing progression to advanced disease. Each scenario achieves the incidence reduction targets around 13 years before the mortality reduction targets.

With the no treatment scenario, prevalent infections are estimated to decrease slightly from 1.57 million in 2015 to 1.43 million infections by 2050 due to a declining epidemic. Nonetheless, the estimated number of new infections is projected to remain fairly stable (between 34,000-37,000 annual infections during 2015-2050), resulting in 1.29 million total new infections over the 35-year period. Elimination by 2036 would prevent around 900,000 of these new infections (70% of the no treatment scenario) while 2045 elimination would prevent about 739,000 infections (57%); figure 2a.

Under the no treatment scenario HCV-related deaths increase from 9,000 annually in 2015 to 12,500 in 2050; cumulatively over 429,000 deaths by 2050. The 2036 scenario would prevent around 203,000 deaths from 2018-2050 (47% of the no treatment scenario), while the 2045 scenario would avert over 158,000 deaths (37%); figure 2b.

Around 362,000 individuals are expected to develop CC and 90,000 DC by 2050 under the no treatment scenario. Elimination by 2036 would result in around 220,000 fewer individuals with CC and 78,000 fewer with DC in 2050. Elimination by 2045 is estimated to result in 173,000 fewer people with CC and 73,000 fewer with DC in 2050. Supplementary table 2 shows the number of CC and DC cases, respectively, over time for the different scenarios.

Costs

The cost of a five-year program under the 2045 scenario is estimated at approximately $347 million. Table 3 shows the breakdown by priority area. Of the $347 million, DAA diagnosis and treatment represent 58% of the five-year costs ($202 million) and screening accounts for 17% ($59 million). The 2018 Indonesian MoH budget is $7.0 billion and projected at $8.4 billion in 2019, so on average HCV scale-up could amount to less than 1% of the Indonesian health budget for the first five years(35).

Under the 2045 scenario, the total costs of elimination were estimated at about $5.6 billion for 2018-2050 (table 4). Around 44% of costs would be for treatment, 28% for screening, 8% for diagnostic evaluations, and 20% for other supporting activities**.** When conservatively assuming a constant MoH budget, HCV elimination would require, on average, 2.1% of the budget from 2018-2050(32).

If a price of $600 per treatment course is secured before scale-up begins (price reduction 1), total program costs for 2018-2050 would be reduced by 30% to $3.9 billion. If DAA prices in Indonesia can be reduced gradually to $150 over the next five years, the total costs of elimination could be lowered by 48% to $2.9 billion (price reduction 2). If VL test prices are reduced to $40 over the next five years, this would cut total program costs by 5% (price reduction 3). A combination of reduced DAA and VL costs over the next five years could reduce the total program cost by around 52%, to an estimated $2.7 billion (price reduction 4).

Under the no treatment scenario, the total costs of treating advanced liver disease would be $8.1 billion for 2018-2050. Under the 2045 elimination scenario, these treatment costs would be reduced to $6.4 billion; saving around $1.7 billion.

Cost-effectiveness analysis

The ICER of the 2045 scenario was $1,247 per YLS compared to the no treatment scenario, about one third of Indonesia's GDP per capita ($3,847)(36). If the DAA price of $600 is secured (price reduction 1), the ICER per YLS would be $712 while at the even lower $150 per cure (price reduction 2) the ICER would drop to $390 per YLS. If the cost of drugs and VL testing are lowered together as in price reduction 4, elimination would generate an ICER of $300 per YLS, less than a tenth of Indonesia's GDP per capita. Even at baseline prices for DAAs and VL testing, the ICER for HCV elimination compares favourably to the ICERs associated with the proposed scale-up of other disease interventions in Indonesia(37-39).

