



# Submerged People with Chronic HCV Infection: An Important Global Health Problem in the Era of Direct-Acting Antiviral Agents

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## ABSTRACT

Globally, the World Health Organization (WHO) estimated that 71 million people have chronic Hepatitis C Virus (HCV) infection. A significant number of these will develop cirrhosis or liver cancer. Currently, new direct-acting antiviral agents can cure more than 90% of HCV-infected patients. The new WHO strategy has introduced global goals-against viral hepatitis, including a reduction of 30% of new cases of HCV and a 10% reduction in mortality by 2020. However, a considerable number of people in the developing world have very limited access to diagnoses and treatment.

The HCV transmission has considerably changed, reflecting both the evolution of medicine and the health and social changes. The HCV is usually spread through blood-to-blood contact. After the discovery of HCV in 1989, antibody screening has drastically decreased the incidence of post-transfusion hepatitis. Currently, in many countries, routine blood donor screening by nucleic acid amplification testing for the presence of HCV RNA has been introduced. It is conceivable that the HCV screening could be offered to people born between the years 1946 and 1964 in the developed world and to people at major risk for HCV infection such as those who have received blood transfusions, blood products or organ donations before the 90s, prisoners, health care workers, drug users, infants born to HCV-infected women.

In conclusion, to achieve the HCV elimination the sanitary programmes should include: Improvement to health care services access, increased screening and new projects to identify a submerged portion of patients with HCV infection.

**Keywords:** Hepatitis C virus; Epidemiology; Screening; Public health

**Abbreviations:** HCV: Hepatitis C Virus; PWID: People Who Inject Drugs; CDC: Centers for Disease Control and Prevention; MSM: Men who have Sex with Men

## INTRODUCTION

Acute Hepatitis C Virus (HCV) infection in most cases (55%-85%) becomes chronic [1]. Chronic infection can either lead to mild illness or develop into liver cirrhosis, liver failure and hepatocellular carcinoma. According to the Centers for Disease Control and prevention (CDC), on 100 people infected with HCV, around 60-70 will develop chronic liver disease,

5 to 20 will develop cirrhosis in a period ranging from 20 to 30 years and from 1 to 5 people will die from the consequences of cirrhosis or Hepatocellular Carcinoma (HCC).

Chronic HCV infection without cirrhosis is however associated with worse quality of life and symptoms (eg. mood disorders and fatigue) than those who do not have this infection.

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On large cohorts of patients, it is also widely demonstrated that chronic HCV infection is accompanied by extrahepatic manifestations including lymphoproliferative disorders (eg. cryoglobulinemic syndrome and non-Hodgkin's lymphoma), type II diabetes mellitus, resistance to insulin, cardiovascular disease and kidney disease [2].

In 2015 about 71 million people lived with HCV infection, in 2017 19% (13.1 million) of them knew their infection status and only 15% (2 million) of people already diagnosed with infection with HCV received curative treatment in the same year. Overall, between 2014 and 2017, 5 million people received HCV infection eradication treatment, but in the same year, 1.75 million people recently developed a chronic HCV infection.

According to CDC data (2019) the number of deaths due to HCV infection in 2012 compared to 2015 increased from 18,650 to 19,629 (from 4.9 to 5.0 deaths/100,000) and decreased to 18,153 in 2016 (4.5 deaths/100,000). According to Eurostat data, Italy ranks in first place for the highest mortality rate due to viral hepatitis among the EU member states, with 40 deaths from viral hepatitis per million inhabitants. In a recent Italian study, conducted by analyzing data from the national registry of causes of death, on all deaths of subjects aged  $\geq 20$  years, HCV infection was found in 1.6% (corresponding to 27,730 deaths). The mortality rate associated with HCV infection increases exponentially with age in both sexes and it is higher in southern Italy, with the highest peak among elderly people  $\geq 60$  years old [3].

