

Systematic Review Of Viral Hepatitis C Screening And Diagnosis: From The World To Cameroon

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Abstract

A diagnostic test is a tool that uses a technique or method based on a proven scientific principle and may or may not use equipment or materials to make a diagnosis of a disease. It is the starting point for the proper management of an infectious or non-infectious disease. This document is based on national, continental and international consensus on screening and diagnosis of hepatitis C. Articles from researchers in institutes and hospitals were also used. The selected papers are the most recent ones dealing with screening and diagnosis of hepatitis C. Whether in Cameroon or worldwide, the biological tests used in the screening and diagnostic algorithms for hepatitis C (HCV) include all the tests for anti-HCV antibody and HCV RNA detection. International consensus and strategies recommend screening with HCV EIA tests. However, in low- and middle-income countries such as Cameroon, rapid tests for hepatitis C antibodies are used. Cameroon, like other low and middle income countries in the world, should adopt algorithms that are adapted to their socio-economic context while ensuring the quality of the tests used.

1. Introduction

A diagnostic test is a tool using a technique or method based on a proven scientific principle and whether or not using equipment or material to make the diagnosis of a disease. This is the starting point for any good management of a disease be it infectious or not. Thus, a poor quality diagnostic test will lead to an inadequate drug prescription. The quality of a diagnostic test is therefore of paramount importance, and even more since the data it produces often enables decision-making in the field of public health. Thus, a poor quality test can mislead clinicians, but also be responsible for the wrong decisions made by decision-makers.

The close relationship between the quality of a test, the management of a patient and public health decisions has compelled the scientific communities to take steps to ensure the clarification, specificity, sensitivity and accuracy of diagnostic tests and any products involved in the performance of that test. Indeed, several scientific communities have focused on the quality of tests and continue to propose and sometimes impose on manufacturers norms and standards that govern the quality of any diagnostic test meant to be serious. Communities are sometimes regional, continental or international. An international standard or norm may sometimes not have no greater impact at the regional or continental level. Indeed, norms and standards can vary from one continent to another. While this variation can sometimes be controversial, the common goal of ensuring quality testing for quality diagnoses and reality-based public health decisions is to be welcomed.

If on the European continent there is a test validation community, in North America the FDA and internationally ISO standards, Africa is one

of the continents that does not have an African community for the quality of marketed diagnostic tests validation. Although every country in Africa is taking steps to ensure the commercialization of quality tests on the market, there are many tests marketed in Africa that have not received the endorsement of either the European community or the FDA or even the ISO standard. And even, if these diagnostic tests had been approved by one of these bodies, it would not immediately qualify that the said test is adequate for the African population, when we know that for some tests, the genetic diversity of the patient sought can have an impact on the results.

As diagnostic tests are variable and numerous and involve several different areas, we will focus our review on biological diagnostic tests for viral hepatitis C in Cameroon. We will first review the techniques and methods used for the screening and diagnosis of viral hepatitis C in the world and in Cameroon and, expose the standards of tests and algorithms that govern the use of these diagnostic methods.

2. Methodology

This document has been developed based on national, continental and international consensus on the screening and diagnosis of viral hepatitis C. Articles from researchers from institutes and hospitals were also used. The selected documents are the most recent that deal with hepatitis C screening and diagnosis.

3. Reminders (epidemiology & global strategy)

The viral hepatitis pandemic is taking a heavy toll on human lives, populations and health

systems. In 2013, viral hepatitis was the seventh leading cause of death worldwide. It is estimated to be responsible for 1.4 million deaths per year from acute infections as well as liver cancer and cirrhosis related to hepatitis, a figure comparable to those of HIV and tuberculosis. Of these, about 47% are attributable to hepatitis B virus, 48% to hepatitis C virus, and the rest to hepatitis A and E viruses. Viral hepatitis is also an increasing cause of death among people living with HIV. Approximately 2.9 million people living with HIV are co-infected with hepatitis C virus and 2.6 million with hepatitis B virus [1] (see Figure 1).

Viral hepatitis C is caused by the hepatitis C virus, it is a blood-borne infection, with transmission occurring mainly in early life and through injections or medical procedures performed in poor sanitary conditions, and less frequently through sexual contact. Hepatitis C is present all over the world. The most affected regions are central and eastern Asia, and northern and western Africa, where most infections are caused by injections or other medical procedures performed in poor sanitary conditions. Hepatitis C epidemics related to injection drug use affect all regions, and an estimated 67% of people who inject drugs are infected with hepatitis C virus [1].

Worldwide, 130 to 150 million people suffer from chronic hepatitis C. The number of people with hepatitis C is currently on the rise, despite the

existence of an effective cure [1].

In view of these alarming data, the World Organization took steps in 2016 to hope to eradicate viral hepatitis. This is the health sector's global strategy against viral hepatitis, 2016-2021[1]. As it can be seen from the architecture of the Global Health Sector Strategy on Viral Hepatitis, 2016-2021 (See Figure 2), the strategy focused on the five hepatitis viruses (hepatitis A, B, C, D and E). It is organized into five strategic orientations spread over 5 components. The objective of this strategy is to eliminate viral hepatitis as a major public health threat by 2030, through national, regional and international measures. To eliminate this threat, WHO in its strategy has invested in five key areas of intervention: vaccines, prevention of mother-to-child transmission, reduction of harmful effects on people who inject drugs, treatment and safety of injections, blood products and surgical procedures [1].

