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Strategies to eliminate hepatitis C in Croatia, a modelling study

Strategije za eliminaciju hepatitisa C u Hrvatskoj, studija modeliranja

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Descriptors
HEPATITIS C – diagnosis, epidemiology, prevention and control; NATIONAL HEALTH PROGRAMS – trends; CROATIA – epidemiology; WORLD HEALTH ORGANIZATION; MODELS, THEORETICAL

SUMMARY. *Background:* Since a 2016 analysis on the epidemiology and disease burden of HCV in Croatia, the HCV treatment paradigm has shifted substantially. Fibrosis restrictions were removed, and the number of patients treated tripled. With these encouraging changes to policy and practice, an updated analysis was completed to guide resource allocation and a national strategic plan for HCV elimination in Croatia. *Methods:* A comprehensive literature review and discussions with in-country experts were used to identify epidemiological factors defining HCV disease burden in Croatia. An HCV disease burden model, seeded with this data, was used to assess the impact of increasing screening rates and delineate the steps needed to reach the World Health Organization's (WHO) Global Health and Sector Strategy hepatitis C elimination targets. *Results:* Achieving WHO elimination targets would reduce the number of viremic cases of HCV from 21,000 in 2015 to 4,000 by 2030 while averting 500 liver-related deaths, and 680 cases of hepatocellular carcinoma and decompensated cirrhosis from 2015 to 2030, relative to the projections under the current standard of care. Screening practices will need to ramp up to testing about 250,000 Croatians annually so that about 1,500 patients can be diagnosed and treated each year. *Conclusions:* Elimination requires a coordinated effort between country and industry leaders including government authorities, policymakers and healthcare and insurance providers. Improved screening mechanisms will be needed for the scale-up required to achieve goals.

Deskriptori
HEPATITIS C – dijagnoza, epidemiologija, prevencija; NACIONALNI ZDRAVSTVENI PROGRAMI – trend; HRVATSKA – epidemiologija; SVJETSKA ZDRAVSTVENA ORGANIZACIJA; TEORETSKI MODELI

SAŽETAK. *Uvod:* Nakon posljednje analize epidemioloških i kliničkih podataka o HCV infekciji iz 2016. godine došlo je do velikih promjena u paradigmi liječenja. Uklonjene su restrikcije vezane uz uznapredovali stadij fibroze jetre, a broj liječenih se utrostručio. S obzirom na ohrabrujuće činjenice u mogućnostima liječenja napravljena je nova analiza, koja će peciznije usmjeriti prioritete i alokaciju resursa za provedbu nacionalnog akcijskog plana za eliminaciju hepatitisa C. *Metode:* Opsežan pregled literature i razgovori s hrvatskim stručnjacima korišteni su za identificiranje epidemioloških čimbenika koji definiraju opterećenje bolešću uzrokovanom virusom hepatitisa C u Hrvatskoj. Dobiveni podatci korišteni su u postojećem matematičkom modelu za procjenu opterećenja bolešću uzrokovanom HCV-om (engl. *HCV disease burden model*), kako bi se procijenio učinak povećanih stopa probira (engl. *screening*) i zacrtao putokaz potrebnih koraka za dostizanje globalnih ciljeva Strategije Svjetske zdravstvene organizacije (SZO) za eliminaciju hepatitisa C. *Rezultati:* Postizanje ciljeva SZO-a značilo bi redukciju HCV viremičnih slučajeva na 4.000 u 2030. uz sprječavanje 500 smrtnih ishoda uzrokovanih bolestima jetre i 680 slučajeva hepatocelularnog karcinoma i dekompenzirane ciroze u razdoblju od 2015. do 2030., za koje se procjenjuje da bi nastali uz sadašnju razinu probira i kliničku praksu. Prema upotrijebljenom matematičkom modelu to bi zahtijevalo povećanje broja testiranja na 250.000 osoba godišnje, kako bi se godišnje dijagnosticiralo i liječilo 1.500 pacijenata. *Zaključak:* Eliminacija virusnih hepatitisa kompleksan je proces koji zahtijeva koordinirane aktivnosti i suradnju između medicinskih stručnjaka, državne politike, donositelja odluka i pružatelja zdravstvenog osiguranja. Povećanje opsega probirnog testiranja bit će ključno za postizanje ciljeva SZO-a u Hrvatskoj.

Background

Viral hepatitis is a leading cause of death and affects one in 50 people worldwide.[1] Around 1% of the world's population has viremic hepatitis C virus (HCV)[2] and are at-risk of developing advanced-stage disease

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Table 1. Epidemiologic inputs used to model the burden of HCV, Croatia
Tablica 1. Epidemiološki podaci koji se koriste za modeliranje opterećenja HCV-bolešću, Hrvatska

Parameter / Parametar	Value (Range) / Vrijednost (Raspon)	Estimate Year (EoY) / Godina procjene (kraj godine)	Source / Izvor
HCV-RNA positive infections / HCV-RNA pozitivne infekcije	21,800 (20,500–34,200)	2010	Vilibić-Čavlek 2014,[11] PC[12]
HCV genotype / HCV genotip	56.6% G1 [18.8% G1a and 23.2% G1b], 37.3% G3, 4.2% G4, 1.6% G2	2018	Vince 2018[13]
Total diagnosed / Ukupno dijagnosticirani (HCV-RNA)	4,000	2014	EC
Annual newly diagnosed / Godišnje novo dijagnosticirani (HCV-RNA)	170	2018	EC
Annual treated / Godišnje liječeni	470	2018	EC
Percent of the infected population infected through transfusion / Postotak populacije zaražene transfuzijom	23%	2018	EC
Percent of the infected population that are people who inject drugs actively / Postotak zaražene populacije koji aktivno injiciraju drogu	14%	2010	PC,[12] Kolaric 2010[15]

