ADULT SCREENING FOR HEPATITIS C AND LINKAGE TO TREATMENT IN HOSPITALS IN COLOMBIA

STUDY PROTOCOL

Principal Investigator

Javier Hernández Blanco

Gastroenterologist and Hepatologist

Colombian Association of Hepatology

Bogotá, Colombia

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1 Problem statement and justification

Hepatitis C virus (HCV) infection is a major cause of chronic hepatitis, cirrhosis, and liver cancer. For some people, hepatitis C is a short-term disease, but for more than half of the people who become infected with the hepatitis C virus, it becomes a long-term chronic infection (1). The risk of developing cirrhosis for people with chronic HCV infection ranges from 15% to 30% over 20 years (2).

According to 2019 data from the World Health Organization (WHO), there are 58 million people are living with chronic hepatitis C infection, and each year there are about 1.5 million new infections, it causes 290,000 deaths per year, mainly from cirrhosis and/or hepatocellular carcinoma (2).

The World Health Organization (WHO) in 2016 defined the global strategy for the elimination of viral hepatitis (hepatitis C virus and hepatitis B), the goals for hepatitis C include a 90% decrease in new cases of infection and a 65% reduction in mortality (3). To achieve this goal by 2030, 90% of people living with hepatitis C virus need to be diagnosed and 80% of these individuals should receive treatment along with a reduction of HCV incidence in high-risk groups (4, 5).

While good progress has been made in several countries, a significant testing and treatment gap remains. In 2019, only 21% of the 58 million with chronic hepatitis C infection had been diagnosed; overall, 13% were treated (3).

The introduction of direct-acting antivirals (DAAs) for HCV treatment in 2013 has led to sustained viral response (SVR) rates greater than 95% after 8 to 12 weeks of treatment, which is a significant advance in the elimination strategy (6), but massive screening and treatment implementation programs are needed to translate the potential of DAA treatment into population-level benefits (7).

The scale-up of DAA treatment is essential to achieve HCV targets, but this is a huge public health challenge. A major obstacle is under-diagnosis; only 20% of people with HCV worldwide have been diagnosed (6), and only 1% of infected people have received treatment worldwide. The effectiveness of governments and their partners in designing and implementing effective screening strategies to identify the "missing millions" will be a critical determinant of the speed with which elimination can be achieved (8).

Despite the effectiveness of DAAs and that in Colombia they are covered by the health system, the main obstacle to achieving the goal of hepatitis C elimination is under-diagnosis. Among the barriers to timely diagnosis are lack of knowledge on the part of health professionals, availability and access to screening tests, as well as stigma and discrimination, as a country it is required to directly address these barriers to advance in the goals of elimination of viral hepatitis (9). Simplifying the HCV care cascade, ideally across all steps of the continuum of care, would help ensure that more patients remain engaged in the care pathway and ultimately achieve WHO goals (10).

In Colombia, according to SIVIGILA, an average of 228 cases of hepatitis C were reported per year in the period between 2011 and 2016, starting in 2017 there was a significant increase with the notification of 571 cases and continued increase in 2018 (886 cases) and 2019 (897 cases) (11), in 2020 (473 cases) and in 2021 (878 cases), which represent an incidence of 1.70 per 100,000 inhabitants (9).

In 2017, the centralized drug purchasing strategy for the treatment of chronic hepatitis C was implemented, in compliance with Resolution 1692, as part of the effort to eradicate viral hepatitis from the country. The strategy is to purchase Direct Action Antiviral (DAA) drugs directly from the Ministry of Health and Social Protection (MSPS) to guarantee access and reduce treatment costs. When Resolution 1692 of 2017 was issued, the strategy was applied only to people diagnosed with chronic hepatitis C in the contributory regime; however, since January 2020, access to centralized purchasing by the subsidized regime was achieved (12).

According to information from the High-Cost Account (CAC for its acronym in Spanish), between January 1st and December 31st, 2021, 962 persons with the infection were identified in Colombia (13). According to the probable mechanism of transmission, the highest proportions are sexual transmission (72.1%) and parenteral/percutaneous (11.8% of cases) (14). According to information published by the Polaris Observatory up to 2021, there is a prevalence of 0.67% (320,000 cases), 10% of cases have been diagnosed, and of these <1% have been treated and 2639 deaths have been registered annually. According to their predictions with the current behavior, it is estimated that by the year 2051 Colombia will achieve the goals established by the WHO (15).

Three-quarters of HCV-infected people live in low- to middle-income countries, some of

which lack budgets for screening, diagnosis, and treatment campaigns. In 2018, Polaris Observatory reported that only 12 countries were on schedule to meet HCV elimination targets by 2030, these countries were Australia, Egypt, France, Georgia, Iceland, Italy, Japan, Mongolia, the Netherlands, Spain, Switzerland, and the United States (6).

Prevalence studies for HCV have been conducted in less than half of the countries in Latin America, and most of them are of poor-quality design. Extrapolating data from countries with registries, the estimated HCV prevalence rate in Latin America is less than 1%. Estimates made by the Polaris Observatory, according to epidemiological data from the online database in 2019, several countries were able to diagnose a significant percentage of the population with HCV infection; however, only Brazil was able to treat the required number of patients to achieve an annual net cure of more than 1% of those infected (16).

A study modeling the impact of DAA treatment on the course of HCV infection showed that achieving the WHO 2030 targets would require a net cure of 7% per year from 2016. "Net cure" was defined as the number of persons with sustained virologic response, minus new HCV infections, plus HCV-related deaths (17).

The American Association for the Study of Liver Diseases (AASLD), the Infectious Diseases Society of America (IDSA), and the Center for Disease Control (CDC) recommend one-time, routine, opt-out HCV screening for all persons aged 18 years and older. Additionally, (18):

- HCV testing should be performed at least once for all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection, occasionally testing should be done periodically if risk conditions persist.
- Perform HCV testing for all pregnant women as part of prenatal care.
- Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and for men who have sex with men taking pre-exposure prophylaxis.