This last fundamental area, namely the safety of injections, blood products and surgical procedures, is the one that most concerns us in this document. Indeed, one of the ways to ensure the safety of blood products or their handling is through quality screenings using quality tests. It also involves strong recommendations, staff training but even better by recommendable screening and diagnostic techniques and methods, which respect norms and standards.

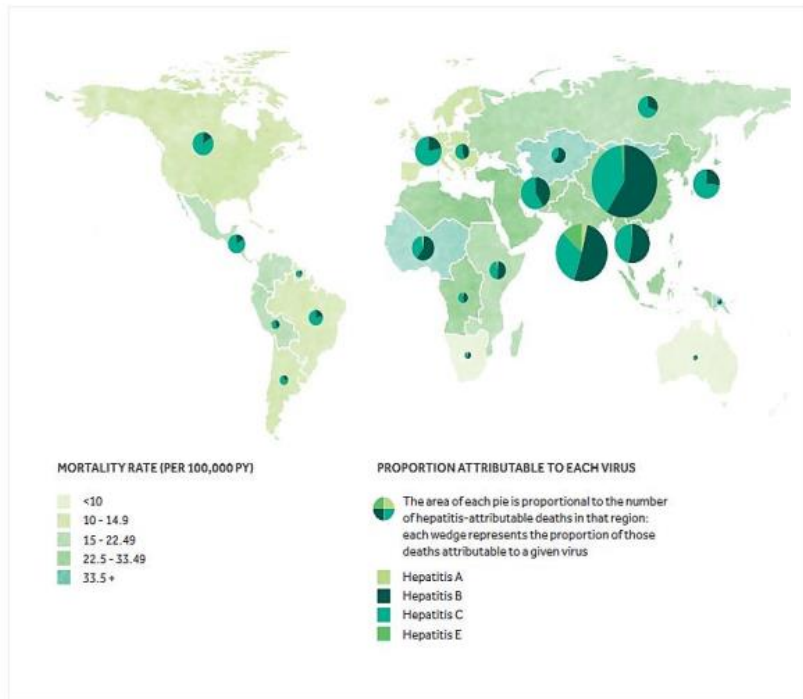
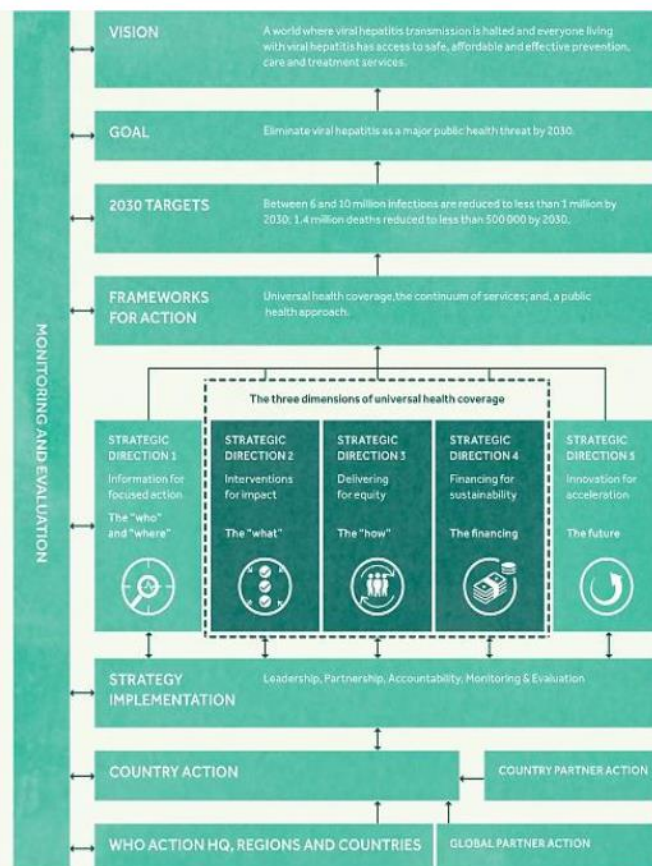


Figure 1. Regional distribution of deaths due to viral hepatitis.



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Figure 2. Framework for the global health sector strategy on viral hepatitis, 2016-2021

4. Techniques and methods, standards and algorithms for screening and diagnosis of viral hepatitis c (HCV)

In this part, we have taken the initiative to present the different diagnostic techniques and methods used to detect or confirm the diagnosis of viral hepatitis C infection.