EC – expert consensus / stručni konsenzus; EoY – end of year / kraj godine; HCV – hepatitis C / virus hepatitisa C; PC – personal communication / osobna komunikacija.

including liver cirrhosis, hepatocellular carcinoma (HCC), and liver-related death. Despite the success of direct-acting antivirals (DAAs), HCC is an ongoing risk for some patients successfully treated for HCV, particularly those with advanced cirrhosis.[3] This research highlights the importance of disease prevention and timely linkage to care following diagnosis.

In 2016, we presented both the historical epidemiology of HCV in Croatia[4] and an analysis of future HCV disease burden.[5] In the past three years, substantial changes have been made to the HCV treatment paradigm in Croatia. Starting in 2018, all fibrosis restrictions were removed, although prioritization remains in place to guarantee prompt treatment for more advanced-stage patients. Treatment eligibility, previously restricted to adults aged 20–70 years, was expanded in 2018 to cover patients aged 18–84 years. The annual number of patients treated also tripled from the 2015 to 2018. With these encouraging changes to policy, an updated analysis was conducted to guide development of a national strategic plan and to strengthen surveillance efforts.

This analysis models the interventions needed to achieve WHO targets in addition to various screening strategies. Since HCV is more prevalent in older aged Croatians and in people who inject drugs, we modeled screening efforts for various population cohorts. Data inputs from previous analyses were also re-evaluated and updated with input from Croatian experts in the field of hepatitis. This analysis serves to guide decision-making and resource allocation to eliminate HCV in Croatia.

Methods

In January 2019, epidemiologists with the Centers for Disease Analysis Foundation (CDAF) completed a comprehensive literature search for epidemiologic factors associated with HCV infection in Croatia. Over the following three months, CDAF employed a Delphi process to facilitate discussions with in-country experts and reach consensus on epidemiologic inputs by reviewing available estimates and sharing unpublished research and insights. The data collected from this exercise were then input into a disease burden model that has been described in detail previously.[2] Analyses using this model have been published extensively in other countries and regions, including the original publication for Croatia in 2016.[5–8]

HCV disease burden model

The Microsoft® Excel-based Markov model uses annual disease progression rates to simulate the natural history of HCV through disease stages from acute hepatitis (considering spontaneous clearance) to chronic fibrosis and end-stage outcomes (including hepatocellular carcinoma, decompensated cirrhosis, liver transplantation and liver-related death).[9] The model is seeded with population and background mortality data specific to Croatia[10]as well as country-level HCV epidemiological data (Table 1). New infections entering the model were back-calculated between 1950 and 2018 using known prevalence. Annual case counts were calculated by applying a progression rate to each disease stage and adjusted for all-cause mortality, ageing, and cure. All-cause mor-

Table 2. Scenarios estimating projections of HCV burden based on annual screening rates, Croatia, 2018–2030
Tablica 2. Scenariji za procjenu opterećenja hepatitisa C na temelju godišnjih stopa probira, Hrvatska. 2018–2030

Scenario / Scenario	Model parameter / Parametar	2018	2019	2020	2022	2024	2026	2028
Base / Polazište	Screened / Broj testiranih	33,400	40,800	40,600	38,600	35,700	33,500	32,000
	Newly diagnosed / Novo dijagnosticirani	170	210	210	210	210	210	210
	Treated / Liječeni	470	470	470	400	320	250	250
	New infections / Nove infekcije	140	140	130	120	120	110	110
Screen / Testirano 75,000	Screened / Broj testiranih	33,400	40,800	75,000 per year				
	Newly diagnosed / Novo dijagnosticirani	170	210	740	710	680	610	610
	Treated / Liječeni	470	470	670	640	610	550	550
	New infections / Nove infekcije	140	140	130	120	110	100	100
Screen / Testirano 100,000	Screened / Broj testiranih	33,400	40,800	100,000 per year				
	Newly diagnosed / Novo dijagnosticirani	170	210	980	930	870	720	720
	Treated / Liječeni	470	470	880	830	780	650	650
	New infections / Nove infekcije	140	140	120	120	100		90
Graduated Screening + Link to Care / Probir+Uključivanje u skrb	Screened / Broj testiranih	33,400	40,800	75,000	100,000 per year			
	Newly diagnosed / Novo dijagnosticirani	170	210	740	940	880	750	750
	Treated / Liječeni	470	470	670+270	850+200	820+90	690+30	680+50
	New infections / Nove infekcije	140	140	130	120	100	90	90
WHO Elimination Targets / SZO eliminacijski ciljevi	Screened / Broj testiranih	33,400	40,800	75,600	151,000	224,000	*avg 273,000 per year	
	Newly diagnosed / Novo dijagnosticirani	170	210	740	1,400	1,800	1,000	1,000
	Treated / Liječeni	470	470	670 +300	1,300+300	1,600+300	900	900
	New infections / Nove infekcije	140	140	130	120	100	40	40

* Average number of patients screened annually from 2026–2028 in the WHO Elimination Targets scenario (278,000 to 324,000 range). / Prosječni broj testiranih godišnje od 2026. do 2030. prema eliminacijskim ciljevima SZO-a (raspon 278,000–324,000)

tality rates (extracted from the United Nations mortality database) were adjusted to increase incrementally in relation to transfusion and injection drug use trends.