According to WHO data, worldwide less than 5% of people with the chronic viral infection are aware of their condition. The increase in early detection of HCV requires the use of effective diagnostic approaches, as well as a link to services for care and treatment. Currently, only 9 countries are on track to achieve the WHO HCV elimination targets by 2030.

According to the European Association for the study of the liver, given the new therapeutic options that allow the eradication of the infection, the emphasis of this branch of hepatology has passed to screening, diagnostic strategies and access to treatment of infected people.

The new DAAs have drastically changed the HCV management and hence the reservoir of infection and infectivity has taken a great interest in terms of HCV elimination. Submerged people with HCV infection is constituted by both people who are unaware of their condition and diagnosed people with HCV but not yet treated [4].

The goal of public health programs is to detect many infected people possibly before they progress to clinical manifestations of

the disease. This goal is possible taking into account all routes of transmission.

Therefore, due to the importance of this matter, this review will examine and discuss the epidemiological changes in contracting HCV, highlighted the ways to identify a submerged portion of patients with HCV infection [5].

## LITERATURE REVIEW

### Epidemiology of chronic hepatitis C virus infection

Gower, et al. showed that the global serological prevalence of people with a history of Hepatitis C Virus infection (HCV)-the presence of anti-HCV antibodies-was 1.6% (range 1.3%-2.1%), the value that reached 2.0% among adults (defined as those older than 15 years old). The test for anti-HCV antibodies may remain positive even after the virus clearance; moreover, a minimum rate may be instead falsely positive.

Therefore, the estimated prevalence of people in whom HCV-RNA is detectable correspond to 1.1% (range 0.9%-1.4%) in the entire population and correspond to 1.4% when we consider only those over 15 years [6].

Saraswat, et al. taking into account 15 countries (Argentina, Finland, Greece, India, Ireland, Israel, Luxembourg, Mexico, Mongolia, Netherlands, New Zealand, Norway, Poland, Russia, South Africa) showed a prevalence of HCV RNA that varied between 0.13% in the Netherlands and 2.91% in Russia.

A recent review published the viraemic prevalence in 17 countries (Bahrain, Bulgaria, Cameroon, Colombia, Croatia, Dominican Republic, Ethiopia, Ghana, Hong Kong, Jordan, Kazakhstan, Malaysia, Morocco, Nigeria, Oman, Qatar, Taiwan). In this study, the viraemic prevalence varied between 0.2% in Hong Kong and 2.4% in Taiwan, while the largest viraemic populations were in Nigeria (2,597,000 cases) and Taiwan (569,000 cases).

Moreover, of the estimated 10.2 million people incarcerated worldwide in 2014, Dolan et al. estimated that 15.1% have HCV infection [7].

The HCV is a major cause of liver disease. The incidence of hepatocellular carcinoma increases in both sexes with increasing age. In HCV patients the cumulative risk of evolving to hepatocellular carcinoma in the age group between 40 and 74 years is 21.6% among males and 8.7% among females. The main routes of HCV transmission are summarized in Table 1.

**Table 1:** People at high risk for HCV.

High risk factors for HCV
People using drug
Recipients of infected blood products or invasive procedures in health-care facilities with inadequate infection control practices
People with HIV infection

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 Children born to mothers infected with HCV
 

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 People interned in prisons
 

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 Household and sexual contacts of people with chronic HCV infection
 

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 People who have had tattoos or piercings.
 

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In April 2014, the WHO published the first guidelines on HCV, which point out how HCV infection takes a different path from other chronic viral infections (including HIV infection) because currently available therapies allow eradication. The guidelines are divided into nine recommendations, which include various aspects: The indication to increase the number of people subject to screening, suggestions on how to reduce the damage to the liver and what treatments to use for different cases, according to drugs approved up to December 2013. These guidelines were then updated in 2016 because other new drugs were approved in the meantime [8]. On 24 May 2014, a WHO's follow-up resolution called on the member states to develop and put into practice a national program based on epidemiological data. The new WHO strategy introduces global goals-against viral hepatitis. This includes a reduction of 30% of new cases of HBV and HCV and 10% reduction in mortality by 2020.