4.1. America: Case of the United States

In the United States, agencies like the Centers

for Disease Control (CDC) and the FDA are heavily involved in quality control of tests and algorithms to be used for infection screening. For "biological testing" for hepatitis C, according to the CDC, two tests (See Figure 3) [2], an HCV antibody test and a qualitative HCV RNA test, should be used. As a first line if the subject to be tested is not immunocompromised, the algorithm recommends the use of an anti-HCV test. In case of positivity of the test, it is necessary to continue with a qualitative RNA test that will confirm an active infection. If the patient is immunocompromised, it is recommended to use a qualitative HCV RNA test as a first line. Anti-HCV and HCV RNA tests must all be approved by the FDA

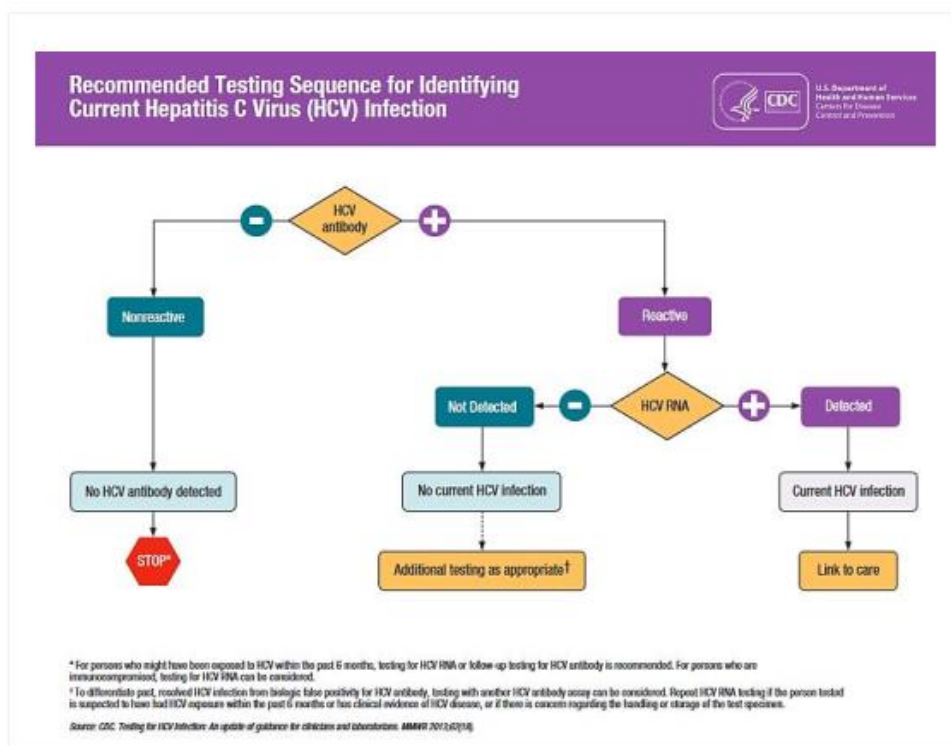


Figure 3. Recommended testing for identifying current hepatitis C virus

In the United States, other organizations, associations or institutes may propose other

algorithms, such as the MAYO CLINIC LABORATORIES algorithm, which offers an

algorithm for the screening and diagnosis of viral hepatitis C (Figure 4). This algorithm gives the indications underlying the use of the tests and,

the conditions that govern or not the continuation of the investigations [3].

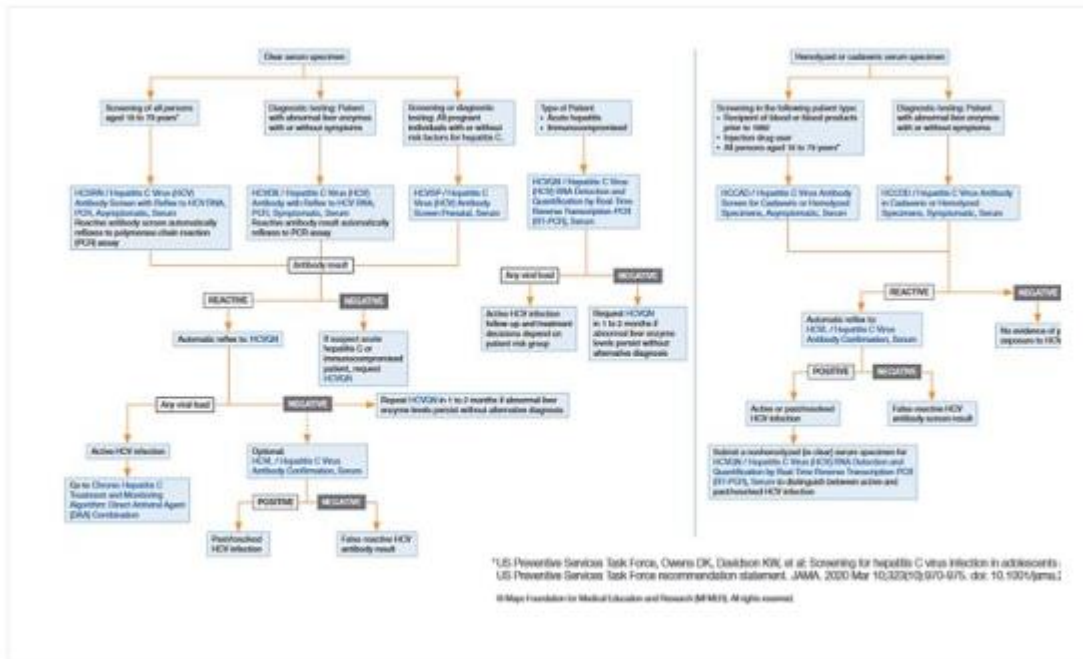


Figure 4. Hepatitis C, Testing Algorithm for Screening and Diagnosis

Regardless of the institution, in the United States two major groups of tests are allowed for the detection and diagnosis of viral hepatitis C: HCV antibody tests and HCV RNA tests.