Epidemiologic inputs to estimate HCV disease burden

A full list of epidemiological inputs is included in Table 1. Since many of the historical inputs have remained consistent with the original analysis[4], only inputs that have changed are described in detail here.

HCV-RNA Positive Infections – There were an estimated 21,980 Croatians chronically infected with viremic HCV (0.51% prevalence) in 2010. This was calculated by adjusting the reported adult anti-HCV prevalence estimate (0.90% anti-HCV among adults aged 20–85 in 2010)[11] to account for all ages (0.73% anti-HCV among all ages in 2010) and applying a 70% viremic rate.[12] *HCV Genotype* – Data from the three largest Croatian national laboratories collected over nine years on 3,655 patients reported the majority of infections were genotype 3, 1b and 1a, respectively.[13] *Total and Annual Diagnosed* – The number of people diagnosed via antibody or RNA testing and reported to the Croatian Institute of Public Health was available annually for 1994–2018.[14] Experts estimated that 4,000 total patients were diagnosed with chronic HCV as of 2014. This is based on an estimated average of 300 diagnoses annually from 1993–2010 and an estimated average of 200 diagnoses annually from 2011–2014, with adjustments for 70% viremia[12], mortality and cured patients.[10] *Annual Treated* – In 2018, about 470 patients were treated, and treatment eligibility was expanded from ≥F3 to remove all restrictions (expert input). *Risk Factors* – Two risk factors associated with a higher HCV-related mortality were included in the model.

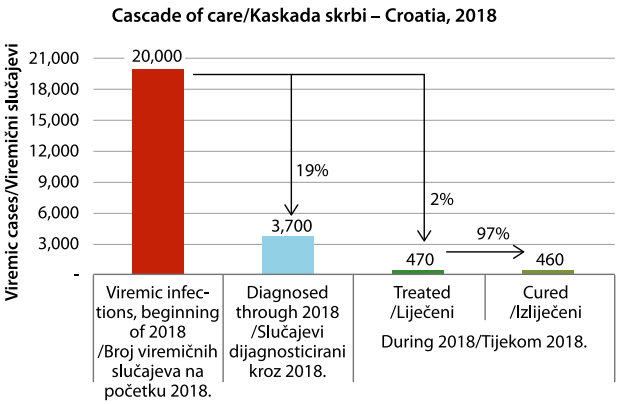

Figure 1. The HCV cascade of care, including the total number of viremic infections, the number of diagnosed patients, and the number of patients treated and cured, Croatia, 2018

Slika 1. HCV-kaskada skrbi, uključujući ukupni broj viremičnih slučajeva, broj dijagnosticiranih pacijenata i broj liječenih i izliječenih pacijenata u Hrvatskoj 2018

Experts estimated that 23% of 2018 total infections resulted from a blood transfusion and that 14% of the infected population were among people who inject drugs actively (injecting within the last year [PWID]). The PWID population was calculated by first estimating the number of drug users in Croatia (n=15,444)[15], of which experts estimated 74% were PWID. After applying a 35% anti-HCV prevalence among PWID[16]and adjusting for 70% viremia[12], 2,800 HCV-RNA positive PWID are estimated for 2018; 14% of total infections (n=2,800/20,000). The number of liver transplants were available from 1999–2017[17], of which 15% were estimated to be HCV-related (expert input).

Scenarios

After seeding the model with Croatia-specific epidemiological factors, the Base scenario and four intervention scenarios were modeled for 2015–2030 (Table 2). Data from 2015 is the baseline measure in the World Health Organization's Global Health Sector Strategy hepatitis elimination targets (WHO elimination targets) and was therefore utilized as the starting point for all scenarios.[2] As of 2018, all treatment restrictions based on fibrosis stage and patient age were dropped, such that for all five scenarios, patients aged 18–84 and fibrosis stages F0-F4 were eligible for treatment with high sustained virologic response (SVR) therapies.[18]

Screening trends were assessed for 2018–2030, under the following assumptions. *Base:* in 2018 and 2019, HCV screening occurred primarily through blood donation centers, voluntary centers, laboratories and screening vans. As a result, the average prevalence in the population screened is estimated to be the same as the general population prevalence in Croatia. *Intervention Scenarios:* Future screening campaigns are expected to target mixed-risk populations through primary care centers (estimated to be an average of twice the general population prevalence, in 2020) (Appendix, Table 2). To account for loss to follow-up within screening campaigns, only 90% of newly diagnosed patients were estimated to be initiated on treatment annually. Finally, it was assumed that procedures would be optimized to screen each individual only once.

Base – *Objective*: Model the current standard of care for HCV in Croatia. *Assumptions*: In 2018 and 2019, 30,000–40,000 patients were screened annually, of which 170 were diagnosed with viremic HCV and reported to the Croatian Institute of Public Health. The number of patients treated each year with DAAs, estimated at 470 patients in 2018, was expected to drop rapidly starting in 2022 to reflect a decreasing pool of previously diagnosed patients (expert input).

Screen 75K – *Objective*: Estimate the impact of an awareness campaign to increase screening rates. *Assumption*: Screen 75,000 Croatians annually, starting in 2020.