The WHO recommends that in places where the general population has a high seroprevalence of anti-HCV antibodies (defined as a seroprevalence of 2% or higher, or 5% or higher), to provide access to HCV screening tests to all adults and to offer them such tests in linkage with prevention, care and treatment services (2).

To date, no HCV infection prevalence studies have been conducted in the general

population in Colombia, which could represent a drawback for decision-making for the control and elimination of HCV infection. However, studies in blood donors and populations with and without risk factors provide important data to know the overall situation of HCV infection in the country, and modeling analysis has contributed to the strategy in the country (Decree No. 1692 of 2017) (11). For Colombia, it is expected that approximately 409,000 people will have the infection in 2030 (9).

In Colombia, the Ministry of Health and Social Protection established in 2018 the National Response Plan for STIs, HIV, TB/HIV coinfection, and hepatitis B and C 2018-2021. In 2018, the clinical practice guideline for the diagnosis and treatment of hepatitis C infection was updated (14), likewise, progress has been made in the implementation of financing strategies for DAAs, however, it is still pending to improve screening strategies that do not only focus on risk factors and at the same time have generic treatment options available (9).

The country's achievements and challenges in hepatitis C correspond to (13):

- Timely identification of persons who have contracted the infection, so that they can quickly access treatment with direct-acting antivirals (DAAs).
- Maintain the decrease in treatment initiation time and effectiveness above 95%, which translates into a higher rate of cure of the disease.
- Staging for liver fibrosis to all patients at the time of diagnosis and decrease the progression of the disease to advanced stages.
- Continue working on decreasing the progression of fibrosis, liver cirrhosis, hepatocellular cancer, and virus transmission.

Through this observational, multicenter, hospital population study, the prevalence will be determined by screening patients with risk factors for hepatitis C by rapid antibody test, to subsequently perform confirmation with viral load PCR in those seropositive. In addition, support will be provided to patients to facilitate their treatment adherence.

The benefits would be related to raising awareness of the importance of the active search for these patients, reducing the health impact for the screened population, incorporating these strategies in the country's hospital institutions, and obtaining epidemiological information that helps to understand the magnitude of the disease and the opportunity for its elimination.

2 Theoretical framework and state-of-the-art

In 2016, the World Health Assembly endorsed the elimination of viral hepatitis as a public health threat by 2030. WHO-recommended interventions are childhood immunization against hepatitis B, prevention of mother-to-child transmission of hepatitis B virus (HBV) through timely vaccination at birth against hepatitis B and other approaches, safe transfusions, harm reduction for people who inject drugs, and HBV and hepatitis C virus (HCV) testing and treatment (19). Since then, tremendous efforts have been underway to accelerate countries' progress toward HCV elimination through data collection, predictive modeling, and screening and treatment linkage projects (20).

In May 2022, the 75th World Health Assembly took note of a set of comprehensive global health sector strategies against HIV, viral hepatitis, and sexually transmitted infections for the period 2022-2030. Building on the 2016 and new Assembly strategies, some Member States have developed comprehensive national hepatitis programs. To achieve the global viral hepatitis targets under the 2030 Agenda for Sustainable Development, the areas that should be worked on are a. raising awareness, promoting partnerships, and mobilizing resources for diagnosis and linkage to treatment; b. formulating evidence-based policies and compiling data for action; c. improving health equity in the hepatitis response; d. preventing transmission; and e. expanding screening, care, and treatment services (2).

Chronic HCV infection can remain asymptomatic until the late stages, leading to low awareness of the patient's infection status and a significant proportion of undiagnosed individuals (21). HCV infection is diagnosed in two stages: a. Detection of anti-HCV antibodies with a serological test reveals infection. b. If the test is positive for anti-HCV antibodies, a nucleic acid test for HCV ribonucleic acid (RNA) (viral load) is needed to confirm chronic infection and the need for treatment (2).

A study presented at the American Association for the Study of Liver Diseases (AASLD) Annual Meeting has concluded that the prevalence of viremic hepatitis C virus (HCV) infections declined from 66 million in early 2015 to 59 million in early 2020 (22); hepatitis C is a curable disease that if not diagnosed and treated on time can progress to liver cirrhosis, hepatocellular carcinoma, and death related to these and other hepatic or extrahepatic problems (20). The worldwide prevalence of HCV infection is estimated to be 0.75% (95% CI 0.6-0.8%) in the early 2020s (22).

Researchers at the Center for Disease Analysis Foundation (CDA) estimated from 2015 to 2019 7.5 million new chronic HCV infections, 1.3 million newly diagnosed that year (22). By 2019, of the 59 million HCV-infected persons worldwide, an estimated 21% (15.2 million) were diagnosed and, by the end of 2019, 9.4 million had been treated with Direct-Acting Antivirals (DAAs) (62% of persons diagnosed with chronic HCV infection), 8.8 million infections cured, and 5.5 million all-cause and liver-related deaths (2, 22).

Globally, more than three-quarters of HCV viremic infections remained undiagnosed at the beginning of 2020, and more than 90% of people with active hepatitis C remained untreated with DAAs. In high-income countries in 2020, ADC researchers estimated that 6 million people had a viral infection, of whom 47% had been diagnosed and 11% of those diagnosed were receiving treatment. The percentage of people with active hepatitis C is estimated to be 27% in upper-middle-income countries, 15% in lower-middle-income countries, and 16% in low-income countries. As for the percentage of people diagnosed and treated with DAAs, it is 3 % in upper-middle-income countries, 4 % in lower-middle-income countries, and 4 % in low-income countries (23).

In conclusion, the investigators note that DAA treatment is highly concentrated in a few countries, and low diagnosis rates and lack of large-scale HCV screening programs remain barriers to liver virus clearance. Despite the decrease in the number of cases versus 2015, these data suggest that currently, the world is still far from meeting global elimination targets by 2030 (23).