HCV antibody tests [4]: These are tests that use the enzyme immunoassay or immunoblot (EIA) method for the detection of the HCV antibody. Tests approved by the FDA include:

- ABBOTT HCV EIA 2.0 :
- Chiron RIBA HCV 3.0 Strip Immunoblot Assay
- ABBOTT PRISM HCV
- Ortho HCV Version 3.0 ELISA Test System

HCV RNA detection tests [4]: these tests use the Polymerase Chain (PCR) technique. Being able to use different methods, automated or not, HCV RNA detection tests are based on the principle of a transition repeat of temperature cycles, allowing the amplification of hepatitis C

RNA so that it is detectable. Tests approved by the FDA include

- UltraQual HCV RT - PCR Assay
- COBAS AmpliScreen HCV Test
- Procleix HIV-1/HCV Assay
- Procleix Ultrio Assay
- Procleix Ultrio Plus Assays
- Hepatitis C Virus (HCV) Reverse Transcription (RT) Polymerase Chain Reaction (PCR) Assay

Regardless of the cost, the algorithms using antibody and HCV RNA detection tests used in the states in our opinion, make it possible not to miss a possible infection. There remains the problem of the seroconversion patient tested with anti-HCV. It is essential to take into account the notion of seroconversion when using the antibody test, the specialists here therefore recommend that even in case of negativity, the test should be repeated one to three months

later.

4.2. Europe: The case of France

Europe as in America organizes the "testing" of hepatitis C mainly around the detection of anti-HCV and the detection of HCV RNA with obviously some variables.

In Europe, the European Centre for Disease Prevention and Control is planning guidelines to reduce HCV transmission among vulnerable groups, and in particular among drug addicts, migrants and political prisoners [4,5]. In France, a national strategy recommends that doctors offer hepatitis C screening in subjects at risk (hemodialyzed, transfused before 1991, drug addicts, exposed health personnel, etc.).

Also in France, in 2011, a working group proposed to the High Authority of Health (HAS) "algorithms for the improvement of the screening of viral hepatitis B and C" [6]. Thus, the

biological HCV screening algorithm proposed by this working group is a sequential algorithm that begins with the search for anti-HCV. Following this work, the HAS validated the following recommendations (Figure 5):

« In case of HCV-negative AC, the screening result should be reported as follows: no contact with HCV unless recent infection before seroconversion or severe immunosuppression. In case of suspicion of recent infection, the HAS recommends retesting anti-HCV Antibodies (Ac) 3 months later. In a highly immunocompromised person, the HAS recommends performing a PCR search for HCV RNA on the first sample. In case of positive HCV anti-HCV Ac, the HAS recommends the control of serology by a new enzyme immunoassay (EIA) with another reagent on a second sample as provided for in the nomenclature of medical biology acts

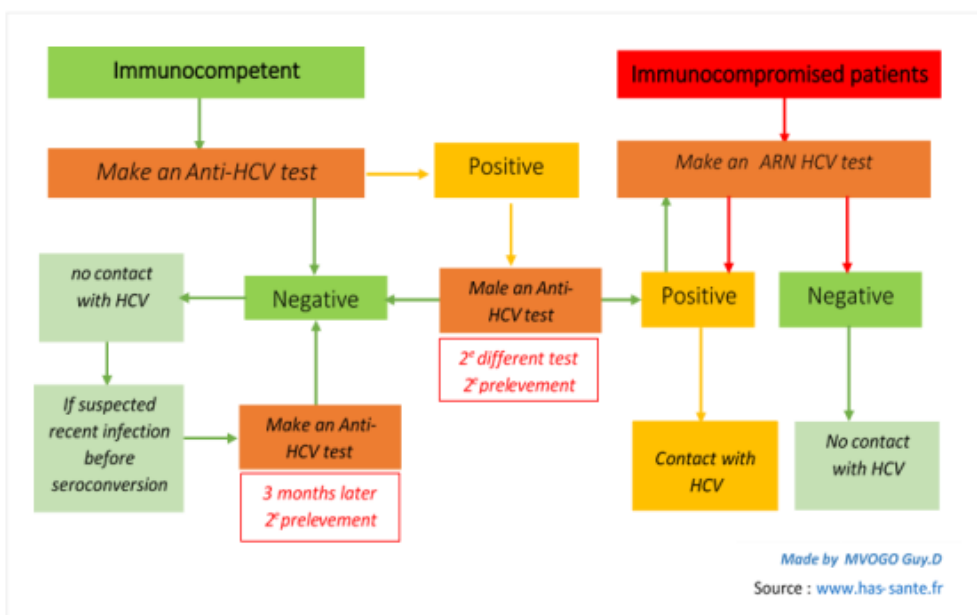


Figure 5. Recommended testing sequence by HAS

(act 3785). In case of positive control serology on the second sample, the result to be announced is contact with the HCV. In this situation, the HAS

recommends the search for HCV RNA by qualitative or quantitative PCR on this same second sample" [6].

