Epidemiology of hepatitis C virus infection in the world, Europe, Italy and Campania: an overview *

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Abstract

HCV infection is today the viral epidemic disease second only to AIDS. It is estimated that 3% of the world population is infected by hepatitis C and chronic related diseases, with markedly different prevalences between different geographical areas and different categories in the same area.
The Authors analyse the epidemiological data available to trace the situation worldwide, in Europe, in Italy and in Campania, currently and in the last few years. Also researched was the role that the risk factors related to the different transmission routes play in the spread of the infection.
Despite the decrease in the incidence reported in recent years, the numerous cases linked to drug abuse, to infections occurring while in health care and after unsafe sexual intercourse reveal the need for further information to be spread on HCV infection and on its modes of transmission.

Key words: hepatitis C, epidemiology, transmission modes

The hepatitis C virus (HCV) is one of the six viruses identified so far as the etiological agents of viral hepatitis. From 1965, the year the diagnostic test was developed to determine the antigens of the hepatitis B virus (HBV), and 1973, those of the hepatitis A virus (HAV), it became clear that many cases of post-transfusion and sporadic hepatitis were not attributable to these two viruses, but to agents that for a long time remained unknown and were thus termed non-A non-B (NANB) viruses.The hepatitis Delta virus (HDV) was identified in 1977, and the hepatitis E virus (HEV) in 1980.

The HCV genome was characterized in 1989; this made it possible to clone a recombinant antigen associated to it that could identify the anti-HCV antibodies present in the serum of subjects with NANB hepatitis, thus leading to the development of the first diagnostic tests.

After the identification of HCV, which proved to be responsible for about 80% of NANB hepatitis, it was still clear that some viral liver diseases were not caused by any of the five known viruses; even with the subsequent identification of the hepatitis G virus (HGV) it was not always possible to establish the etiology.[1]

Because of the philogenetic relation with the Flavivirus and Pestivirus genera, HCV is at present classified to the family of Flaviviridae. The virus is made up of a spherical particle of about 50 nm in diameter with a lipoproteic envelope covering a single-stranded positive-sense RNA molecule of around 9400 nucleotides. This genome contains one open reading frame (ORF) gene, which encodes a polyprotein of around 3011 amino acids from which the various viral proteins derive due to a combined host/virus protease action.

Based on the genetic heterogeneity of HCV, it is divided into at least six genotypes, defined according to the classification proposed by Simmonds in 1993, that differ in about 30% of the nucleotide sequences. Each genotype in turn is made up of a number of subtypes that differ in about 20% of the nucleotide sequences; each subtype comprises numerous variants (quasispecies) that have 85-98% of the sequences in common.[2,3] Despite the fact that the continual discovery of genetically different viral strains shows that the genome of the virus is subject to continuous modification, this classification is still generally applied.[1]

The marked tendency to chronicity of the infection, reinfection sustained by strains that are genotypically very similar to those responsible for the primary infection, the often unsatisfactory efficacy of therapy and the difficulty incurred in developing vaccines are due to the genetic variability of HCV and to its high capacity to mutate.[1] This heterogeneity, the presence of host predisposing factors and repeated exposure account for the wide distribution of HCV infection.

Table 1. Estimated world prevalence of hepatitis C and number infected (Weekly Epidemiological Record No. 49, 1999; modified)

WHO regions	population (millions)	rate (%)	infected subjects (millions)	data not available *
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
East Mediterranean	466	4.6	21.3	5
Europe	858	1.0	8.9	19
South-East Asia	1500	2.1	32.3	3
West Pacific	1600	3.9	62.2	11
TOTAL	**5811**	**18.7**	**169.7**	**57**

* Number of countries

In the last two decades hepatitis C has become the second most widespread disease after AIDS and constitutes one of the greatest health problems worldwide.[4] The WHO estimates that about 169.7 million subjects, i.e. 3% of the world population, are infected by HCV, with higher prevalences in Africa and the Eastern Mediterranean, the Western Pacific and South-East Asia than in America and Europe (Table 1).[5] In 2001 the WHO estimated a total of 46,000 deaths related to HCV infection, reporting for South-East Asia and the Western Pacific values about twice those of the rest of the world.[6]

Besides a different diffusion of the infection there is a varying geographical distribution of the different viral genotypes: while 1, 2 and 3 and their subtypes are ubiquitous (with a higher prevalence in Western Europe and in the USA), 4 is more widespread in North and Central Africa, 5 is more frequent in South Africa, and 6 in Asia.[7]