Scaling up interventions for hepatitis screening and treatment from baseline to elimination targets, within the perspective of universal health coverage and in the context of the Sustainable Development Goals entails an additional 1.5% investment, but the effect is proportionally larger, leading to about a 5% reduction in mortality and a 10% increase in healthy life years (19).

The recent WHO global health sector strategy sets new actions and targets to eliminate viral hepatitis by 2030 by reducing new infections to 90% and deaths to 65%, i.e., to half a million each worldwide. For this to happen, care must be more accessible to more people in need. The recommendations given have the potential to substantially expand access to testing and treatment in low- and middle-income countries. The 3 new key recommendations include (3): a. Simplified service delivery and task sharing: testing, care, and treatment of

persons with chronic hepatitis C infection can be provided by non-specialist trained physicians and nurses so that care can be delivered in primary care facilities, harm reduction services, and prisons, which is more accessible and convenient for patients. b. More efficient and simplified hepatitis diagnostics: use of HCV ribonucleic acid (RNA) assays at the point-of-care (POC) as an additional approach alongside laboratory-based RNA assays to diagnose infection. Especially applicable to marginalized populations, such as people who inject drugs, and hard-to-reach communities with limited access to care and high rates of loss to follow-up. c. Harmonized and simplified hepatitis treatment (3).

For testing in all settings, WHO recommends testing focused on persons with signs and symptoms of chronic liver disease and groups with a high prevalence of HCV infection. However, if the prevalence of infection in the general population exceeds 2-5%, WHO recommends testing in the general population (19). WHO recommends treatment with pangenotypic direct-acting antivirals (DAAs) for all adults with chronic hepatitis C infection. In Colombia, according to data from the high-cost account, the currently available DAA sofosbuvir/velpatasvir achieves an efficacy of 98.7% of HCV-infected patients, and a treatment duration of 12 weeks (9).

Early diagnosis of infection and linkage to treatment is one of the priority lines of action. Policies on HCV screening should be articulated in different settings (24). Key issues impeding HCV elimination are the lack of reliable and up-to-date estimates of active HCV infections and related disease burden (21).

The WHO strategy defines ambitious targets to eliminate HCV as a public health threat by 2030, to achieve which the scale-up of DAA treatment is essential, but this is a huge public health challenge. Identification of patients who are unaware of their HCV status represents the main barrier to be overcome, by 2017 according to WHO report only 20% of people with HCV worldwide had been diagnosed (6). Micro-elimination strategies targeting small fractions of the population, as opposed to nationwide elimination programs, have shown improvement in diagnosis and treatment rates resulting in great benefits in expanding the HCV care cascade and achieving WHO targets (21).

According to the epidemiological situation of HCV infection in the general population and the most affected populations, and of the hepatitis C approach plans, the clinical guidelines of countries such as Spain, United Kingdom, Germany, France, Ireland, Canada or Australia

recommend population and opportunistic screening, i.e. HCV screening of persons with exposures and risk situations for infection such as injecting and/or inhaled drug use, risky sexual intercourse, HIV/HBV co-infection, cosmetic procedures performed with sharps without proper safety precautions, admission to correctional facilities (24), anyone who received blood transfusions before HCV serological testing of blood donors was initiated, who received medical or dental interventions in health care settings with substandard infection control practices (25).

The indications for HCV screening by risk exposures instead of population screening allow focusing efforts and resources, responding to the principle of equity in the design, implementation, and evaluation of HCV screening programs in different territories, which allows addressing the barriers to access and use of services in each context (24). Targeted screening would identify a high rate of infected subjects, due to the higher rate of infection related to risk factors, and simultaneously reduce viral transmission by allowing HCV to be eliminated from individuals at higher risk of spreading the infection (26).

The results of the study by Rosato, et al (2022) indicate that opportunistic hospital screening in patients with various comorbidities is a feasible strategy to diagnose and then easily link infected patients to care. They also clearly show the need for increased awareness among general practitioners and other health care specialists, who care for patients with different comorbidities, to address HCV disease management. This is also important because HCV eradication has been shown to significantly improve not only liver disease outcomes but also various comorbidities, such as cryoglobulinemic vasculitis, diabetes, cardiovascular and renal diseases, etc. (27).

Care cascade monitoring (CoC) is an important component of the response to the global hepatitis C virus (HCV) epidemic. The function of a CoC is to represent how many members of a population have progressed through each stage in a sequence of stages required for effective disease control: e.g., diagnosis, treatment, and cure; the findings obtained will enable health system decision-makers to determine where the greatest gaps are in testing, linkage to care, and treatment among persons with chronic HCV infection (28).

A hospital-centered HCV micro-elimination approach provides a framework for expanding linkages to care and treatment on the path to achieving WHO's 2030 targets (21). It is less complex and costly than large-scale national efforts to eliminate HCV, and it can build

momentum by producing small victories that inspire more ambitious efforts (6). Fragile populations require dedicated screening and integrated care programs, which can begin in hospitals and continue in a network involving all processes including telehealth (21), promoting the adoption of new models of care in specific populations (6).

Micro-elimination approaches in populations at high risk for HCV transmission can potentially contribute to "treatment as prevention." The concept of treatment as prevention is to successfully treat an HCV-infected person at risk of transmitting HCV to others and eliminate the possibility of further transmission, thus achieving "prevention." While there is not yet a real-world demonstration of the potency of treatment as prevention, the model indicates that carrying out this strategy on a sufficiently large scale accelerates progression toward population elimination. The goal of treatment as prevention is to successfully treat enough people to reach a threshold at which new infections are significantly reduced. Because of the potential to prevent more infections, many of whom would incur the high costs of treating end-stage liver disease (6).

Targeting those at the highest risk for disease may generate broader community benefits and long-term cost-effectiveness. In support of this approach to HCV eradication, modeling studies by Martin and colleagues (2011 and 2013) have indicated that chronic HCV prevalence could be reduced by treating those at risk for ongoing HCV transmission (29).