Despite the quality strategies proposed in Europe, and the approved tests marketed, screening in countries such as France has not yet reached the desired level [4, 7-11]. A recent study on HCV morbidity in Europe estimated that screening needed to increase from 88,800 new cases diagnosed each year in 2015 in Europe to 180,000 in 2025 to meet the WHO target [4, 12].

4.3. Asia: The Case of China

In China, viral hepatitis C is an important cause of liver cirrhosis and hepatocellular carcinoma. There are about 10 million cases of chronic HCV infection in China, but more than 70% of HCV-infected patients in China still go undetected. In line with the World Health Organization's goal of eliminating viral hepatitis as a public health hazard by 2030.

Joint work by the China Union Liver Health Promotion Center, the Chinese Medical Association, the Chinese Society of Hepatology, the Chinese Medical Association, the Chinese Society of Laboratory Medicine, the Chinese Hospital Association and the Hospital Infection Management Committee [13], has provided a process for managing hospital-based viral hepatitis C screening in China. This trial established a hospital-based algorithm for multidisciplinary collaboration to eradicate viral hepatitis C.

As in the United States and France, tests for HCV infection include serological tests and nucleic acid tests. The difference here is that in China, in addition to HCV tests, HCV antigen tests are used. Specific tests and their meaning are included in

the Hepatitis C Guidelines (2019 edition) [14]. The process for managing viral hepatitis C testing in a hospital setting is as follows [13]:

- For patients who present for the first time, the first service must ask the appropriate services to carry out an HCV test and, if this test is negative, HCV infection can be largely eliminated.
- Once HCV is positive, the information service will alert the first consultation service through the hospital's information system and advise the hospital to consult the infectious diseases/liver disease department or request an HCV RNA test. If HCV RNA is still negative, the patient should not have a current HCV infection.
- If HCV RNA is positive, remind outpatients to seek prompt access to infection and hepatology services to evaluate antiviral therapy and inpatients to seek prompt access to infection and hepatology services to be referred to infection and hepatology services if necessary.

Xue Mei and Hongzhou Lu's 2021 review at Mainland China [15] already explained the approach to screening and diagnosis of viral hepatitis C in hospitals (Figure 6). A multidisciplinary approach (Figure 7) that focuses on promoting cost-effective screening among people at risk. According to them, this is an effective way to eradicate viral hepatitis C from China by 2030. At present, the prevalence of HCV antibodies in mainland China is about 0.91%, and injected drug use has become the main route of HCV transmission.