## DISCUSSION

### People at risk of hepatitis C virus infection transmission and reservoir of infection

**HCV transmission by blood:** The HCV transmission has considerably changed, reflecting both the evolution of medicine, in particular, the cloning of the HCV and the health and social changes. The main ways of HCV transmission are parenteral exposure, in apparent parenteral transmission and occupational exposure. Blood transfusion was the major risk factor for HCV infection before donor screening for surrogate marker testing for non-A, non-B hepatitis began in the mid-1980s, followed by screening for antibody to HCV in 1990. After 1985, the incidence of post-transfusion HCV infection has been halved by excluding HIV-positive people in developed countries. Besides, since 1993 the availability of more sensitive tests has further reduced this prevalence. However, given that in recently infected donors' blood the anti-HCV antibodies aren't detectable for several weeks or months, in some countries all donations are tested by nucleic acid amplification tests for the presence of HCV RNA. WHO reports that 39 countries do not routinely screen blood transfusions for blood-borne viruses. The generalized epidemic of HCV infection in Egypt is an example of health-care-associated transmission originating from unsafe injection practices, where, in 2015, HCV RNA prevalence was 7.7% in some regions [9].

In Italy, in 2013, the prevalence resulted in 80.8/100,000 first time donors and the incidence rate resulted in 2.5/100,000 first time donors.

Blood-to-blood HCV transmission also occurs through hemodialysis and it is more evident in developing populations. According to recent data, the range is between 8.5% and 62.7%. However, the results of the dialysis outcomes and practice patterns study, conducted in 308 dialysis centers in the industrialized world (France, Germany, Italy, Spain, United Kingdom, Japan and the United States) for a total of 8,615 patients on hemodialysis showed a prevalence of anti-HCV positive patients ranged between 3% and 23%. In Italy, from 1995 to 2003, the prevalence of HCV infection among long-term dialysis patients decreased significantly from 30.6% to 15.1% ( $P < 0.001$ ).

**Baby boomers:** Baby boomers are people born after the second world war roughly between the years of 1946 and 1964. HCV infection is common in the baby boomers probably because the age cohort of the baby boomer comprised a large proportion of persons who have used illicit drugs in their lifetimes [10].

Considering the ongoing transmission of HCV in People Who Inject Drugs (PWID), it is of importance to highlight the harm reduction efforts due to needle and syringe programs and opioid substitution therapy. Moreover, the DAA treatment in these populations at higher risk of contracting infection could potentially decrease transmission but much more re-infections.

Joy, et al. in a recent review reveal the early HCV epidemic dynamics in north America. In particular, they demonstrate that the expansion of genotype 1a before 1965 could be due to nosocomial or iatrogenic factors rather than past sporadic behavioral risk (such as experimentation with injection drug use, unsafe tattooing, high-risk sex) were key contributors to the HCV epidemic in north America. These results, therefore, suggest to increase rates of HCV screening and treatment and reduce stigmatization around HCV screening and diagnosis. Starting from 2012, the Centers for Disease Control and prevention (CDC) recommended 1-time HCV testing of all baby boomers.

**Intravenous drug users:** The HCV infection is very common in persons who inject drugs, in whom the HIV co-infection is very common. Injection drug use is the main risk factor for HCV transmission in both Europe and the United States. A recent systematic review has been conducted to estimate the anti-HCV prevalence on PWID, identifying eligible 77 countries out of 152 countries considered, corresponding to about 82% of the estimated world population of PWID. The results of this review showed that the prevalence of HCV infection in drug users exceeded 80% in 12 countries including Italy, it was between 60% and 80% in 25 countries including the United States and

Asia, it was between 40% and 80% in 24 countries including Australia and Britain, it was less than 40% in 16 countries, including Turkey. The data were not available for 74 countries. The number of new cases of HCV declined precipitously between 1990 and 2005.