The scale-up of HCV treatment is largely dependent on the availability and affordability of diagnostics and drugs. A large portion of the costs is attributable to testing because screening large numbers of people is required to identify 90% of those infected in low-prevalence settings (19).

Since 2017, in Colombia, the High-Cost Account (CAC) has been following up on cases identified with chronic hepatitis C infection, in compliance with the provisions of Resolution 1692 of 2017, which is part of the centralized negotiation and purchase strategy for direct-acting antivirals (30).

According to the Follow-up report on cases with chronic hepatitis C under the centralized drug negotiation and purchase strategy - Cut-off June 30, 2020, in follow-up by the EPS on compliance with what is contemplated in the clinical pathway for the treatment of chronic hepatitis C, 634 cases and 326 cases were reported in the 2019 and 2020 cohort, respectively, for a total of 2,102 patients with a diagnosis of chronic hepatitis C reported to

the high-cost account (including those in the 2017-2018 cohort). Of the 634 users enrolled in the 2019 cohort, 584 initiated treatments, of which 97.6% (570) did so with centrally purchased drugs. Of the 326 cases included in the 2020 cohort, 219 initiated treatments, 98.6% (216) with centrally purchased drugs, which made evident the almost exclusive use of the strategy, except in cases of stage 4-5 chronic kidney disease. Of the 1,142 patients reported to the CAC in 2017 and 2018, 1,079 had initiated treatment and of these 84.2% (n=909), were included in the centralized purchasing model, the most frequently used treatment in 98.2% of cases in the 2019-2020-2021 cohort was sofosbuvir/velpatasvir, reaching 98.77 in 2021 (12).

Regarding the effectiveness of the treatment, it was found that for the 2017-2018 cohort, with centrally purchased drugs, the effectiveness was 95.1% and with drugs outside the centralized purchasing model it was 96.4%. For the 2019 cohort, the effectiveness was 98% and 100% respectively. In the 2020 cohort, treatment effectiveness is at 100% (12).

The report concludes that there is high effectiveness of direct-acting antiviral treatments (greater than 95%), follow-up is observed in the application of the clinical route and practically exclusive use of drugs included in the centralized purchasing model; however, there is a need to encourage screening in the population over 50 years of age and according to risk exposure, as established in resolution 3280 of 2018 (12).

3 Research question

What is the prevalence of HCV in the population with risk factors for hepatitis C virus infection captured by screening with rapid tests in health care institutions in Colombia?

4 Objectives

4.1 General objective

To determine the prevalence of HCV in patients with risk factors for HCV captured through opportunity screening in the hospital institutions included.

4.2 Specific objectives

- Characterize the study population socio-demographically.
- Describe the epidemiological characteristics of HCV antibody-positive patients.

- Determine the proportion of patients with positive HCV antibodies and positive viral load (quantitative) for HCV.
- Perform an exploratory analysis of the association of positive cases and the different risk factors for HCV infection.
- Quantify how many HCV-positive individuals were able to access the management pathway and treatment.

5 Methodology

5.1 Type of study

Descriptive multicenter cross-sectional study.

5.2 Study population

All persons over 18 years of age who are treated in the included health care institutions (IPS) and who are users of hospitalization, emergency, outpatient and any other hospital care services.

5.3 Inclusion criteria

Have at least one of the following risk factors for hepatitis C.

- Over 50 years of age with no risk factors.
- Over 18 years old and < 50 years old, with risk factors for hepatitis C:

✓ Persons who have received medical or dental interventions in health care settings.

✓ Persons who have had tattoos, body piercings, or scarification procedures.

✓ Persons with HIV or hepatitis B infection.

✓ Persons who inject drugs.

✓ Persons who have used intranasal drugs.

✓ Persons deprived of liberty and previously incarcerated persons.

✓ Anyone with abnormal liver tests or liver disease.

✓ Students, health care workers, or members of public safety (e.g. correctional

service officers or police) who have come into contact with blood at work through needlestick or sharps injuries.

✓ Anyone who has undergone hemodialysis.

✓ Persons who received transfusions in Colombia before 1996.

✓ Persons with comorbidities potentially associated with CH: diabetes, ischemic heart disease, cryoglobulinemia, chronic renal failure, Sjögren's syndrome, hypothyroidism, lichen planus, rheumatoid arthritis, HIV, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, waldenstrom's macroglobulinemia.

- Individuals previously treated for HCV with sustained viral response in whom reinfection is suspected (individuals who continue to engage in risk behaviors)
- Accept to participate in the study by signing the informed consent form.

5.4 Exclusion criteria

- Have or have had hepatitis C with a proven cure by viral load at 12 weeks after the end of treatment without risk behaviors for reinfection.
- Be on antiviral treatment against chronic hepatitis C virus.
- That the patient voluntarily and consciously refuses to sign the informed consent form or is unable to give it due to any type of physical and/or mental disability.

5.5 Variables

Table 1. Study variables

Category	Variable name	Conceptual definition	Operational definition	Measuring scale
Sociodemographic	ID Number	ID Number	Personal identification number under which you are registered in the country of origin	Nominal
	Age	Duration of an individual's existence measured in units of time.	Number in years	Continual
	Gender	Categorizes the	1. Female	Nominal

Category	Variable name	Conceptual definition	Operational definition	Measuring scale
		individual according to her biological characteristics.	0. Male 2. Undetermined	
	Nationality	Country of birth	Name of country	Nominal
	Department of Residence	A geographic place to which the municipality or city where the person usually resides belongs.	Name of department	Nominal
	Municipality of residence	Geographic place municipality/city where the person usually resides.	Name of municipality/city	Nominal
	Health Service Provider Institution (IPS)	Place where the screening was performed.	1= Fundación cardioinfantil 2= Fundación Santafé 3= Clínica Colombia 4= Hospital Universitario San Ignacio 5= Fundación Valle de Lili 6= Hospital Pablo Tobón Uribe 7= Hospital Universitario Julio Méndez Barreneche E.S.E.	Nominal, polytomous
	Affiliation regime	Category of affiliation to the health system.	0=Not insured 1=Subsidized 2=Contributory 3=Special 4=Exception	Nominal, polytomous
	Entity Benefit plan administrator (EAPB) or Entity obliged to compensate (EOC)	The entity in charge of health care coverage.	Name of entity	Nominal
Risk Factors	Transfusion of blood products	Administration of hemocomponents before 1996.	0. No 1. Yes	Nominal, dichotomous