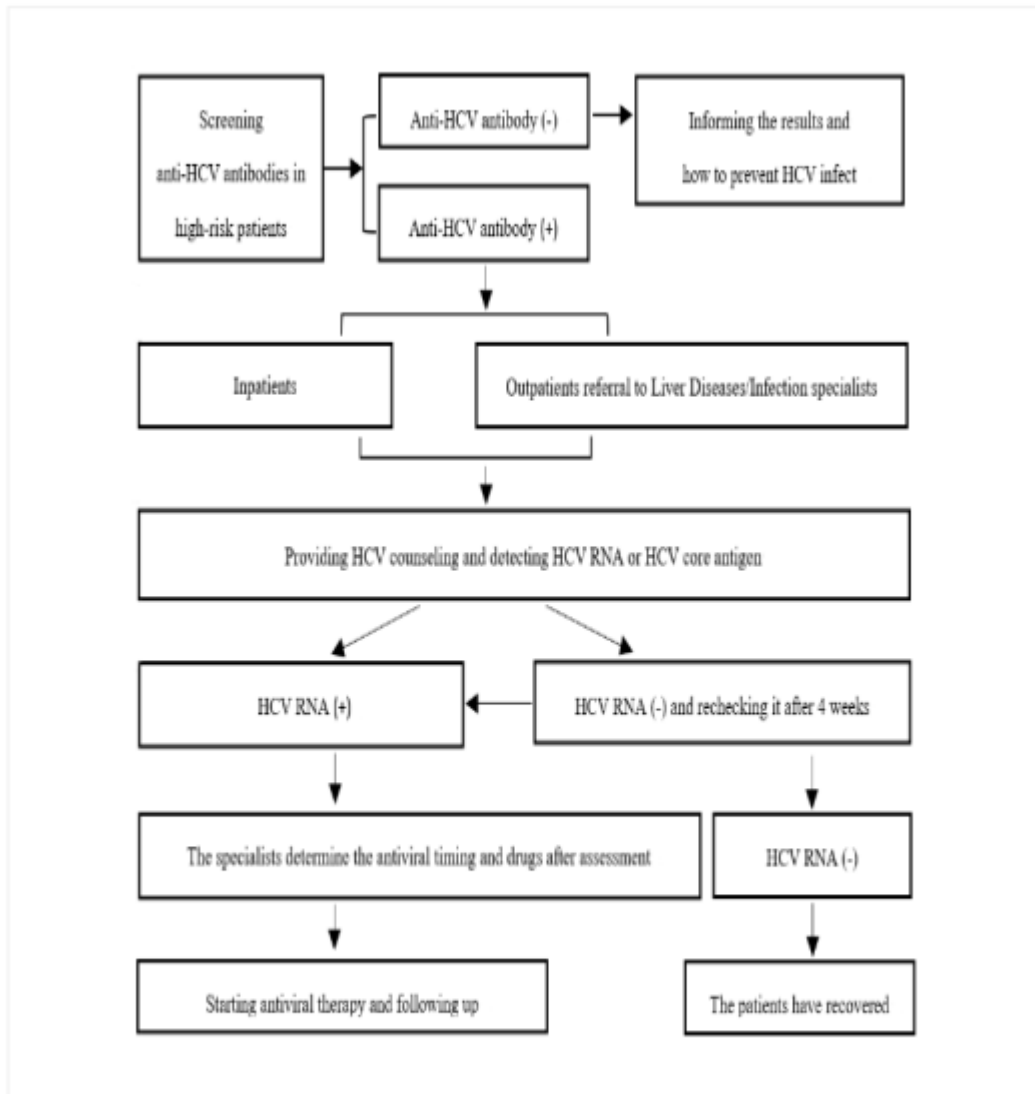


Figure 6. Flow chart for the process of in-hospital screening for hepatitis C in China

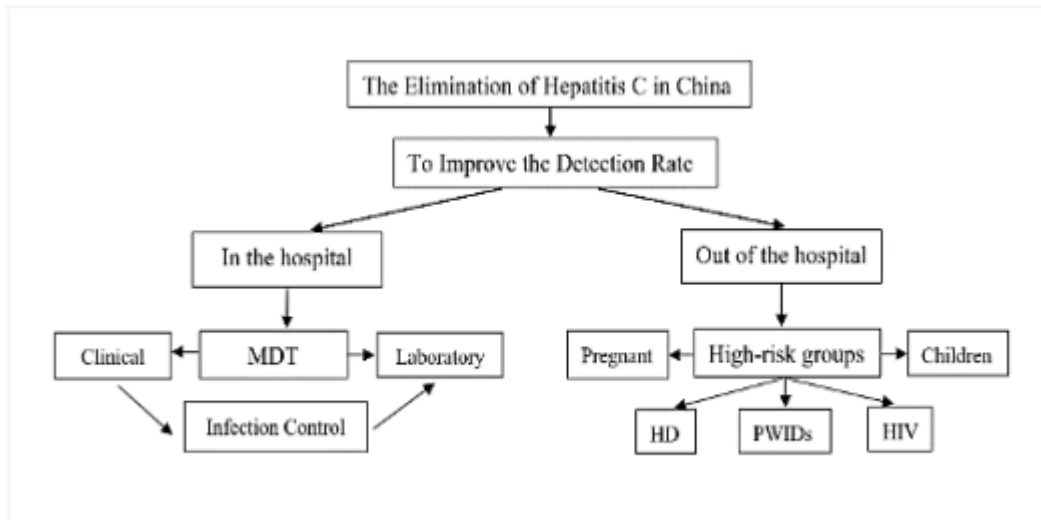


Figure 7. The elimination of hepatitis C in China. Abbreviations: MDT, multidisciplinary team; HD, hemodialysis; PWID patients who inject drugs; HIV, human immunodeficiency virus

4.4. Australia

In Australia, people at risk should be tested (Figure 7). According to Australian

recommendations for the management of hepatitis C virus infection: Consensus Statement (June 2020) [16], the appropriate screening test for HCV is serology (anti-HCV antibody), which indicates HCV exposure, either a recent or past infection. Recent HCV infection should be confirmed by a polymerase chain reaction (PCR) test for HCV RNA

- Box 2. Populations to consider for a hepatitis C virus (HCV) screening test**
- People who inject drugs or who have ever injected drugs
 - People in custodial settings
 - People with tattoos or body piercing
 - People who received a blood transfusion or organ transplant before 1990
 - People with coagulation disorders who received blood products or plasma-derived clotting factor treatment products before 1993
 - Children born to HCV-infected mothers
 - People infected with human immunodeficiency virus (HIV) or hepatitis B virus
 - Sexual partners of an HCV-infected person (individuals at higher risk of sexual transmission include men who have sex with men and people with HCV–HIV coinfection)
 - People with evidence of liver disease (persistently elevated alanine aminotransferase level)
 - People who have had a needle-stick injury
 - Migrants from high-prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Asia)

Figure 8. Populations to consider for a hepatitis C virus (HCV) screening Test

The figure 9 below summarizes these recommendations

Consensus recommendations	Grade
HCV seronegative people with risk factors for HCV transmission should be screened annually for HCV infection.	A1
The appropriate initial screening test for HCV infection is HCV serology (HCV antibodies).	A1
If HCV antibodies are detected, current infection should be confirmed by testing for HCV RNA using a sensitive PCR assay.	A1
Chronic HCV infection is defined by repeated HCV antibody positivity and HCV RNA positivity with a duration of infection longer than 6 months.	A1
HCV seropositive people with undetectable HCV RNA (either spontaneous or after treatment) and with ongoing risk factors for HCV transmission should be screened annually for HCV infection with HCV RNA (PCR).	A1

Figure 9. Consensus recommendations for screening and diagnosis of HCV in Australia

The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B) or low (C).