Screen 100K – *Objective*: Estimate the impact of an awareness campaign to ambitiously increase screening rates. *Assumption*: Screen 100,000 Croatians annually, starting in 2020.

Graduated Screening + Link to Care – *Objective*: Estimate the impact of an awareness campaign to ramp up screening over time while improving linkage to treatment for previously diagnosed patients. *Assumptions*: Increase screening to 100,000 people annually, by 2022. Treat patients who were diagnosed in previous years but were lost to follow-up.

WHO Elimination Targets – *Objective*: Quantify the level of effort needed to eliminate HCV in Croatia based on the four WHO elimination targets. *Assumptions*: Reduce new infections by 80%, diagnose 90% of all infections, treat 80% of eligible patients, and reduce liver-related mortality by 65%, between 2015 and 2030.[2]

Sensitivity analysis

Crystal Ball, an Excel add-in by Oracle, was used to run Monte Carlo simulations to generate 95% uncertainty intervals and sensitivity analysis. Beta-PERT distributions were used for all uncertain inputs.

Results

Estimates of disease burden

At the beginning of 2018, there were an estimated 20,000 (95% uncertainty interval (UI): 14,500 – 24,000) viremic infections in Croatia. By the end of

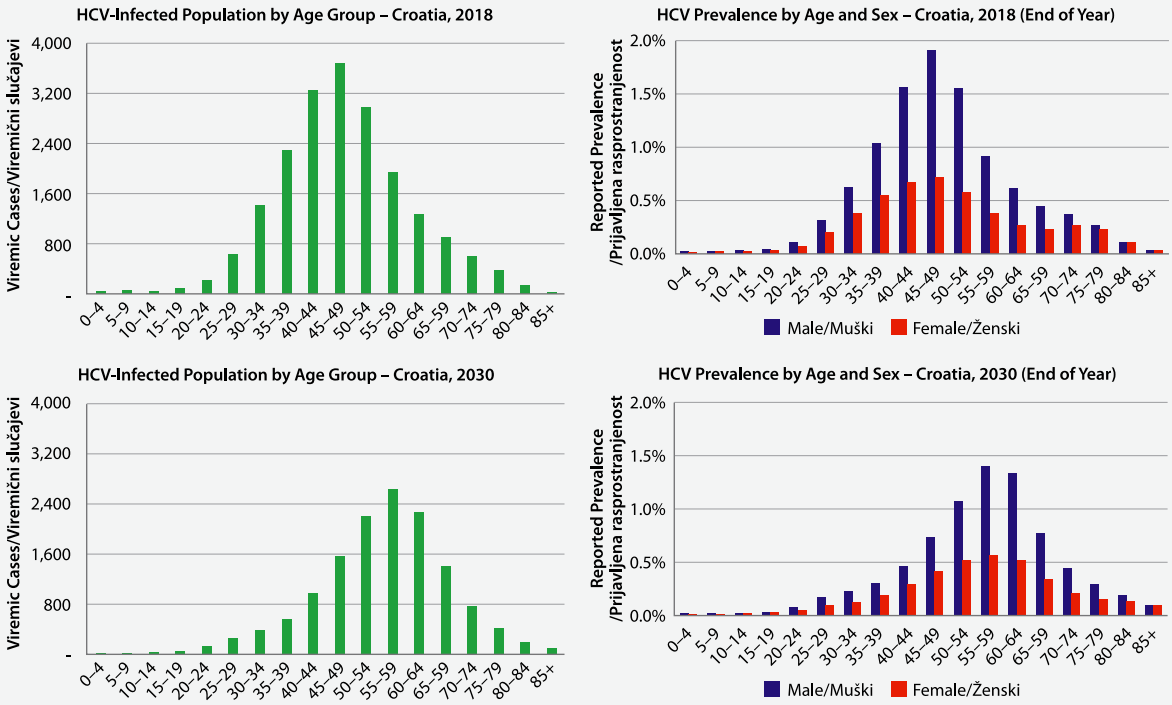

Figure 2. Age and sex distribution of hepatitis C cases, Croatia, 2018

Slika 2. Dobna i spolna distribucija slučajeva hepatitisa C u Hrvatskoj 2018. godine

2018, 19% (n=3,700) of infections were diagnosed. Of the total infected population, only 2% (n=470) were initiated on treatment. At an SVR rate of 97%, 460 of these patients were estimated to be cured (Figure 1). Sixty percent of patients with HCV in 2018 were estimated to have no fibrosis or early stage fibrosis (F0-F1), 30% had F2-F3, and 10% had F4 cirrhosis or end-stage liver-disease. Most infections (n=20%) were in adults aged 45–49 years.

Under the Base, the number of viremic cases peaked in 2007 and will continue to decline by 30% between 2015 and 2030, resulting in 14,100 cases by the end of 2030. This decline is largely due to mortality. If no change is made to the HCV treatment paradigm in Croatia, liver-related deaths (LRD), incident hepatocellular carcinoma (HCC), and incident decompensated cirrhosis (DC) will increase by 70%, 80% and 90%, respectively. LRD will increase from 60 in 2015 to 110 in 2030, and incident HCC will increase from 50 in 2015 to 90 in 2030. Annually, new cases of DC will also increase from 40 in 2015 to 70 in 2030 (Table 3, Figure 3). Croatia is estimated to screen a total of 460,000 patients and diagnose 2,700 patients from 2018–2030 (Figure 4).