In the USA hepatitis C is the most widespread of the hemotransmitted diseases; the Third National Health and Nutrition Examination Survey (NHANES III) indicated that about 3.9 million (1.8%) Americans were infected by HCV between 1988 and 1994. The death rate for non-A non-B hepatitis rose from 0.4 to 1.8/100,000 subjects per year from 1982 to 1999, the year in which 3759 deaths were related to hepatitis C alone; the number of new cases estimated by the Centers for Disease Control and Prevention (CDC) in 2001 was 25,000.[8,9]

In Australia, where the number of cases notified per year is 500 but the actual number estimated is as high as 16,000, around 210,000 individuals are estimated to be infected.[10]

In Africa the WHO estimates a prevalence of 5.3%, with a different distribution in the different regions: in Sub-Saharan Africa, where the overall rate is 3%, the prevalences are 6% in the central regions, 2.4% in the west and 1.6% in the east and south.[11]

In Japan the number of individuals infected is two million.[12]

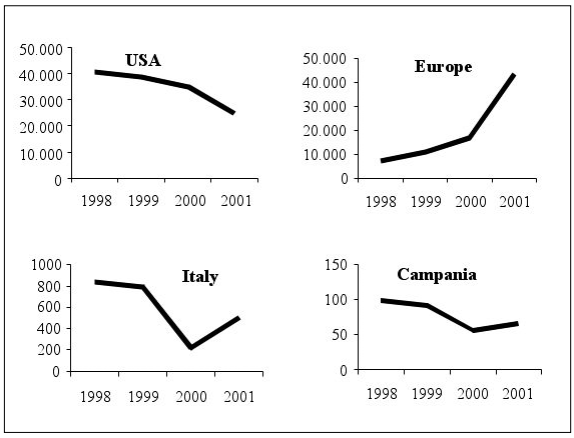
In Europe the WHO reported an average prevalence for 2001 between 1 and 2.5%; only in Ukraine and Romania higher values were reported (2.5-10%), while for Estonia, Leetonia and Lithuania the prevalence was below 1%.[13]

For Italy the prevalence is 0.5%.[5] On its website www.who.dk, the WHO Regional Office for Europe reports 503 new cases of HCV infection registered in 2001. According to the Sistema Nazionale di Sorveglianza Epidemiologica Integrata delle Epatiti Virali Acute (SEIEVA), (data available on the website www.seieva.iss.it), the incidence of NANB hepatitis in Italy dropped from 4 to 1/100,000 from 1986 to 1999 independently of geographical area and sex, particularly in the 15-24 age group; no significant differences were recorded between areas in the North and those in the South; the related death rate is 0.3%.[14]

For the Campania region, the Sistema Informatizzato delle Malattie Infettive (SIMI) recorded 580 new cases of NANB hepatitis from 1996 to 2002. In those years the incidence followed a downward trend, going from 2.72 to 0.26% (data available on the website http://www.simi.iss.it).

The infection involves subjects of all ages. However, the incidence reported in the USA is higher in the 20-39 age group, with slightly higher values for males; in the general population the prevalence is highest in subjects between 30 and

Figure 1. New cases of hepatitis C, 1998-2001 (CDC, WHO Regional Office for Europe, SEIEVA and SIMI, modified)



49 years and in males.[8] In Italy, SEIEVA recorded up to a few years ago the highest incidence in the 14 to 25 age group; today, instead, the cases notified for subjects over 25 years are just as frequent, and the highest prevalence (>30%) is recorded for the elderly.[14,15] For Campania, SIMI has found the highest frequency in the 25-64 age groups, although the number of new cases has decreased in recent years also in these age groups.

As seen in Figure 1, the available epidemiological data indicate a decrease for Italy and Campania in the incidence of hepatitis C in recent years, similar to the trend in USA but not in Europe. We must remember, however, that the information regarding Europe as a whole does not reflect the real situation, since official data are not always available for all European countries, and where they are available are somewhat discordant.