Sensitivity analyses

The sensitivity analyses for the epidemiological modelling assumptions all produce similar ICERs to the baseline assumptions, except the assumptions regarding the progression rate from chronic infection to cirrhosis (table 5). For all assumptions ICERs were cost-effective. When, for the same treatment levels as the 2045 elimination scenario, we allocated the first three years of treatment to people with compensated cirrhosis, the number of HCV-related deaths in 2030 was slightly lower (10,021 vs 10,179). When these treatments were allocated to those with decompensated cirrhosis, there was a slightly higher number of HCV-related deaths in 2030 (10,310 vs 10,179). When allocating the first three years of treatments to PWID, there was a slightly lower number of incident infections in 2030 (20,228 vs 20,679). If assuming that 50% of remaining infections are treated, rather than 80%, when the annual treatment spots available are greater than the remaining

infections, elimination is reached only one year later (supplementary table 10). When it was assumed yield from general population screening was 50% less at 1.50%, the total costs of the program increased to $7.6 billion. At a yield of 4.5%, total program costs are estimated to be reduced to $4.9 billion. Supplementary figure 3 gives the estimated costs of elimination for the full range of 1.5-4.5% screening yield among high-risk groups in the general population. The sensitivity of the program's cost-effectiveness to assumptions on access to advanced liver disease care are described in supplementary table 12.

Discussion

This study is the first to propose a framework for HCV elimination in Indonesia, a country with one of the world's largest HCV burdens(40). The analysis provides evidence to support a decision to pursue HCV elimination in Indonesia and offers inputs that could help shape subsequent planning efforts. This program's benefits in terms of deaths and infections averted and reductions in liver disease would be significant.

We focus on an elimination scenario endorsed by local stakeholders accounting for the reality that time will be required to mobilize resources and build capacity for a large-scale elimination program. The program achieves elimination by 2045, while meeting the incidence reduction target by 2032. Over the first five years, this 2045 scenario would grow to treat 40,000 patients annually and is projected to cost $347 million, an average of around $69 million a year. This path to elimination would reach its peak intensity treating 250,000 patients annually from 2028-2031. In addition to eliminating HCV, over 184,000 deaths and 735,000 new HCV infections would be prevented between 2018-2050 and there would be 247,000 fewer individuals living with liver cirrhosis in 2050.

The total cost of elimination through 2050 was estimated at $5.7 billion, a significant amount of money for Indonesia, averaging around $180 million per year. These additional investments would likely be highly cost-effective, as the cost per YLS ($1,247) is less than Indonesia's GDP per capita ($3,847)(36). If price reductions for drugs and tests are achieved, HCV elimination would become even more cost-effective. The ICERs presented compare favourably to the ICERs associated with other proposed interventions in Indonesia such as an improved targeted screening policy for noncommunicable disease (~3,700 per disability adjusted life year [DALY] averted)(39), school-based delivery of the oral cholera vaccine (~$2,500 per DALY averted)(37), and improved sanitation interventions ($1,400-$2,700 per DALY averted)(38).

Indonesia's 2018 MoH budget was approximately $7.0 billion and was projected to increase to $8.4 billion in 2019(35). We approximate that at these levels, the first five years of the national program would require less than 1% of Indonesia' health budget and less than 2.5% on average over the course of elimination. Further analysis must be conducted on the short-term and long-term financing options for Indonesia, accounting for the MoH budget, current spending on hepatitis, fiscal space for the hepatitis elimination program, and potential for obtaining financing from external sources such as development banks.

This analysis highlights the influence of specific policies on program costs, such as securing price reductions for treatment and diagnosis inputs and targeted screening strategies among the general

population. This will be driven by prices negotiated by the MoH for DAAs and viral load tests, with potential cost savings of $3 billion. In the sensitivity analysis, we found that targeting treatment first to PWID or those with compensated cirrhosis could avert more new infections or deaths. Targeting treatment in the early years would require a screening strategy that enables the program to identify these specific populations. This approach for Indonesia could be even more important given the sensitivity of program costs to the screening strategy effectiveness (yield of testing). Inefficient screening approaches could jeopardize the overall program affordability in the Indonesian context. Higher screening yield can be achieved by developing targeted screening strategies and maintaining high linkage to care. In many countries, there is evidence that high screening yields can be attained in early HCV treatment programs when PWID are targeted since they often bear a disproportionate high burden of disease (41, 42). Individuals with compensated cirrhosis could be easier to link to treatment if already known to providers, but additional groups to target could include individuals who received blood transfusions before the introduction of HCV blood screening(43); populations with high-risk healthcare exposures (eg. re-use of medical injections); and prisoners(44). Further analysis of the HCV burden among these groups in Indonesia is warranted.