Considering the ongoing transmission of HCV in PWID, it is of importance to highlight the harm reduction efforts due to needle and syringe programs and opioid substitution therapy. Moreover, the direct-acting antiviral treatment in these populations at higher risk of contracting infection could potentially decrease transmission but much more re-infections [11].

Currently, PWIDs represent the majority of people with HCV in many countries throughout the world. New cases of HCV have increased three-fold between 2005 and 2015. Approximately 50% of PWID have been exposed to HCV and 25% of these persons are under the age of 25 years. However, PWID access healthcare and receive HCV treatment at much lower rates than “baby boomers”. There are many reasons for this, such as no other medical disorders associated with HCV that require or seek medical care, a higher rate of mental health issues, which is why physicians consider PWID to be non-compliant.

**Sexually transmitted disease:** This route of transmission is possible in HCV patients, but lesser frequent than in HBV patients (about 1%). The incidence rate of HCV transmission of 0.37 per 1,000 person-years were observed in monogamous couplet during a follow-up period of 10 years. HCV transmission is higher in heterosexuals with multiple partners, or in those in whom coexists a sexually transmitted infection (0.4%-1.8% per year) compared to monogamous heterosexual’s transmission. Recently, HCV is considered an emerging infection among sexually transmitted infections among Men who have Sex with Men (MSM), particularly in HIV-infected patients. People with HIV are at high risk of HCV infection. The HCV/HIV coinfection is common, the prevalence is between 9% and 37.3% and it is probably due to the common route of transmission of these infections.

A UK survey of HIV has revealed an increase in new cases of HCV in MSM from 6.86 cases/person-years in 2002 to 11.58 in 2006, almost doubled, with no apparent change in the test policy. Recently, there was a change of current HCV infection, with an increased incidence of MSM than PWID. This trend was confirmed in the analysis of the Swiss study outlining an increase of 18 times the incidence of new cases of MSM from 0.23 (95% CI: 0.08 to 0.54) per 100 person-years in 1998 to 4.09 (95% CI: 2.57 to 6.18) in 2011.

In the European studies, the predominant genotype in the MSM was the genotype 1a (59%), with a surprisingly high percentage of 4d genotype (23%).

Worldwide about 30% of HIV people are HCV or HBV co-infected. Generally, HIV/HCV co-infection is more common in individuals who have a history of injection drug use. Several studies have also shown that these co-infections are at major risk of liver fibrosis progression with consequent evolution to cirrhosis. HIV infected subjects are at risk of contracting viral

hepatitis. In Tuscany, in five years of monitoring, it has been seen that co-infected patients showed a prevalence of 7.8%, of whom 91.5% were Italian. In HIV/HCV co-infected people, 52.8% were injection drug users. The HCV patients didn’t show a particular association with advanced HIV disease, possibly because the tests were performed earlier. The reasons associated with the execution of the tests were mainly related to the perception of the risk, or the test was carried out because it was offered by the drug addiction services or offered in prison. Therefore, these data do not represent a random sample of the whole sub-population. These data show a higher prevalence of HCV infection in HIV-positive foreigners than Italians. Moreover, HIV/HBV co-infected patients were at higher risk to be late presenter, advanced HIV disease and AIDS. The prevalence of HIV/HCV is high in injection drug users and the age group 35-59 years. This also confirms the finding of a less advanced stage of the disease in these patients, reasonably due to a greater perception of risk of disease that could induce them to run the earlier tests.

**Interfamilial transmission:** According to a recent meta-analysis, the vertical transmission has resulted in 5.8% (95% CI=4.2%-7.8%) in children of mothers with anti-HCV antibodies and HCV-RNA positive. Prevalence was up to 10.8% (95% CI, 7.6%-15.2%) for children of HIV-positive women.

Contrary to what was observed for HIV transmission, in the case of HCV, the execution of caesarean section has not proved useful in reducing the risk of neonatal infection, although the prolonged rupture of the membrane can increase the risk. There are no pieces of evidence of infection transmission through breast-feeding, which is therefore not contraindicated.