The GRADE system offers two grades of recommendation: strong (1) or weak (2). See figure 10 below. [17]

Evidence quality	Notes	Grade
High	Further research is very unlikely to change our confidence in the estimate of effect.	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	B
Low	Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate. Any change of estimate is uncertain.	C
Recommendation	Notes	Grade
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost.	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or higher resource consumption.	2

Figure 10. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

4.5. Africa: The case of Cameroon

The context in which screening and diagnosis of viral hepatitis C is carried out in Cameroon is that of low- and middle-income countries. Outside of low population income, the use of conventional serological enzyme immunoassays (AIEs) for screening is limited due to inadequate infrastructure, including laboratories, poorly or badly trained staff, and a poor management system. These problems are obstacles to quality screening. In these contexts, rapid tests are promising [18].

Indeed in Cameroon, rapid tests for the detection of HCV antibodies are used for the detection of viral hepatitis C. These tests offer definite advantages in this context. They are less expensive, do not require a high technical platform and are easy to use. In Cameroon, rapid tests are the most used in the periphery, they

allow first-line screening. If the patient has the means he will be able to confirm his serological status in appropriate laboratories that use EIA tests and even RNA detection tests. It can therefore be seen that in Cameroon, although there are EIA anti-HCV tests and HCV-RNA tests, the choice of rapid tests is appropriate for first-line screening. However, there is one problem that will be the subject of another article namely the quality of the tests. Indeed, on the Cameroonian market, rapid tests abound sometimes not approved by any learned society, nor by the Ministry of Public Health. These tests, sometimes of poor quality, are responsible for an underestimation or overestimation of the seroprevalence of viral hepatitis C. To overcome this problem, it is recommended to use only tests approved by learned societies. Because to be acceptable, a rapid test must meet standards, it must have a sensitivity and specificity almost equal to the EIA anti-HCV tests, they must be reproducible and of excellent accuracy. Unfortunately, the clinical performance of different tests is heterogeneous and varies

considerably [4, 19, 20].

Comparative studies show that rapid tests vary depending on the manufacturer and the nature of the sample [4, 21]. It is imperative to be vigilant in using rapid tests, and conduct independent research in order to evaluate their qualities in real conditions. Biologists should not rely solely on the indications of specificity and sensitivity mentioned in manufacturers' instructions. WHO has taken the initiative to evaluate two new HCV rapid tests, circulating in Cameroon, and, to date, has prequalified two RDTs that have shown excellent clinical sensitivity and specificity compared to standard EIA tests. These are the OraQuick and SD Bioline HCV rapid anti-HCV tests [4].

Although adding rapid tests, Cameroon respects the international algorithms that govern the

5. Conclusion and outlook

After touring the world and focusing on the how to test and diagnose viral hepatitis C, it seems obvious to us that Cameroon is a good student who respects international algorithms. However, these international algorithms that work more or less in other parts of the world are not always adapted to the socio-economic context of low- and middle-income countries. This is why rapid tests have been introduced into the screening process. An introduction that brings its share of problems, given that there are tests of dubious quality that deserve to be evaluated on the basis of a strict methodology.

The cost of EIA tests for the detection of HCV antibodies and the detection of HCV-RNA are not accessible to all classes of society, this issue, added to the fair technical platform are factors that will be a real obstacle to the achievement of the WHO objectives by 2030. Cameroon should, like other low- and middle-income countries in

screening and diagnosis of viral hepatitis C. EIA tests for the detection of antibodies of the virus are available, as well as tests for the detection of HCV-RNA. The problem is that this algorithm imposes a great financial cost that all layers of Cameroonian society cannot assume.

It should also be noted in Cameroon the presence, although rare, of tests for the detection of hepatitis C virus capsid antigen (cAg), which can be used as an alternative to the HCV-RNA test. This test offers the advantage of being less expensive and as specific as the HCV-RNA test. The Abbott HCV cAg test showed high performance also in patients co-infected with HIV and HBV in Cameroon [4, 22, 23]. The only problem is that this test requires a certain technical platform.

the world, adopt algorithms that are adapted to their socio-economic context while ensuring the quality of the tests used. We need screening and diagnostic algorithms that offer alternatives capable of replacing standard tests with new tests that are just as effective but at a lower cost. It is only through alternatives that countries such as Cameroon, in the context of low incomes, will be able to improve screening for viral hepatitis C and thus facilitate the referral of the patient for possible treatment.