Other literature

To our knowledge, no other published study has investigated treatment costs of a national treatment program to eliminate HCV in Indonesia or has proposed a framework for designing a national hepatitis elimination program. A limited number of studies have estimated the epidemiological burden. Sibley et al estimated around 24,800 new cases of HCV in Indonesia occurred in 2014, Heffernan et al estimated 37,000, whilst we estimated around 34,000(28, 45). Sibley et al estimated around 20,000 people will have DC in 2030, whilst we estimated a much higher figure of 90,000(28). In 2030, Sibley et al estimated around 8,000 HCV-related deaths will occur, Heffernan et al estimated 13,000, and we estimated around 12,000(28, 45). The discrepancies between Sibley's paper and those by ourselves and Heffernan are partly due to different methods used to estimate annual incidence (expert consensus vs dynamic modelling). Sibley et al used lower estimates of chronic prevalent infections in the general population and lower HCV prevalence among PWID(28), which we explored in sensitivity analyses. There were also disparities in model parameterisation regarding disease progression; we assumed an average of around 48 years to progress from chronic infection to cirrhosis, in line with other evidence(46), varying this parameter in sensitivity analyses to account for uncertainty. Several other studies have looked at the cost-effectiveness of HCV elimination in different settings. Despite the differences in the model types used and the units of analysis, eg. YLS, disability adjusted life years saved, all the analyses identified found HCV elimination to be cost-effective (in Australia(47), South Africa(48), Morocco(14), and Greece(49)), whilst a study in Pakistan, found it cost saving(50).

Strengths and limitations

The strengths of this study's epidemiological modelling include accounting for the HCV epidemic amongst PWID in Indonesia, vertical HCV transmission, age demographics, and population growth. One limitation was the lack of high-quality data. National estimates for the size of the PWID population, the HCV prevalence among the general population, and the HCV prevalence among PWID were important parameters with limited evidence. However, uncertainty extended to all parameters modelled, hence the reason we carried out wide-ranging sensitivity analyses.

Another challenge was the lack of a strategy and operational plan to inform the scenarios and costing. Due to this, we adopted a strategic plan framework based on examples from other countries(13, 14, 17). For some areas, eg. prevention and lab strengthening, costing data were unavailable, and we were forced to use broad coefficients from these other countries. Once a national elimination strategy for Indonesia is finalized, new cost estimations should be made using more precise unit costs and other assumptions, in consultation with stakeholders.

Further work is required to understand best practices and effectiveness of mass screening strategies in LMIC settings(44). Most evidence exists for high-income countries, with few studies in LMICs. This analysis's cost estimates could be improved by linking a dynamic screening model to our dynamic transmission model.

Importantly, the interpretation of cost-effectiveness is partially driven by the assumption that in the absence of DAAs, patients with advanced liver disease would seek and receive treatment and thus there are cost offsets to be gained from averting healthcare costs. Due to the lack of Indonesia-specific data, we assumed that 75% of patients with advanced liver disease would be treated. If these patients did not seek and receive treatment in Indonesia, these costs would not be incurred and would not be counted as savings. We accounted for this uncertainty in our sensitivity analysis, but additional data collection on access to care for patients with advanced liver disease are needed.

Policy Relevance

This paper shows how a combination of epidemiological and economic analyses can be used to produce evidence on the likely costs and benefits of HCV elimination over several decades. These analyses help to define what actions must be taken, the resources required, and the expected public health impacts that can be achieved. In Indonesia, PKNI has presented our findings to the Committee of the Indonesian Legislature Body, the committee for health affairs, and directly to the Minister of Health. Looking forward, this study could help the government to develop a national strategic plan that could prevent 739,000 new infections and 158,000 deaths and put Indonesia on the road to HCV elimination by the middle of this century.