The virus is transmitted parenterally and, albeit to a lesser degree, also by unapparent parenteral routes. Infection occurs directly and through contaminating vehicles: HCV-RNA can persist in a dry environment at room temperature up to 48 hours.[1,2,16]

Since the routes of transmission are the same as for HIV, subjects with AIDS are often infected by hepatitis C. In USA around 200,000 subjects are infected by HCV and HIV.[18] Ten per cent of HCV-positive subjects are also HIV-positive, and 25% of the HIV-positive are also HCV-positive.[19] Several studies have shown that hepatitis C evolves more rapidly in subjects with AIDS, because HIV-induced immunodepression determines an increase in the HCV levels in the blood, while the liver damage caused by HCV negatively influences the therapeutic management of HIV infection.[19]

The onset of the disease in 15-25% of subjects is acute and rarely resolves without further problems. In the majority of cases (80-85%) it progresses to a chronic infection and in 60-70% of these to chronic hepatitis. Ten to twenty per cent of subjects with chronic hepatitis progress to liver cirrhosis over a period of 20-30 years, and 1-5% to hepatocellular carcinoma.[2,8,16] In the USA these chronic diseases are the main causes of liver transplant in adults, which have increased 5-fold in the decade 1990-2000 for HCV-infected subjects.[9] According to the CDC chronic liver diseases (involving 2,700,000 subjects in the USA and causing around 25,000 deaths per year) are the 10th highest cause of death in adults and 40% of these are related to HCV alone.[8] Projections for the future envisage a 4-fold increase in the number of subjects at risk of developing a chronic liver disease.[9] With one million new cases per year liver carcinoma is the 5th most frequent tumour worldwide and it is estimated to cause one million deaths per year; it is endemic in South-East Asia and Sub-Saharan Africa; it develops in general two or more decades after infection and the risk is greater for subjects with cirrhosis or severe fibrosis. Other predisposing factors are age, male sex, HBV co-infection and alcohol consumption.[20,21] HCV also plays an important role in the development of colangiocarcinoma: in Japan 30% of patients with this disease have anti-HCV antibodies.[22] Several studies, conducted in Italy, demonstrated a correlation between HCV infection and lymphoproliferative diseases.[12]

Chronic hepatitis C is often asymptomatic or paucisymptomatic: many subjects are infected by HCV without being aware of it and are, therefore, a dangerous source of infection.[1,8]

The prevalence rate of hepatitis C varies according to the risk factors involved. Since the virus is mainly transmitted through percutaneous contact with infected blood, the prevalences are higher for intra-venous drug users (IVDUs) and for haemophiliacs and blood transfusion recipients who in the past were administered unscreened blood products than for those with a lesser percutaneous exposure, such as subjects undergoing haemodialysis. A lower prevalence is found for subjects with unapparent percutaneous or mucosal exposure like high-risk sexual intercourse; an even lower prevalence is reported for subjects not exposed to risk factors (Figure 2).[8] In Italy, the most frequently identified risk factors are i.v. drug use, surgery and dental care, but also largely implicated are other types of parenteral exposure: manicure, pedicure, shaving at the barber's, piercing, diathermocoagulation, tattooing, acupuncture, etc. (Figure 3).[14]

HCV transmission by infected needles has increased over the years and is the most common

Figure 2. Cases of hepatitis C by risk factor, USA 1980-2001 (NANB hepatitis in the period 1980-90) (http://www.cdc.gov, modified)

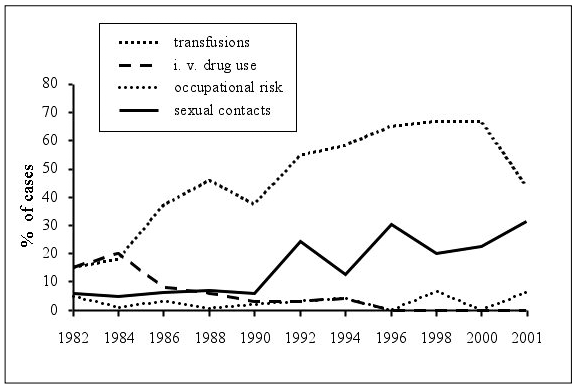
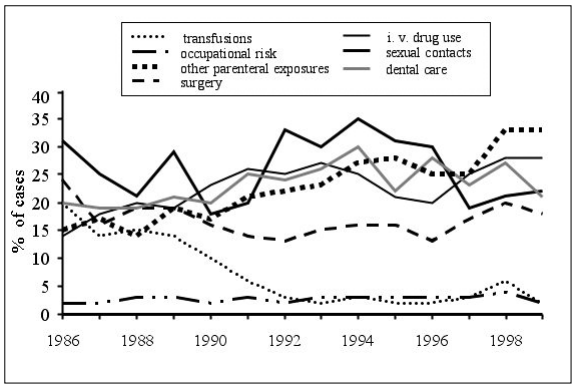