By screening 75,000 Croatians annually and linking 90% of newly diagnosed patients to treatment, total infections would decline by 45%, but LRDs, incident HCC and incident DC would increase 45–55% from 2015–2030. Alternatively, if 100,000 Croatians are screened each year (with 90% of diagnosed patients linked to treatment), total infections would decline by 50%, compared with a 20–30% increase in LRD, incident HCC and incident DC. With graduated screening and linkage to care for previously diagnosed patients, total infections would decrease 55%, with a 5% reduction in LRD and 13–20% increase in HCC and DC from 2015–2030 (Table 3, Figure 3). All three enhanced screening scenarios require a 3–4-fold increase in total screenings and 2–3-fold increase in total diagnoses, compared to current practices (Figure 4).

Compared with the base scenario, eliminating HCV would avert 500 LRDs, 380 incident cases of HCC and 300 incident cases of DC by 2030 (Table 2). Achieving WHO elimination targets would reduce total infections by 17,000, decrease annual LRD by 40, and decrease incident cases of HCC and DC by 30 and 20, respectively, from 2015–2030 (Table 3, Figure 3). Elimination targets can be achieved by increasing screening, treatment, and linkage to care. Screening must ramp up to about 250,000 tests annually so that around 1,500 patients can be diagnosed and treated each year (Table 2). Compared to the Base, 5–6 times the total number of patients must be screened and diagnosed from 2018–2030 to achieve elimination targets (Figure 4).

Discussion

Now that a cure for HCV is available, case-finding has become the major obstacle to achieve elimination.

Table 3. Cases of viremic HCV infection, decompensated cirrhosis, hepatocellular carcinoma and liver-related deaths by scenario and percent change of case counts between 2018 and 2030, Croatia

Tablica 3. Slučajevi viremične infekcije HCV, dekompenzirane ciroze, hepatocelularnog karcinoma i smrti od bolesti jetre prema različitim scenarijima i postotne promjene u broju slučajeva od 2018. do 2030., Hrvatska

	Annual Outcomes* / Godišnji Ishodi		Cumulative Outcomes / Kumulativni Ishodi	
	2015	2030	Change from 2015 to 2030 / Promjene između 2015. i 2030	Incident cases averted from 2015 to 2030
Total viremic infections / Ukupni broj viremičnih slučajeva				
Base / Polazište	21,000	14,100	↓ 30%	–
Screen / Testirano 75,000		11,700	↓ 45%	90
Screen / Testirano 100,000		10,300	↓ 50%	150
Graduated Screening+LTC / Probir+Uključivanje u skrb		9,300	↓ 55%	190
WHO Elimination Targets / SZO eliminacijski ciljevi		4,000	↓ 80%	370
Annual liver-related deaths (LRD) / Godišnji broj smrti od bolesti jetre				
Base / Polazište	60	110	↑ 70%	–
Screen / Testirano 75,000		90	↑ 40%	100
Screen / Testirano 100,000		70	↑ 20%	190
Graduated Screening+LTC / Probir+Uključivanje u skrb		60	↓ 5%	290
WHO Elimination Targets / SZO eliminacijski ciljevi		20	↓ 65%	500
Incident hepatocellular carcinoma (HCC) / Incidencija hepatocelularnog karcinoma (HCC)				
Base / Polazište	50	90	↑ 80%	–
Screen / Testirano 75,000		80	↑ 45%	90
Screen / Testirano 100,000		70	↑ 25%	150
Graduated Screening+LTC / Probir+Uključivanje u skrb		60	↑ 13%	200
WHO Elimination Targets / SZO eliminacijski ciljevi		20	↓ 60%	380
Incident decompensated cirrhosis (DC) / Incidencija dekompenzirane ciroze				
Base / Polazište	40	70	↑ 90%	–
Screen / Testirano 75,000		60	↑ 55%	70
Screen / Testirano 100,000		50	↑ 30%	120
Graduated Screening+LTC / Probir+Uključivanje u skrb		50	↑ 20%	150
WHO Elimination Targets / SZO eliminacijski ciljevi		17	↓ 55%	300

*End of year/Kraj godine

Based on current disease burden assumptions, the model estimates that only 20% of infected Croatians are aware of their disease status, and only 2% of the infected population began treatment in 2018. In recent years, Croatia has enhanced effort to address HCV by removing fibrosis-level treatment restrictions and increasing the number of patients initiated on treatment, however a comprehensive strategy is needed to continue the momentum of action and to guide next steps. Four intervention scenarios were modeled to inform one data-driven, national screening strategy. Results demonstrate that as screening efforts are amplified (and assuming timely linkage to treatment for most patients) morbidity and mortality will decline in tandem (Figure 3, Figure 4). Achieving WHO elimination targets by 2030 is the best-case scenario: estimated to prevent nearly 1,200 cases of end-stage disease and HCV-related mortality. To achieve WHO elimination targets, treatment will have to scale faster than screening. This means that the approach to case-finding will need to be two-pronged: 1) finding and linking previously diagnosed patients to care and 2) increasing screening to increase new diagnoses. Current screening techniques in Croatia are inefficient, with some patients tested multiple times. The high volume of unique individuals that must be screened to achieve targets means that tracking systems must be improved so patients are tested no more than once or twice. As a compliment to the national plan, a central location should be elected to house and manage these data, and data should be routinely and completely reported for tracking purposes. Currently, experts believe that the number of people diagnosed with chronic HCV may be underreported because not all data are sent to the Croatian Institute of Public Health. It is imperative that reporting systems are improved so that progress can be tracked.