Category	Variable name	Conceptual definition	Operational definition	Measuring scale
	The year in which you received the transfusion	Date (year) in which you received the transfusion.	The year in which you received the transfusion transfusion	Continual
	Major surgery	Surgical procedure performed in the operating room under general or regional sedation that may require post-procedural in-hospital monitoring.	Abdominal laparotomy: 0. no; 1 Yes Gynecologic surgery of any type: 0. No; 1 Yes Orthopedic surgery of any type: 0. No; 1 Yes Any surgery that required in-hospital post-procedure surveillance for more than 24 hours: 0. 0. No; 1 Yes	Nominal, dichotomous
	Intravenous drug use	Having consumed intravenous drugs at any time.	0. No 1. Yes	Nominal, dichotomous
	Inhaled or intranasal drug use	Having consumed inhaled drugs at any time.	0. No 1. Yes	Nominal, dichotomous
	Men who have sex with men	Man who has had sex with men.	0. No 1. Yes	Nominal, dichotomous
	Known hepatitis B virus infection	Refer to have a diagnosis of hepatitis B virus.	0. No 1. Yes	Nominal, dichotomous
	Known HIV infection	Refer to HIV diagnosis.	0. No 1. Yes	Nominal, dichotomous
	People who have had tattoos, body piercings, scarification, etc.	Presence of tattoos or piercing or scarification.	0. No 1. Yes	Nominal, dichotomous
	Population deprived of liberty or previously incarcerated persons	Being or having been deprived of liberty in a penitentiary center.	0. No 1. Yes	Nominal, dichotomous
	Liver disorders or disease	A person with abnormal liver	0. No 1. Yes	Nominal, dichotomous

Category	Variable name	Conceptual definition	Operational definition	Measuring scale
		tests or liver disease.		
	Occupational exposure	Healthcare workers or members of public safety (e.g., correctional service officers or police) who have been in contact with blood at work through needlestick or sharps injuries.	0. No 1. Yes	Nominal, dichotomous
	Hemodialysis	A person who has undergone hemodialysis.	0. No 1. Yes	Nominal, dichotomous
	Comorbidities potentially associated with HCV infection.	Diabetes, Ischemic heart disease, Cryoglobulinemia, Chronic renal failure, Sjögren's syndrome, Hypothyroidism, Flat lichen, Rheumatoid arthritis, Non-Hodgkin's lymphoma, Acute lymphoblastic leukemia, Waldenstrom's macroglobulinemia, Chronic renal insufficiency, Sjögren's syndrome	0. No 1. Yes	Nominal, dichotomous
Missed opportunity	Doctor visits	Doctor visits in the last month	How many?	Continued
Sample results	HCV antibody screening test	Report of HCV antibody test result.	0. Non-reactive 1. Reactive	Nominal, dichotomous
	Viral load test	Report the viral load result of those patients who presented reactive HCV antibodies.	0. Non-reactive 1. Reactive	Nominal, dichotomous

Category	Variable name	Conceptual definition	Operational definition	Measuring scale
Follow-up	SIVIGILA Report	The confirmed cases of HCV as a public health event are reported to the surveillance system utilizing form 340.	0: Not reported 1: If reported	Nominal, dichotomous
	Follow-up of confirmed case	Follow-up that each case confirmed in the study has access to consultation by a clinical specialist.	0. No Why? 1. Yes	Nominal, dichotomous
		Monitoring patient access to treatment	0. No Why? 1. Yes	Nominal, dichotomous

5.6 Sampling frame

The sample frame is made up of all persons over 18 years of age who attended health service provider institutions (IPS) participating in the study in hospitalization, emergency, outpatient, and any other hospital care services.

5.7 Sample selection method

Non-probabilistic convenience sampling will include all patients who meet the eligibility criteria. The inclusion of participants will be consecutive until the calculated sample size is completed.

5.8 Sample size

Considering that the prevalence of HCV in the hospital population with risk factors is unknown, 50% will be considered, with a confidence level of 95%, an error of 5%, a design effect of 3, and a population served on average for the institutions included of 280,186 during 2021, the minimum sample size required per institution is 1,151 and the maximum with a confidence level of 99.99% is 4,519 (Table 1).

Table 1. Sample size for frequency in a population

Population size (for finite population correction factor or fcp)(N):	280.186
Hypothetical % frequency of the outcome factor in the population (p):	50%+/-5
Confidence limits as % of 100(absolute +/-%)(d):	5%
Design effect (for group surveys-EDFF):	3

Sample Size (n) for Various Confidence Levels	
Confidence Interval (%)	**Sample size**
95%	1151
80%	493
90%	811
97%	1411
99%	1986
99.90%	3236
99.99%	4519

Sample size n = [EDFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)].

Source: Results from OpenEpi, version 3, the SSPropor open-source calculator.

5.9 Sampling and data collection procedure

Once approval for the present study has been obtained from the research ethics committee, the standardized data collection phase will begin. Search strategy through opportunity screening. For each person who meets the inclusion criteria and wishes to participate, informed consent will be requested and a data collection form will be filled out (Annex 1). These patients will undergo pre-test counseling, a presumptive rapid test for HCV, and if positive, contact information will be requested for post-test counseling and evaluation through teleconsultation by one of the principal investigating hepatologists who will guide them to access the confirmatory test for HCV, the study will assume the responsibility for its realization. Once the care pathway is established, the subsequent follow-up of the patient with a reactive hepatitis C antibody test will be done through their EAPB or EOC.