Because we share the findings of Fourati S et al. (see figs. 11 and 12) [4], for the screening and diagnosis of viral hepatitis C, we propose for low- and middle-income countries such as Cameroon:

- The substitution in first line of EIA anti-HCV tests by approved rapid tests that have demonstrated a specificity and sensitivity almost equal to 100%
- Substitution of HCV-RNA tests by hepatitis C virus nucleocapsid antigen tests

- For the choice of tests for the detection of hepatitis C virus nucleocapsid antigen, favor "point of care" which does not require a large technical platform and whose use is easy
- If the HCV-RNA test is to be used, choose "point of care" for the qualitative detection of the RNA of the virus. These tests can be used at the periphery and do not require a large technical platform.

	HCV RNA using NAAT	HCV RNA using DBS	HCV RNA POCT	HCV c Ag
Analytical performances	Excellent sensitivity <25 IU/ml	Should only be used as a qualitative result	Expected to be excellent. Need to be determined in real life settings	Equivalent to 500 to 3000 IU/ml, according to the HCV genotype
Target population	Centralized settings* High income countries	Lack of access to sites or nearby laboratory facilities for NAAT Persons with poor venous access (e.g. in drug treatment programs, prisons).	Lack of access to sites or nearby laboratory facilities for NAAT if using fingerstick: Persons with poor venous access (e.g. in drug treatment programs, prisons).	Centralized settings Low and middle income countries
Specimen type	Serum/plasma requires venipuncture to obtain specimen	Fingerstick capillary whole blood samples	Whole blood samples but more data are warranted	Serum requires venipuncture to obtain specimen. Whole blood from DBS but sensitivity is poor
Time of result	Time to result: several hours/days and generally batched as one run	Several days	<120 min	<60 min
Laboratory infrastructure	Requires trained laboratory technician Requires laboratory facilities and equipment	Can be performed in decentralized settings	Can be performed in decentralized settings	Requires laboratory facilities and equipment
Standardization		Need for development of standardized protocols by manufacturers		

NAAT, nucleic acid amplification technologies; POC, point-of-care; HCV cAg , HCV core antigen.

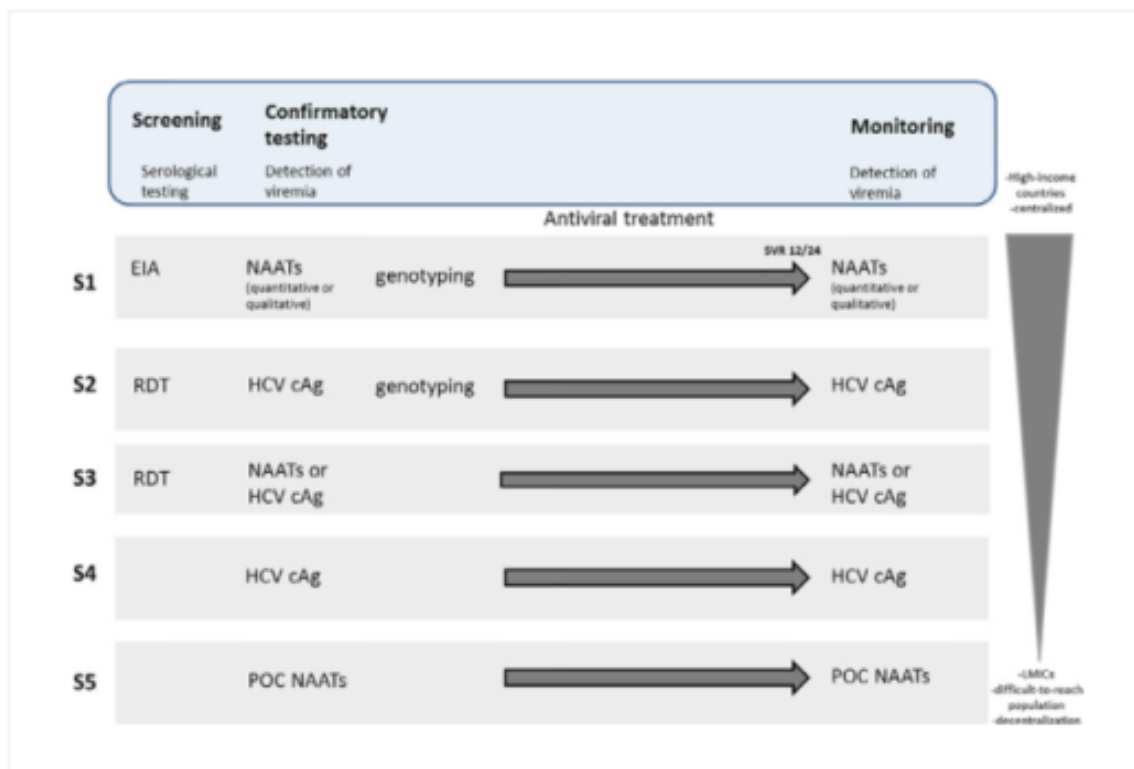


Figure 12. Proposed simplified algorithms using serological and virological tools for HCV screening, diagnosis and treatment follow-up. Several strategies are suggested with varying combinations (S1 to S4). EIA= enzyme

immunoassay; RDT=rapid diagnostic test; NAAT=nucleic acid amplification technologies; POC=point-of-care; HCV cAg=HCV core antigen. LMICs= Low and Middle Income Countries

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