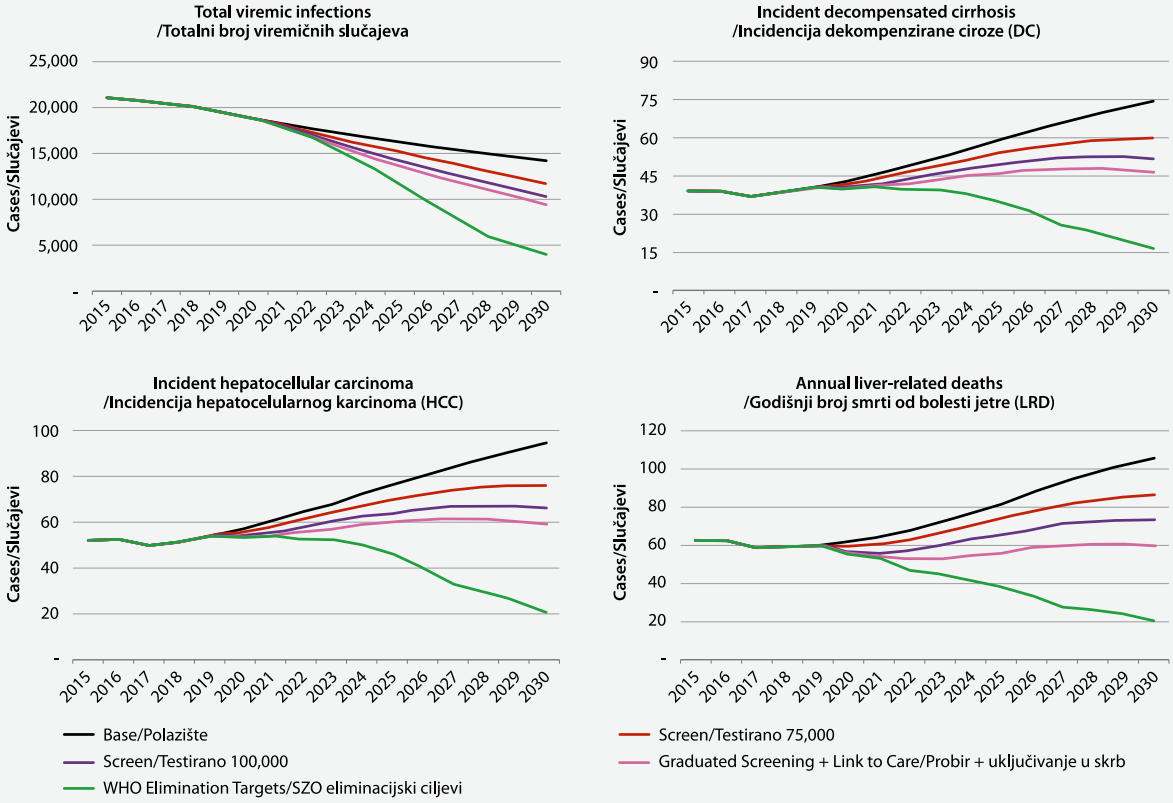

Figure 3. Total infected cases, prevalent decompensated cirrhosis, prevalent HCC, and liver-related deaths, Croatia, 2015–2030

Slika 3. Ukupni broj slučajeva, prevalencija dekompenzirane ciroze, prevalencija HCC-a i broj smrti od jetrenih bolesti, Hrvatska, 2015.–2030.

The next crucial decision for Croatian health authorities developing a national plan is to determine which populations to target in the screening campaign. Focused testing among high-risk groups or birth cohorts are the most common method of screening expansion, both shown to be cost-effective.[19] Most new infections occur among PWID, however, social stigma is a significant barrier to case identification. Blood donation centers in Croatia refer a significant number of patients to primary care testing, reporting that many at-risk individuals seek testing at blood banks to avoid disclosing risky behaviors. Screening can be effectively conducted in these at-risk populations to reduce transmission; however, innovative campaigns are needed to identify patients who may not self-identify with a risk factor. According to our analysis, of all chronic HCV infections, 14% were estimated to be active PWID, with the remainder of infections occurring among persons with other or unknown risk factor (including but not limited to former-PWID, nosocomial or transfusion related risks, etc.). In the absence of comprehensive estimates of populations based on risk, the age distribution of the infected population (Figure 2) could be used to inform or support age-based (or birth cohort) screening conducted in primary care settings. As part of the awareness campaign, experts envision expanding annual screening counts from about 40,000 Croatians (current) to 75,000 Croatians, starting in 2020, with a focus on primary care settings (Appendix, Section 4). Primary care facilities currently outsource all laboratory testing; however, experts agree that screening capacity can be significantly ramped-up if conducted in-house. This would involve a comprehensive, national action plan focused on increased testing capacity in primary care settings and maintaining screening levels in other settings. Significant investment would be needed to reach these goals; however, aggressive implementation of prevention and treatment strategies has been shown to reduce long-term economic and societal costs associated with HCV.[20–22] In other country settings, agencies such as the World Bank have also loaned monetary support for the up-front cost of HCV screening.[23]

Slight but significant changes were made to this analysis compared to previous reports. Guided by expert review and approval, this report updates data in