The sample will be taken by trained personnel by capillary puncture of the thumb region of the fingers of the right hand, after asepsis and antisepsis, the rapid diagnostic test HCV Ab Plus Rapid test with INVIMA registration 2018RD-0002353-R1 will be used with operational characteristics that allow its performance at the point of care obtaining a result in 15 to 20 minutes. This rapid test for antibodies against HCV may be replaced by another test with similar operational characteristics (sensitivity and specificity). The recommendations described by the test manufacturer should be followed.

Once the capillary blood sampling is performed, the used implements and the blood samples obtained will be discarded according to biosafety protocols and no additional studies will be performed with these samples. The spaces designed to dispose of the material used will be the guardian to dispose of sharps and items contaminated with blood in a red biohazard bag that will go to final disposal by the company in charge of this purpose in the institution where the sample collection is carried out.

Cases with reactive hepatitis C antibody tests will be reported to the hepatologist, gastroenterologist, or infectologist linked to the institution and who acts as the leading physician of the strategy in each institution and to the epidemiology service or unit of the respective institution for follow-up and notification to the National Public Health Surveillance System - SIVIGILA.

Performing hepatitis C viral load for cases with positive hepatitis C antibodies either through a reference laboratory (Colcan) with which ACH has established an agreement or by payment to the Clinical Laboratory of the Hospital.

All the information obtained will be recorded and processed individually (case by case) through a digital information system with cloud backup in real-time using a Case Report Form (CRF), with the use of a tablet. The review and validation of the data capture will be performed weekly. The information will be guarded and encrypted for the exclusive use of the principal investigators belonging to the Colombian Association of Hepatology, periodic quarterly reports and a final report will be submitted to each of the participating institutions. The information will be anonymized for their use. Access to the information will be independent for each institution.

5.10 Data Analysis Plan

Descriptive analysis will be performed for all variables of interest proposed in this study. Descriptive statistics (frequencies and percentages) will be estimated. For continuous quantitative variables, measures of central tendency (mean and median) and measures of dispersion (variance, standard deviation) will be estimated. Possible relationships between sociodemographic variables, risk factors, and documentation of positive HCV antibodies will be explored, for which a bivariate analysis will be performed using X2 (chi-square) tests to explore the proposed associations. All analyses will be performed with Stata version 18.

5.11 Tools to be used

A form will be used to collect demographic data and the variables to be studied (Annex 1).

6 Ethical considerations

This protocol will be submitted for review and evaluation by the Research Ethics Committee in each of the participating institutions to obtain the respective approval for its execution.

The study is by the provisions of Resolution 8430 of 1993 of the Colombian Ministry of Health, according to article 11 numeral b, is classified as minimal risk, given that data records were used through common procedures consisting of a sample collection (blood) by capillary puncture. In addition, the criterion of respect for the dignity and protection of the rights and welfare of the participants will prevail.

Informed consent will be requested in written form to all participants, giving clear and easily understandable information about the objectives of the research. The consent will be explained and doubts about it will be resolved, and complete freedom will be given to withdraw consent at any time during the study, for the reasons that the subject considers (Annex 2).

The study will be coordinated by health professionals and the sampling and data collection will be performed by trained nursing assistants. The confidentiality of the data collected will be guaranteed, the information obtained will not be used for purposes other than the current research process, and at the time of disclosure of the information, sensitive data or data that allow the identification of the participating individuals will not be published, the rules outlined in the law 1581 of 2012 on habeas data will be followed.

None of the authors have conflicts of interest to declare.

7 Expected results & impact

Strengthening of the scientific community

Expected Result/Outcome	Indicator	Beneficiary
Screening adults with risk factors for hepatitis C	The proportion of people diagnosed with hepatitis C	Users affiliated with the SGSSS, benefit plan administrators, and health personnel.
Linkage to treatment of confirmed positive cases for HCV infection in the hospitals included in the study.	The proportion of people diagnosed with chronic hepatitis C who started treatment	Users affiliated with the SGSSS, benefit plan administrators, and health personnel.

Social appropriation of knowledge

Expected Result/Output	Indicator	Beneficiary
Circulation of specialized knowledge: Presentation of results in scientific events (national and international).	Participation in scientific events presenting research results.	Medical-scientific community, decision makers, hospital institutions.
Circulation of specialized knowledge: Presentation of results to stakeholders of the Colombian SSSSS.	Participation in events with different stakeholders of the USGS.	Insurers and providers of the SGSSS, patients at the national level.

Generation of new knowledge

Expected Result/Output	Indicator	Beneficiary
Research article submitted to a journal indexed in one of the bibliographic citation indexes such as ISI-Web of Knowledge (Science Citation Index (Raffone et al.) and Social Sciences Citation Index [SSCI]) or SCOPUS, Publindex, Lilacs, BVS, Latindex, among others.	Scientific articles published.	Medical-scientific community, decision makers, hospital institutions.

Expected impacts from the use of results

Expected Impact	Time (years) after completion of project* 1-4 years	Verifiable indicator	Assumptions
Improved timeliness of detection of new cases of hepatitis C in the hospital setting.	1-4 years	Increase in incidence rate for hepatitis C	Medical staff adhering to the screening and diagnostic algorithm - applicability of the algorithm in people with risk conditions and exposures.
Improved time between confirmatory PCR diagnosis and initiation of treatment.	1-4 years	Increase in the number of persons diagnosed with chronic hepatitis C who initiated treatment	Standardization of route that allows compliance with all stages for the diagnosis, treatment, and follow-up of the patient with CH.
Successful completion of treatment	1-4 years	Increase in the proportion of patients with cure (sustained viral response)	Timeliness of follow-up, patient adherence to treatment regimen.
Changes in chronic hepatitis C prevalence figures	5-9	Trend in the crude prevalence of chronic hepatitis C	Timely detection and treatment cause a decrease in the risk of transmission.