Figure 3. Cases of NANB hepatitis by risk factor, Italy 1986-1999 (Mele et al., ISTISAN report 00/32, modified)



vehicle of transmission in USA (60% of infections).[8] In Australia IVDUs account for 80% of the population infected; within this category the incidence of infection is 10-20/100 subjects per year and the prevalence 50-55%, with particularly high levels among the young and the incarcerated.[10] Also in the EU the spread of hepatitis C among IVDUs has become one of the most serious health problem, as the use of i.v. drugs is the main risk factor for the transmission of the virus.[23] According to the studies carried out, the estimated prevalence of anti-HCV-positive subjects among IVDUs in Western Europe varies between 37 and 98%; the prevalence of HCV-RNA-positive subjects ranges 26 to 86%.[24] Despite having the same transmission routes as other hemotransmitted viruses, the high prevalence of chronic HCV infection in these subjects causes the virus to spread more rapidly than HBV or HIV.[8] It is estimated that the prevalence of HCV-HIV co-infection among IVDUs can be 90-95%.[18]

In the USA there is a prevalence of HCV infection of around 90% in subjects who received unscreened blood derivatives before 1987. At present blood products undergo virus inactivation procedures and are tested for HCV-RNA, which guarantee their safety for commercial use. The increasing sensitivity of the tests to screen blood donors for HIV and hepatitis has steadily decreased the risk of post-transfusion infection to 0.001%/unit transfused, and brought about a subsequent decrease in the rate of transmitted infections from 1/200 units to 1/250,000 units.[8,25] In Italy the percentage of cases attributable to blood transfusion decreased from 20% in 1986 to 2% in 1999 and the residual risk of transmission by anti-HCV-negative infected blood has been estimated at 1/127,000 blood donations.[14,26]

Transplantation of infected organs also involves a high risk of virus transmission.[8] It is estimated that HCV is present in 2-50% of kidney transplants recipients; the transplant saves the lives of these subjects but recent studies have reported an increase in the death rate related to the onset of liver disease.[27] As occurs for the blood, the use of organs and tissues from healthy donors eliminates or greatly reduces the risk of transmission.[8] Most organ procuring organisations carry out routine screening for antibodies against HCV; the prevalence of anti-HCV positivity with ELISA test in donor organs varies worldwide from 1.08% to 11.8%. Not all anti-HCV positive donors are always infective; nevertheless, the use of organs from these subjects is in general limited to life-saving transplants (heart, liver, lungs). Transplants from anti-HCV positive donors to anti-HCV positive or HCV-RNA positive recipients are, until further data are available, experimental.[28] In any case, HCV positive patients undergoing kidney or spleen transplant are at a greater risk of infection and death than HCV negative recipients.[29,30]

Case-control studies have correlated hepatitis C with unsafe sexual contact.[8,31] However, HCV is less efficiently sexually transmitted than other viruses like HBV and HIV. Individuals with a single partner are at a lower risk of contracting the infection (0-0.6% per year) compared to those with more partners or at risk for sexually transmitted diseases (STD) (0.4-1.8% per year).[32]

In the USA the estimated prevalence is 6% among individuals practicing unsafe sexual intercourse, such as with a number of partners, or a history of STD and not using condoms, both for hetero- and homosexuals.[8] In subjects at risk for STD the mean sero-prevalence of anti-HCV antibodies is 4% (range 1.6-25.5%). HCV-HIV co-infection seems to increase the risk of HCV transmission by sexual route.[34] As is the case recipients for other hemotransmitted viruses, male to female infection is more frequent than vice versa.[8]

Vertical transmission of the virus has been the subject of extensive debate: initially it was not thought possible or that it occurred only with HIV-positive mothers; subsequent studies indicated that the risk of mother to foetus transmission of HCV is real and is directly proportionate to the viremia level of the mother ($>10^5$ copies/ml), and is higher in HIV-HCV co-infection.[33,34] Other factors linked to the condition of the mother (drug use), to the type of delivery and feeding and to the virus genotype might influence vertical transmission of the virus.[33,35,36]. It has not been established whether infection occurs *in utero* or at delivery;[37] however, some studies indicate that caesarean section can reduce the risk.[38,35,39] The presence of anti-HCV serum antibodies and viral RNA in the colostrum has been demonstrated, but there is no experimental evidence to date of increased transmission of the virus through breastfeeding (16, 37, 40). This is probably due to the low viral load in breast milk, three times lower than in the serum, and to the viral RNA inactivation exerted by molecules present in the milk and in the gastrointestinal tract of the newborn.[41,36]