References

1. World Health Organization. Hepatitis C Fact sheet. In; 2017.
2. Florian J, Mishra P, Arya V, et al. Direct-acting antiviral drugs for the treatment of chronic hepatitis C virus infection: Interferon free is now. Clin Pharmacol Ther 2015;98:394-402.
3. World Health Organization. Combating hepatitis B and C to reach elimination by 2030. 2016.
4. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016-2021. In; 2016.
5. MapCrowd. In; 2018.
6. Indonesian Ministry of Health. Serological test disease with that can be prevented immunization and infectious disease in Biomedical Specimens RISKESDAS; 2013.
7. Denovan A, (JOTHI) INPN. The Negative Impact of the War on Drugs on Public Health: the Hidden Hepatitis C Epidemic. In: 1st South and Southeast Asia Regional Community Meeting: HIV/HCV 24 Global Commission on Drug Policy; 2013.
8. 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.
9. Hill AM, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. J Virus Erad 2017;3:117-123.
10. World Health Organization. Access to hepatitis C treatment 2018. 2018.
11. Muljono DH, Lesmana LA, Sulaiman A, et al. Eliminating Hepatitis C Virus (HCV) in Indonesia. 2018.
12. Clinton Health Access. Press Release: CHAI announces partnership with governments in six low- and middle-income countries to initiate and expand hepatitis C treatment programs. In; 2016.
13. Hecht R, Hiebert L, Spearman WC, et al. The investment case for hepatitis B and C in South Africa: adaptation and innovation in policy analysis for disease program scale-up. Health Policy and Planning 2018;33:528-538.
14. Hecht R, Kaddar M, Resch S, et al. Morocco investment case for hepatitis C: Using analysis to drive the translation of political commitment to action. Journal of Global Health Reports 2019.
15. Nayagam S, Chan P, Zhao K, et al. Investment Case for a Comprehensive Package of Interventions against Hepatitis B in China. Journal of Hepatology 2016;64:S469-S469.
16. Pedrana A, Howell J, Schroder S, et al. Eliminating Viral Hepatitis: The Investment Case. Doha, Qatar: World Innovation Summit for Health, 2018; 2018.
17. Senegalese Ministry of Health. National Action Plan for the Control of Viral Hepatitis 2019-2023. In: Senegalese Ministry of Health, editor. Dakar; 2018.
18. United Nations Department of Economic and Social Affairs Population Division. In.
19. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health 2017.
20. Persaudaraan Korban Napza Indonesia (PKNI). Peer-Driven Intervention on Hepatitis C Testing and Treatment Literacy among People Who Inject Drugs in Jakarta, Indonesia. 2014.
21. Persaudaraan Korban Napza Indonesia (PKNI). Email communication. In; 2018.
22. World Health Organization. WHO guide to cost-effectiveness analysis. Geneva; 2003.
23. World Health Organization. Progress Report on Access to Hepatitis C Treatment 2017. Geneva; 2017.
24. Clinton Health Access, Foundation for Innovative New Diagnostics (FIND). HCV Diagnostics Market Intelligence Report 2017; 2017.
25. Clinton Health Access Initiative. Email communication. In; 2018.
26. Chhatwal J, Chen QS, Bethea ED, et al. Hep C Calculator: an online tool for cost-effectiveness analysis of DAAs. Lancet Gastroenterology & Hepatology 2018;3:819-819.
27. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bulletin of the World Health Organization 2015;93:118-124.