Short (1-4), medium (5-9), long (10 or more)

8 Communication strategies

Each institution will use its mechanisms for the dissemination of the project and participatory strategies that it determines appropriate according to the type of clinical research and its institutional policies after consultation with the Colombian Association of Hepatology.

9 Trajectory of the researchers participating in the research project

Javier Enrique Hernández Blanco. Specialist in Internal Medicine, Gastroenterology and Digestive Endoscopy, Master in Liver Diseases and Clinical Epidemiology. University Research Professor, President of the Colombian Association of Hepatology (2021-2023). Active participant in the National Plan for the Elimination of Viral Hepatitis, national lecturer in Viral Hepatitis B and C, former advisor in public health for the Secretary of District Health of Santa Marta, extensive experience in screening activities of viral hepatitis in the

community, co-author Colciencias project - CALL 777: Prevalence and modeling of Hepatitis C Virus infection in Colombia.

10 Schedule of activities

The duration of the project will be 11 months.

Activities	Start date	End Date
Development of the final protocol, consent reports, and approval by the ethics committees of each institution.	Month 1	Month 2
Training of nursing staff for data capture, sample collection, referral to treatment, and follow-up	Month 3	Month 3
Recruitment of participants - Identification of at-risk populations to be screened - Screening tests - Entry of data collected	Month 3	Month 8
Verification of the quality of the collected information - Data analysis	Month 3	Month 8
Data analysis	Month 7	Month 9
Presentation of a final report	Month 10	Month 10
Writing and submission of article for publication	Month 11	Month 11

11 Budget

This project will be executed by the Colombian Association of Hepatology (ACH), and is an initiative of the ACH in response to its commitment to join efforts to achieve the World Health Organization's goal of eliminating viral hepatitis by 2030, and is financed with ACH resources, which in turn are obtained from the association's activities and resources obtained in calls for project funding.

At the Hospital, the study is under the direction of the lead physician and hospital staff assigned to perform the rapid tests and paid for with project resources. The hospital will incur no additional costs for the conduct of the project beyond allowing the use of its physical area for patient recruitment and point-of-care rapid testing outside the clinical laboratory. The cost of performing viral loads will also be borne by the ACH, for which a contract has already been established with the COLCAN reference laboratory, but they could also be

performed in the laboratory of the same institution at the cost of the project at a rate of COP 238,000 (USD 49,96) for each viral load if the institutional laboratory expresses interest in processing the viral load samples of the cases with positive antibodies and after signing an agreement.

Leadership in the communication and management of project resources vis-à-vis healthcare institutions is provided by the ACH, its board of directors, and the acting president or designee, along with alignment with each participating project institution leader.

ACH is the author of the project and will provide the resources for the execution of the project. The items covered in the execution of the study do not include the costs of treatment or any clinical management procedure (for example, visits to the doctor, or follow-up laboratories) since they are part of the usual treatment for hepatitis C virus infection and it is contemplated in the Colombian regulations that once the case of confirmed hepatitis C is notified to SIVIGILA (file 340), every quarter the High Cost Account downloads that information, includes the patient in the national cohort of high-cost diseases-Hepatitis C, establishes communication/audit with the Benefit Plan Management Company (EAPB) to which the patient belongs and guarantees their linkage to treatment, treatment against hepatitis C which is free, at no cost to the EAPB or out-of-pocket expense for the patient and which is acquired in annual purchases by the CAC since 2017 through the centralized purchasing mechanism from the Pan American Health Organization.

12 Annexes

12.1 Annex 1. Data collection instrument

<table>
<tr><th colspan="2">Adult screening for hepatitis C and linkage to treatment in Colombian hospitals</th></tr>
<tr><td>Patient's name:</td><td>Identification number:</td></tr>
<tr><td>Age (in years):</td><td>Sex: Male:____ Female:___</td></tr>
<tr><td>Contact phone number:</td><td>Residence address:
Department of Residence:
Municipality of residence:</td></tr>
<tr><td>Affiliation scheme:
0. Uninsured: _____
1. Subsidized: _____
2. Contributory: _____
3. Special: _____
4. Exception: _____</td><td>Institución prestadora de servicio de salud (IPS):
Fundación cardioinfantil _____
Fundación Santafé _____
Clínica Colombia _____
Hospital Universitario San Ignacio _____
Fundación Valle de Lili _____
Hospital Pablo Tobón Uribe _____
Hospital Universitario Julio Méndez Barreneche E.S.E. _____</td></tr>
<tr><td colspan="2">E-mail: _____ Nationality:_____</td></tr>
<tr><td>Received blood transfusion before 1996:
YES___ NO___</td><td>Year of transfusion:</td></tr>
<tr><td>Name of EAPB or Entity obliged to compensate:</td><td>Major Surgery: Yes___ No___
Type of surgery:
Abdominal laparotomy: Yes__ No__
Gynecologic surgery of any type: Yes__ No__
Orthopedic surgery of any type: Yes__ No__
Any surgery that has required post-procedure in-hospital surveillance: Yes__ No__</td></tr>
<tr><td>Tattoos:
Yes__ No__</td><td>Intravenous drug user:
Yes__ No__

Nasal drug user:
Yes__ No__</td></tr>
<tr><td>Man who has sex with men:
Yes__ No__</td><td>Known hepatitis B virus infection:
Yes__ No__</td></tr>
<tr><td>Known HIV infection:
Yes__ No__</td><td>Have you ever had tattoos or body piercings?
Yes__ No__</td></tr>
<tr><td>Abnormal liver tests or with liver disease:</td><td>Healthcare workers or members of public</td></tr>
</table>

Yes__ No__	safety (e.g., correctional service officers or police) who have come into contact with blood at work through needle sticks or sharps injuries: Yes__ No__
A person who has undergone hemodialysis: YES__ NO__	Diagnosis of diabetes: YES__ NO__
Diagnosis of Cryoglobulinemia: YES__ NO__	Diagnosis of coronary artery disease: YES__ NO__
Diagnosis of renal failure: YES__ NO__	
Population deprived of liberty or previously incarcerated persons: YES _NO__	
HCV antibody detection test: Non-reactive: _____ Reactive: _____	
Viral load test: Positive: _____ Negative: _____ Not applicable: _____(in all cases where HCV antibody screening test is non-reactive).	
Case reported to Sivigila YES__ NO__	
The positive case has been followed up YES _NO__	
The patient has had access to a specialized consultation YES _NO__ Why?	
The patient was able to access treatment YES _NO__ Why?	
Date of completion:	
Name of the person doing the diligence:	

12.2 Annex 2. Information security for web applications in Hostinger with MySQL

Information security is a critical priority in the development and operation of web, mobile, and desktop applications. This section aims to provide an overview of best practices and security measures implemented and best practices to be performed during project execution to protect sensitive information and ensure the availability and integrity of the application.