The estimated prevalence rate for babies born of infected mothers varies according to positivity in the test for anti-HCV antibodies or HCV-RNA: 5% for the former and 6% for the latter. In HCV-HIV co-infection the rates are 14 and 17%, respectively. Infection of the neonate from an anti-HCV positive mother can be confirmed only by seeking HCV-RNA in the serum, since the passively acquired maternal antibodies can persist in the baby up to a year after birth.[8] The sequences of HCV-RNA isolated from mothers and from infected neonates by vertical transmission show 100% homology.[2]

In the USA about 240,000 babies have antibodies against HCV and from 68,000 to 100,000 have a chronic infection.[42] According to studies carried out in Europe and in USA, anti-HCV antibodies are present in 1-4% of pregnant women, but no routine screening is recommended for them.[37] Each year in Australia 125-250 babies acquire vertically transmitted HCV infection.[43] In children, low levels of viremia, low ALT values and more limited histological lesions are found compared to adults.Although the natural history of the infection in children has not been well defined, it is estimated that 50-80% of them develop chronic hepatitis.[44]

The risk of hospital acquired HCV infection is now recognised, especially in certain departments. Hospital transmission can follow three patterns: from the environment to the patient or between patients; from the patient to the hospital staff; from the hospital staff to the patient.

The main causes of hospital outbreaks are a failure to observe the necessary preventive measures and inadequate disinfecting and sterilising of equipment. The 10% seroprevalence of anti-HCV antibodies reported for hemodialysed patients in USA might indicate an improper application of the procedures to control the infection.[8] Piazza et al. found, using PCR, a marked contamination by HCV-RNA of the dentistry instruments after treatment of anti-HCV positive subjects; improper sterilisation therefore constitutes a serious risk of virus transmission, as seen from the high percentage (22%) of cases attributed to dental care in Italy in 2001 (SEIEVA 2001).[45] The use of non-disposable glass syringes in health care is most certainly associated to cases of HCV infection that occurred before the 1970s in Italy.[46]

Health and public safety workers frequently come into contact with blood in the workplace. A study carried out on the injuries with a biological risk involving the health care workers of the University Hospital of the Second University of Naples showed that in source patients anti-HCV antibody positivity was about six times higher than that for anti-HBV.[47]

The association with HCV infection has been shown both for accidental needlestick with infected needles, with an incidence of seroconversion of 1.8%, and for contamination of the conjunctiva by blood splashes. However, the prevalence of HCV infection reported for health care workers, including those involved in general, dental and orthopaedic surgery, is generally lower than 1-2%, and is 10 times lower than that reported for HBV.[8] The epidemiological data also indicate that, unlike for the HB virus, environmental contamination by infected blood is not a significant risk factor for hospital transmission.[48] In a study carried out in five hospitals in Turin a prevalence of anti-HCV antibodies of 1.97% was reported for 4517 health workers, with no correlation to occupational risk factors.[49]

The risk of transmission associated to dental care and surgery that may expose the patient to the blood of the operator seems to be very low.[8]

Several studies have been carried out in USA to clarify the role of tattooing, body piercing and beauty care in the transmission of HCV.[50,51] However, an association was shown only in certain categories of subjects, and there are no data available that would allow the results to be

extended to the general population: for example, less than 1% of the cases reported in the last 20 years by the CDC have been related to tattooing.[8] Conversely, in Italy SEIEVA attributed a large proportion of the cases notified in 1999 to this parenteral exposure.[14]

Case control studies have shown an association between non-sexual household contact and hepatitis C, presumably through exposure to contaminated blood or other biological fluids by direct, unapparent percutaneous or permucosal route.[52] Although not sufficiently documented, it seems that the risk of intrafamily infection is relatively low (around 4%), and involves in particular the spouses of infected individuals.[53,54]

For around 10% of Americans infected by HCV the source of infection has not been identified. Probably the low socio-economic level to which most of these subjects belong plays a fundamental role.[8]

In conclusion, the decrease in the number of cases of hepatitis C reported in Italy, as in the USA, is certainly attributable to factors influencing the major causes of infection, like the use of disposable syringes and the introduction of screening tests for blood donors but above all to the spread of information on the nature of the infection and on the modes of transmission of the virus.

The recent case in the literature of a health worker being infected by an HCV/HIV-positive patient suggests that prophylactic measures currently advised are still not universally applied.[55]

It is to be hoped that, both for the general population and in particular for the categories most at risk, prevention programs be increased to spread further information on the most important risk factors, preventive measures and proper sterilisation, considering that in the absence of an effective vaccine these are the only means at our disposal to combat the spread of the infection.

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