28. Sibley A, Han KH, Abourached A, et al. The present and future disease burden of hepatitis C virus infections with today's treatment paradigm - volume 3. Journal of Viral Hepatitis 2015;22:21-41.
29. Liakina V, Hamid S, Tanaka J, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 3. Journal of Viral Hepatitis 2015;22:4-20.
30. Ministry of Health Republic Indonesia. Estimates and projection of HIV/AIDS in Indonesia 2015-2020. Indonesia; 2017.
31. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
32. D HM. Epidemiology of Hepatitis B and C in Republic of Indonesia. Euroasian J Hepatogastroenterol 2017;7:55-59.
33. Martin NK, Vickerman P, Dore GJ, Hickman M. The hepatitis C virus epidemics in key populations (including people who inject drugs, prisoners and MSM): the use of direct-acting antivirals as treatment for prevention. Current Opinion in Hiv and Aids 2015;10:374-380.
34. Hallager S, Ladelund S, Christensen PB, et al. Liver-related morbidity and mortality in patients with chronic hepatitis C and cirrhosis with and without sustained virologic response. Clin Epidemiol 2017;9:501-516.
35. Decree of the Minister of Health of the Republic of Indonesia. Strategic Planning Ministry of Health 2015-2019. 2015.
36. World Bank. GDP per capita 2018 (US$); 2018.
37. Jeuland M, Cook J, Poulos C, et al. Cost-effectiveness of new-generation oral cholera vaccines: a multisite analysis. Value Health 2009;12:899-908.
38. The World Bank. Economic Assessment of Sanitation Interventions in Indonesia; 2011.
39. Rattanavipapong W, Luz ACG, Kumluang S, et al. One Step Back, Two Steps Forward: An Economic Evaluation of the PEN Program in Indonesia. Health Systems & Reform 2016;2:84-98.
40. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61:S45-57.
41. Trickey A, Fraser H, Lim AG, et al. The contribution of injecting drug use as a risk factor for Hepatitis C virus transmission globally, regionally, and at country level: a modelling study. Lancet Gastroenterol Hepatol 2018.
42. Degenhardt L, Charlson F, Stanaway J, et al. Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. Lancet Infect Dis 2016;16:1385-1398.
43. Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. J Hepatol 2006;45:607-616.
44. Chemaitelly H, Mahmud S, Kouyoumjian S, et al. Who to Test for Hepatitis C Virus in the Middle East and North Africa?: Pooled Analyses of 2,500 Prevalence Measures, Including 49 Million Tests. Hepatology Communications 2019;3:325-339.
45. Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. Lancet 2019.
46. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418-431.
47. Scott N, McBryde ES, Thompson A, Doyle JS, Hellard ME. Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model. Gut 2017;66:1507-1515.
48. Hecht R, Hiebert L, Spearman WC, et al. The investment case for hepatitis B and C in South Africa: adaptation and innovation in policy analysis for disease program scale-up. Health Policy Plan 2018;33:528-538.

49. Gountas I, Sypsa V, Papatheodoridis G, et al. Economic evaluation of the hepatitis C elimination strategy in Greece in the era of affordable direct-acting antivirals. World J Gastroenterol 2019;25:1327-1340.
50. Chhatwal J, Chen Q, Wang X, et al. Assessment of the Feasibility and Cost of Hepatitis C Elimination in Pakistan. JAMA Netw Open 2019;2:e193613.

Table 1: Proposed strategic framework for five-year national plan

Priority Interventions		Activities
Supporting areas	1. Awareness Raising	A. Conduct a national awareness campaign
		B. Participate in World Hepatitis Day Activities
		C. Conduct community workshops in high burden areas
	2. Healthcare Training	A. Disseminate guidelines to healthcare workers
		B. Conduct treatment educator training
		C. Train medical and paramedical personnel involved in screening for HCV
	3. Prevention Activities	A. Support harm reduction activities
		B. Promote bloody safety
		C. Promote injection safety in healthcare settings
	4. Strategic Information	A. Conduct a national serosurvey study
		B. Conduct special survey of high–risk populations
	5. Lab strengthening	A. Decentralize viral load testing
		B. Decentralize diagnostic capabilities for liver fibrosis screening
Core program	6. Screening	A. Implement routine screening in high-risk populations (PWID, MSM)
		B. Implement general population screening
	7. Treatment	A. Improve access to diagnostics
		B. Improve access to DAA therapy
8. M&E		Improve surveillance to support routine data collection
9. Management & Coordination		Oversee program implementation and improve efficiencies when possible

†HCV: Hepatitis C virus; PWID: People who inject drugs; MSM: Men who have sex with men

Table 2: Key costing assumptions for baseline scenarios

Key price assumptions	Cost (USD)	Cost (IDR M)	Source
Hepatitis C virus rapid diagnostic test (RDT)	10	0.1	Ministry of Health
Viral load test (VL)	139	1.9	St Carolus Hospital
Fibroscan	74	1.0	PPHI (Liver Association of Indonesia)
Direct acting antivirals (DAAs), per 12-week course	1,314	18.0	PKNI
Average cost per activity (including all cost inputs, i.e. service delivery, drugs, etc)	**Cost (USD)**	**Cost (IDR M)**	**Source**
Average cost per person screened	17	0.2	Ministry of Health, St Carolus Hospital
Average cost per person diagnosed	191	2.6	PPHI, St Carolus Hospital
Average cost per person treated	1,437	19.8	PKNI

Table 3: Costs in US dollars (USD) of a five-year hepatitis program under the 2045 elimination scenario