As outlined by Indolfi, et al., the limits of several studies on horizontal transmission are due to the limited phylogenetic analyses, demonstrating that different individuals of the same family or households are infected with viruses with very similar genomic sequences. The virological confirmation that a horizontal transmission event has appeared is supported by a high rate of sequence homology found between the HCV genome of infected patients and the HCV genome of their infected contacts. Moreover, interfamilial HCV transmission is called into question for both the non-sexual transmission mediated by close contact with infected domestic objects and sexual transmission. It is for this reason that the prevalence reported in several studies is extremely variable.

**Health care worker’s transmission:** The unapparent blood contact causes HCV transmission. Therefore, in addition to patients, health care workers may be at risk of contracting HCV infection, in the event of accidental exposure to the blood of infected individuals. The studies reveal if one ignores the limitations of the data, an average risk after parenteral exposure of 1.9%.

### The screening: Is this the correct way?

On the occasion of world hepatitis day in July 2019, the WHO called on all states to “invest in eliminating hepatitis”. 124 countries out of 194 have developed plans to reach this goal, but over 40% of national plans do not have dedicated budget lines



to support the acts aimed at achieving the objective of elimination. Furthermore, globally less than 5% of people with chronic viral infection know their status (unknown infection). Against this background, the screening for HCV infection can be considered a useful pathway aimed at the emergence of the unknown infected people. Already in 2016, the centers for disease control and prevention considered adults to be screened adults born between 1945 and 1965 (Baby boomers). These subjects must be tested at least once for HCV infection (without prior assessment of HCV risk factors). The anti-HCV test was also recommended for drug users; to those who have always used drugs by injection or to those who have used drugs a few times in previous years; people who received concentrations of coagulation factors produced before 1987; or that are subjected to long-term hemodialysis; or with persistently abnormal levels of ALT or HIV infection. Screening for HCV is also recommended for individuals who have been recipients of previous transfusions or organ transplants, including people who have been informed that they received blood from a donor who reported that it is significantly positive within the HCV infection or who had received a blood transfusion, blood components or organ transplant before July 1992. The CDC recommended performing the HCV test following exposure recognized by the skin or mucous membranes to needles, sharp objects contaminated with blood HCV positive for HCV-positive agents. Besides, for people who may have been exposed to HCV within the last 6 months, the execution of the HCV-RNA test or follow-up for HCV antibody is recommended. In 2017, the insurance of the American association for the study of liver diseases and the infectious diseases society of America recommended instead of performing the HCV test for people born between 1945 and 1965 (ascertained by the country of birth) without a risk assessment. All other people recommended screening for HCV infection risk factors and performing a one-off test for all people with associated changes, conditions and conditions and risk of HCV infection. According to them, all people with active HCV infection must be taken in charge of managing a complete disease.

Recently, recommendations for "Screening for hepatitis C virus infection in adolescents and adults: A systematic update of the review" have been published by the US preventive services task force. These suggestions have an extension of the proportion of the population to be screened screening for HCV infection is foreseen in all adults aged 18 to 79 years (USA task force preventive services, 2019). The assessments are qualified with a type B level of proof or there is a high certainty that the net benefit is moderate or there is an unmistakable certainty that the net benefit is moderate to substantial [12].

## CONCLUSION

This review provides evidence of changing epidemiology of HCV transmission with a major prevalence in old population. Therefore, given the high prevalence in these groups of patients, it is conceivable that an anti-HCV screening, with subsequent detection of HCV-RNA, could be offered to people born

between the years of 1946 and 1964 to greatly reduce by anti-viral treatment the HCV infection in the world. Programmes to eliminate HCV should include: Improvement to health care services access, increased screening and new projects to identify a submerged portion of patients with chronic HCV infection.

Yet it is really necessary to remember the hundreds of thousands of people in the developing world who have very limited access to HCV diagnostics and treatment.

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