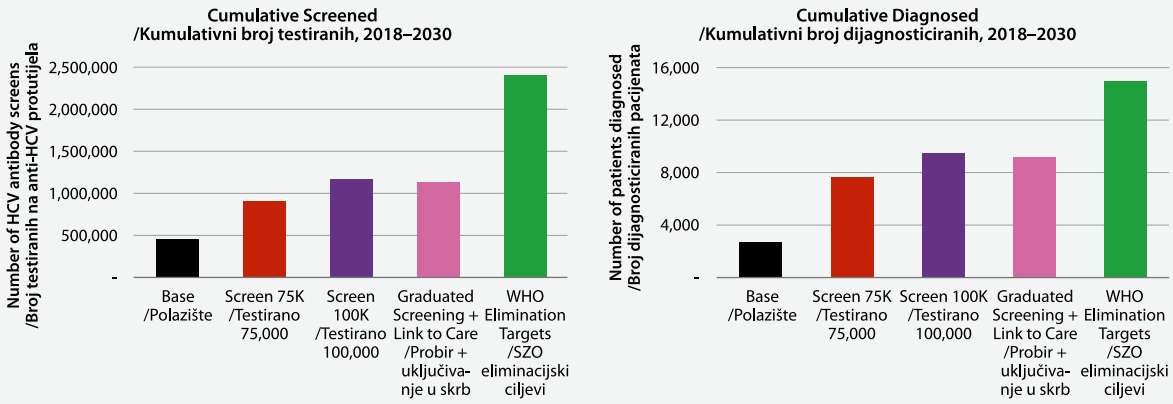

Figure 4. Cumulative number of patients screened and diagnosed, by scenario, Croatia, 2018–2030

Slika 4. Kumulativni broj testiranih i dijagnosticiranih pacijenata prema scenariju 2018.–2030.

the 2016 analysis[4] for the following epidemiological characteristics: genotype, fibrosis and age treatment restrictions, population diagnosed, population treated, and number of HCV-related liver transplants. Compared to the 2016 analysis, estimates for the population diagnosed increased and estimates for the population treated decreased, resulting in fewer total cases and fewer end-stage outcomes but similar disease burden trends overall.[5] Epidemiological data were also validated, when available. Data from local diagnosis registries (the distribution of prevalent cases by age and sex for 2018) were used to compare the distribution of cases by age and sex in the model for 2018. As well, one prominent healthcare facility in Croatia reported that about 60% of diagnosed cases were male, validating the sex distribution used in the model (about 55% male).[24] A sensitivity analysis was conducted to account for the depleting pool of infected individuals over time, expected to occur with the success of the screening campaign (Appendix, Section 3).

Limitations inherent to modelling affected this analysis, including the estimation of disease burden based on multiple data sources. Application of the Delphi process, however, ensured that the data were reviewed and vetted by experts and determined to be the best available. Shortcomings in data quality, however, make it difficult to model screening scenarios because current diagnosis and screening data are likely under-reported. Once a formal screening campaign included in a national action plan begins, the data should be used to re-evaluate progress toward elimination and strategic plans. It is also important to acknowledge that projections are dependent on the data inputs and assumptions. The model assumes that DAAs are consistently available to the diagnosed population and that treatment uptake, initiation and retention will remain high, even in difficult-to-treat populations. However, real-world fluctuations in these variables over time could impact projections.

Findings

If WHO elimination targets are achieved, 500 liver-related deaths and 680 cases of hepatocellular carcinoma and decompensated cirrhosis could be prevented, and viremic cases of HCV could be reduced from 21,000 to 4,000 between 2015 and 2030. Elimination requires a coordinated effort between various country and industry leaders including government authorities, policymakers and healthcare and insurance providers. Improved screening mechanisms and patient registries (for tracking screening and diagnosis) will be needed for the scale-up required to achieve goals.

Declarations

Statement on Financial and Other Relationships

This project was supported by Gilead Sciences. Gilead Sciences had no input on the content, study design, data selection, decision to publish, or preparation of the manuscript.

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APPENDIX

SECTION 1.
Data available for epidemiological inputs

Reports of the number of patients diagnosed with chronic HCV were provided by in-country experts for 2014–2018. Case counts were adjusted assuming 80% were viremic (expert input). Experts agree underreporting exists in Croatia, as some patients seek anonymous testing in blood donor clinics and these cases are not consistently reported. The rate of underreporting is unknown; however, experts estimate about 20% of the total infected population is diagnosed. The data shown in Table 1 represent known diagnosed cases, however true estimates are likely higher. Annual treatment estimates were based on the number of patients covered by insurance and therefore received DAAs, and an additional cohort who obtained treatment from alternative sources (expert input).

SECTION 2.
Description of the screening module in the HCV disease burden model

The screening module was developed to calculate the number of screening tests necessary to diagnose a given number of HCV-infections. The module used aforementioned epidemiological inputs (the infected population stratified by age and the number of annual diagnoses) to calculate the population eligible for screening, i.e., the undiagnosed, HCV-infected population that was either asymptomatic or not linked-to-care.

In the model, the more advanced stages of liver disease were assumed to be diagnosed first. It was also assumed that cases of spontaneous clearance were diagnosed at the same rate as asymptomatic, chronically infected cases.

To calculate the size of the population eligible for screening, the module tracked the populations with a history of screening, diagnosis, or SVR. It was assumed that each individual would receive at most one HCV antibody screen, and populations with a history of diagnosis or SVR would be excluded from future screening. Populations outside of the age range eligible for screening were excluded.