I. **Authentication and Authorization**

1. Application access password: Secure and complex passwords must be used. The use of combinations of upper- and lower-case letters, numbers, and special characters is recommended. The password will be assigned directly at the time of user creation.

2. Two-factor authentication (2FA): Implement two-factor authentication to add a layer of security to application and database access. Two-factor authentication will work for access

to Hostinger, where the VPS server administration, MySql database, and web hosting configuration are located.

3. Role-based authorization for Hostinger: Establish appropriate roles and permissions to ensure access to the dashboard and administration of the server, hosting, and database of the project. The administration will be in charge of Crecemos - Laboratorio de Estrategias Digitales SAS, a strategic ally for the digital management of the Association, working on management issues, updates, software patches, and product updates. Access and permissions to additional users will be requested and established by the Colombian Association of Hepatology.

4. Role-based authorization for the application: Establish appropriate roles and permissions to ensure that users only have access to the parts of the application according to their responsibility. Three roles were defined with the following permissions:
a. SUPER ADMINISTRATOR: Will have full access to the web application where he/she can manage users, full access to the dashboard and download information, quick test upload, and viral test upload.

b. ADMINISTRATOR: Will have partial access to the web application where he/she will have access to the dashboard filtered by the medical institution to which he/she belongs and will be able to download the corresponding information, upload quick tests, and upload viral tests.
c. OPERATIVE: Will have partial access to the web application where he/she will be able to access the dashboard filtered by the medical institution to which he/she belongs, upload the rapid test, and upload the viral test.

5. Authorization and remote access to the database: Direct access to the database through some database viewer or terminal, you will have to access with user credentials, and password and have SSH authentication, which will be managed by Hostinger administrator staff. It is recommended not to access directly to the database in this way.

II. **Data Protection**

1. Data Encryption: HTTPS (SSL/TLS) implementation to encrypt the communication between the client and the server. Also, a proprietary API was implemented to channel communications with the database, and the storage of confidential information was configured especially for sensitive information:

a. Auto incremental and auto-generated ID for records in the database.

b. Relation of the information employing IDSs specific to each record.

c. Patient's ID only for linking rapid load test with viral load test.

d. Confidentiality of the patient's name in the database storage.

2. API Implementation: Development and implementation of a proprietary API Rest (backend) to channel and control direct communications with the database. The API has access to the database in secret and encrypted files inside the same server.

Authentication and authorization middlewares were implemented for user access and a layer of DTOs (Data Transfer Object) was implemented to validate the information that the API receives and responds to the capture web application (client). The connection to the private API is made by the capture web application (client) using its encrypted keys. The communication protocols allowed by the API:

a. GET: Get information, download information

b. POST: Upload quick test form, upload viral upload form, and user creation.

c. PUT Edit users

d. DELETE: No delete commands are allowed.

III. Updates and Patches

1. Keep Software Updated: Keep the operating system, the web server, the MySQL database, and all libraries and frameworks used updated with the latest security patches.

2. Audit Code: Perform regular security audits of application code to identify potential vulnerabilities and correct them promptly.

IV. Attack Protection

Firewalls and Security Filters: Configuration of firewalls and security filters to block malicious traffic and common attacks, such as brute force attacks and SQL injection. Hostinger features DDoS protection and a configurable firewall for SSH and HTTP protocols and port definition.

Security Monitoring: Periodic security monitoring to detect unusual or potentially malicious activity and generate alerts.

V. Backup and Recovery

1. Backups: Scheduling regular backups of the MySQL database and application files.

Storage of these copies in secure locations. Full server backups perform automated snapshots every week and even the possibility of generating manual snapshots on demand or application updates. In case of any vulnerability or inconvenience, it is possible to revert to a previous version quickly.

2. Business Continuity Plan: In case of any security incident, access vulnerability, or even server downtime, the following recovery and business continuity procedures are in place:

a. Backups and copies of the databases in a server outside Hostinger.

b. Repositories of the capture web application (Frontend) and the API (Backend) in Gitbuh for rapid deployment on a different server.

c. No dependency on a specific server to be able to deploy and run the application again.

d. Restoration of the latest database backup version.

VI. Education and Awareness

User and staff training: Educate Users Association staff and project participants from each medical institution about security practices, the importance of strong passwords, and how to recognize phishing attacks and other fraud attempts.

VII. Legal Compliance

Regulatory Compliance: Hostinger has data centers located in North America, Europe, Asia, and South America. Each server used for hosting web pages, web applications, and other services has encryption and information security certifications. Additionally, the aforementioned document is defined with the architecture and security protocols as requested in the acceptance criteria of the capture web application.

Conclusion

Information security is an ongoing and constantly evolving endeavor. This document provides a foundation for ensuring the security of a web application hosted by Hostinger with a MySQL database, but it is essential to continue to monitor and update security measures as the security threat evolves.

In addition to the measures mentioned above, it is recommended to perform regular penetration testing and collaborate with information security professionals to identify and address potential vulnerabilities.

Information security is an ongoing commitment and a shared responsibility for everyone involved in the development, management, and operation of the web application.

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