Priority area	Year 1	Year 2	Year 3	Year 4	Year 5	Total costs
Awareness raising	0.2 M	0.2 M	0.2 M	0.2 M	0.2 M	1.0 M (<1%)
Healthcare training	0.5 M	4.6 M	0.8 M	4.8 M	0.7 M	11.4 M (3%)
Prevention†	†	†	†	†	†	†
Strategic information	0.03 M	1.9 M	0.03 M	-	2.1 M	4.1 M (1%)
Lab strengthening†	†	†	†	†	†	†
Screening	5.1 M	8.0 M	13.4 M	13.7 M	19.4 M	59.5 M (17%)
Diagnosis + Treatment	15.6 M	22.4 M	32.9 M	44.2 M	86.7 M	201.8 M (58%)
Monitoring & evaluation†	†	†	†	†	†	†
Total	**21.4 M**	**37.1 M**	**47.3 M**	**62.8 M**	**109.2 M**	**277.7 M**
Total + 25%	**26.7 M**	**46.4 M**	**59.1 M**	**78.6 M**	**136.4 M**	**347.1 M**

†These activities were not costed because they are not readily scaled based on treatment coverage estimates. We applied a 25% mark-up to the total costs of the costed activities to account for these priority areas.

Table 4: Total costs of treating liver disease over time with different pricing assumptions, 2018-2050, in US dollars (USD)

	Status quo	Elimination 2045				
	Baseline	Baseline	Price reduction 1	Price reduction 2	Price reduction 3	Price reduction 4
Assumptions						
DAA price	-	1314	600	150 by Y5	1314	150 by Y5
Viral load test price	-	139	1340	139	40	40
Costs						
DAA program costs	-	5.6 B	3.9 B	2.9 B	5.3 B	2.7 B
Advanced liver disease treatment costs	8.1 B	6.4 B	6.4 B	6.4 B	6.4 B	6.4 B
DAA program + Advanced liver disease treatment costs	8.1 B	12.0 B	10.3 B	9.3 B	11.7 B	9.0 B
Cost-effectiveness analysis						
Total incremental costs vs no treatment scenario	-	3.9 B	2.2 B	1.2 B	3.6 B	0.9 B
Incremental YLS vs no treatment scenario	-	3.1 M	3.1 M	3.1 M	3.1 M	3.1 M
Cost-effectiveness ratio (USD per death averted compared to SQ)	-	1,247	712	390	1,157	300

†DAA: Direct-acting antiviral; Y5: Year 5; SQ: Status quo

Table 5: Sensitivity analyses testing various assumptions around the epidemiological inputs of the model, with outputs values given for 2015, and ICERs* per year of life saved given

Scenario	Chronic infections (including cirrhosis)	Compensated cirrhosis cases	Decompensated cirrhosis cases	Incident infections	Annual HCV-related deaths	Baseline ICER*	Price reduction scenario 4 ICER*
Baseline scenario	**1,570,342**	**326,901**	**64,959**	**34,392**	**9,050**	**1,247**	**300**
Assuming a stable, rather than decreasing epidemic	1,593,055	312,671	60,767	45,844	8,477	941	44
Assuming a lower general population HCV prevalence (0.8%)(29)	1,268,104	261,099	51,750	29,506	7,210	1,153	265
Assuming a lower PWID anti-HCV prevalence (50%)	1,564,577	330,648	65,871	31,160	9,206	1,132	255
Assuming a lower proportion of adults that inject drugs (0.02%)(30)	1,559,156	334,596	67,045	26,663	9,363	1,192	264
Assuming a higher viraemic proportion (0.76)(31)	1,872,029	390,359	77,555	40,384	10,755	1,267	326
Assuming a 50% lower progression rate from chronic infection to cirrhosis (0.0105)	1,575,985	177,262	34,836	32,689	4,864	2,370	902
Assuming a 50% higher progression rate from chronic infection to cirrhosis (0.0315)	1,565,838	451,556	91,390	35,937	12,705	859	107

* Incremental cost-effectiveness ratio per death averted in US dollars for 2018-2050

Figure 1: Treatment coverage of the elimination scale-up scenarios, 2018-2050.

Figure 2: Number of new chronic HCV infections (panel a) and HCV-related deaths (panel b) annually for the elimination scale-up scenarios and the status quo, 2018-2050. Dashed lines are WHO reduction targets.