The number of patients needed to screen (NNS) to find one HCV antibody positive case was calculated, as shown in Equations 1–2. We then calculated the annual number of HCV antibody screens performed (Equation 3), of which all HCV antibody-positive tests were assumed to receive confirmatory HCV RNA testing. The case-finding algorithm assumed that persons with advanced liver disease were symptomatic and would seek care with or without active screening campaigns. Thus, each newly diagnosed case of advanced liver disease was assumed to require two screens; one HCV antibody and one confirmatory HCV RNA test.

Equation 1. Number needed to screen to diagnose one HCV antibody-positive case, unadjusted, in year *t*

$$NNS_t^* = \frac{1}{\frac{\text{Undiagnosed, asymptomatic or not linked-to-care HCV antibody-positive cases}_t}{\text{Population eligible for screening}_t}}, \text{ where}$$

Population eligible for screening$_t$ was the population eligible for screening in year *t*. Eligibility of screening was determined by birth year (by scenario), history of having received a screen within the screening strategy (excluded), history of diagnosis (excluded), and history of SVR (excluded).

Equation 2. Number needed to screen to diagnose one HCV antibody-positive case, adjusted, in year *t*

$$NNS_t = \frac{NNS_t^*}{k}, \text{ where}$$

NNS_t^* is the number needed to screen to diagnose one HCV antibody-positive case, unadjusted, in year *t*;

k is the ratio of prevalence in the population where the screening is conducted to that in the general population.

Equation 3. Number of HCV antibody screens performed, in year *t*

Newly diagnosed symptomatic HCV antibody-positive cases$_t$ + NNS_t ×

Newly diagnosed asymptomatic or not yet linked-to-care cases$_t$, where

NNS_t is the number needed to screen to diagnose one HCV antibody-positive case in year *t*.

Appendix Table 1. Sensitivity analysis calculating the average number of patients diagnosed
Dodatak tablica 1. Analiza osjetljivosti u izračunu prosječnog broja dijagnosticiranih

Average prevalence in the population screened / Prosječna prevalencija u skriniranoj populaciji	Average Annual Diagnosed (ages 15+) / Prosječni broj dijagnosticiranih godišnje (dob 15+), 2020–2030																						
	150	200	250	300	350	400	450	500	550	600	650	700	750	800	850	900	950	1,000	1,050	1,100	1,150	1,200
0.46%																						
0.57%																						
0.69%																						
0.80%																						
0.91%																						
1.03%																						
1.14%																						
1.26%																						
1.37%																						
1.48%																						

Screening an average of 40,000 people per year / Prosječni probir od 40,000 osoba godišnje
Screening an average of 75,000 people per year / Prosječni probir od 75,000 osoba godišnje
Screening an average of 100,000 people per year / Prosječni probir od 100,000 osoba godišnje

SECTION 3.
Screening model sensitivity analysis

Appendix Table 1 shows the number of patients we would expect to be diagnosed annually, based on the average number of patients screened each year for 2020 through 2030. An average was calculated to account for the depleting pool of infected individuals over time that necessitates additional screens. A range of 1 to 3 times the 2018 viremic prevalence (0.46%–1.48%) was used to account for screening practices in the general and at-risk populations. A sensitivity of +/– 20% was also considered. Results were as follows:

- Screening an average of 40,000 people/year results in an average of 200–650 new viremic diagnoses annually.
- Screening an average of 75,000 people/year results in an average of 350–900 new viremic diagnoses a year.
- Screening an average of 100,000 people/year results in an average of 450–1,1500 new viremic diagnoses a year.

SECTION 4.
Targeted population screening

Experts estimate that at least 40,000 Croatians were screened in 2018. The majority were tested in blood banks, with no tests conducted in primary care setting (expert input; Dr. Vince). Experts envisioned a goal of

Appendix Table 2. Targeted population screening currently in place (2018) and projected in 2020 to reach 75,000 screens, Croatia
Tablica 2. Aktualni ciljani probir u 2018. i projekcija za 2020. s dosegom 75.000 testiranih

Population / Populacija	Risk of infection in the population* / Rizik infekcije u populaciji	Number screened in 2018 / Broj testiranih u 2018.	Number to screen starting in 2020 / Broj testiranih od 2020.
Blood banks / Transfuziologija	Low / nizak	30,000	30,000
Voluntary centers / Centri za dobrovoljno testiranje	High / visok	5,000	5,000
Primary care/ Laboratories / Primarna zdravstvena zaštita/ različiti laboratoriji	Mixed / mješovit	4,500	39,500
Screening vans / Testiranje u zajednici/mobilne jedinice	High / visok	500	500
	Total / Ukupno	40,000	75,000

* Risk of infection in the population is defined as follows: Low – same prevalence (1x) as the general Croatian population; High – 3x general population prevalence (on average); Mixed – 2x general population prevalence (on average) / Rizik infekcije u populaciji je definiran na slijedeći način: nizak – ista prevalencija kao u općoj populaciji; visok – 3x veća prevalencija nego u općoj populaciji; mješovit – 2x veća prevalencija nego u općoj populaciji

Primary care facilities do not screen in-house, but outsource to laboratories (i.e. the 4,500 screened in 2018) / Testiranje se ne obavlja u ambulantama obiteljske medicine, nego se pacijenti upućuju u različite laboratorije koji pružaju tu uslugu

75,000 Croatians screened annually, starting in 2020 (Appendix Table 2). This would involve initiating a national action plan including an awareness campaign in primary care settings and maintaining testing levels in other settings.

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