

## Review

# The Epidemiology of Chronic Hepatitis C: Where We Are Now

Cristina Stasi <sup>1,2,\*</sup> , Caterina Milli <sup>1</sup>, Fabio Voller <sup>1,†</sup> and Caterina Silvestri <sup>1,†</sup>

<sup>1</sup> Epidemiology Unit, Regional Health Agency of Tuscany, 50141 Florence, Italy; caterina.milli@ars.toscana.it (C.M.); fabio.voller@ars.toscana.it (F.V.); caterina.silvestri@ars.toscana.it (C.S.)

<sup>2</sup> Department of Medicine, Surgery and Neuroscience, University of Siena, 53100 Siena, Italy

\* Correspondence: cristina.stasi@ars.toscana.it or cristina.stasi@gmail.com

† These authors contributed equally to this work.

**Abstract:** One of the main objectives of the World Health Organization is the eradication of viral hepatitis by 2030 by identifying subjects before disease progression. In 2019, only 21% of the 58 million people chronically infected with hepatitis C virus (HCV) had been diagnosed, while overall 13% had been treated. The key recommendation of international screening programs is to reach the people at major risk of viral hepatitis and the general population. National plans, including that in Italy, have dedicated budget lines to support efforts to achieve the objective of elimination. The Italian program involves free screening for HCV in the general population born between 1969 and 1989 and also for all persons in the care of addiction services (Ser.D) and prisoners. The screening programs differed slightly among regions in Italy. In particular, referring to the screening for people born in the period of 1969–1989, in Tuscany, these people received an invitation by SMS to undergo a HCV antibody test. If the test results were positive, the subject was registered on a regional platform and required to undergo HCV RNA testing, prescribed by their GP. In the case of testing positive for HCV RNA, the linkage to care (i.e., patient entry into specialist care after diagnosis) is guaranteed. A strong effort is currently required to eliminate HCV effectively. This review highlights the most recent changes to the epidemiological scenario at the global, European, Italian, and regional (Tuscany) levels.

**Keywords:** screening; chronic hepatitis C; eradication; addiction service; prison; HCV antibody test



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## 1. Global Chronic HCV Epidemiology

Chronic viral hepatitis is among the principal challenges of public health. Currently, one of the main objectives of the World Health Organization is to eradicate viral hepatitis by 2030 [1], which requires the identification of subjects with chronic infection prior to clinical progression. Subjects with chronic hepatitis C virus (HCV) have a 15–30% risk of developing cirrhosis within 20 years [2]. In a recent meta-analysis, Salary et al. [3] reported a cumulative risk of developing liver cancer, with their results reaching 21.6% in males and 8.7% in females in the age range of 40–74 years [3]. In May 2016, the World Health Assembly officially gave its support to the global strategy of eliminating viral hepatitis by 2030 (reducing infections by 90% and mortality by 65% by 2030) [1]. According to data from the WHO, globally, 58 million people live with chronic hepatitis C infection, which causes approximately 400,000 deaths every year. In 2019, only 21% of the 58 million people with chronic hepatitis C had been diagnosed, while overall 13% had been treated [4]. In this regard, according to a recent meta-analysis of 98 studies (with a total of 236,964 subjects), the global prevalence of HCV was 1.8% (95% CI: 1.4–2.3%), with the highest prevalence of HCV being found in Africa (7.1%) [3].

The target of the new WHO actions as part of the global health strategy is to eliminate viral hepatitis by 2030, and more specifically reducing new infections and deaths by 90% and 65%, respectively [1]. The new direct-acting antivirals (DAAs) eliminate HCV in approximately 95% of subjects; this includes subjects with liver cirrhosis, who in the past were very difficult to treat with interferon (INF) and ribavirin (RBV), and even those with

an lower response rate based on genotype at advanced stage of fibrosis (METAVIR F3, F4) compared to subjects at an earlier stage (METAVIR F0-F2). Previous therapeutic regimes were also burdened by numerous side effects.

The new WHO Global Health Sector Strategy (GHSS) on Viral Hepatitis 2022–2030 [5], recently presented at the World Health Assembly, was one of the predominant themes of the 2022 Global Hepatitis Summit. The document includes operational and strategic amendments to ensure the achievement of the goal of eliminating viral hepatitis globally by 2030. In 2020, there was a reduction in the incidence of hepatitis B in children under 5 years old, and the total number of patients receiving antiviral therapy for HCV increased ten-fold. Despite this, most countries failed to achieve the other objectives set for 2020. As highlighted at the World Hepatitis Summit 2022, every 30 s, at least one person dies from the consequences of viral hepatitis. This amounts to over one-million deaths per year, with a higher overall death toll than for HIV and malaria. In this context, the WHO renews its commitment to fulfilling the dream of eliminating viral hepatitis by 2030 as part of a broader commitment to universal health coverage based on strong healthcare basics. Given that viral hepatitis can become chronic and develop into cirrhosis and hepatocellular carcinoma, which account for 96% of mortality, the global strategy focuses precisely on these areas. It is also underlined that coinfection or superinfection with hepatitis D virus in subjects with hepatitis B virus infection accelerates the progression of chronic liver disease. Some of the actions planned by the WHO [6] to eliminate viral hepatitis as a public health threat by 2030 are summarized in Table 1.

**Table 1.** Some key actions and targets planned by the World Health Organization [6].

Key strategic and operational actions required to eliminate viral hepatitis	Promote greater public and political awareness of the importance of prevention, diagnosis, and treatment of hepatitis B and C.
	Greater financial resources, including in the area of prevention; improve diagnosis and treatment of hepatitis; provide universal access to hepatitis B vaccines at birth; improve screening procedures for pregnant women aimed at preventing vertical transmission (mother-child); invest in primary prevention, particularly in people at risk; increase access to testing for subjects infected with chronic hepatitis B and C viruses; improve access to care; promote simplified service delivery models; overcome the barriers encountered by the most affected and at-risk populations; strengthen collaborations aimed at the prevention, diagnosis, and treatment of viral hepatitis.
Targets	Goals of 90–80% hepatitis B or C patients diagnosed and treated; 90% administration of the first dose of hepatitis B vaccine at birth to prevent vertical transmission (from mother with hepatitis B infection to child); 90% vaccination coverage in children (administration of the third dose); distribution of 300 sterile needles and syringes to people who inject drugs; 100% blood units screened and 100% safe injections.

Over 100 countries participated—with delegates, leaders, politicians, and public and private healthcare professionals—in the epidemiological update on viral hepatitis at the global summit [5]. In June 2021, the WHO provided provisional guidance on the criteria for eliminating the virus, but currently many countries, including Italy, are not in line with the expected targets.

The results of a recent US study [7] confirm baby boomers as the target cohort, with an anti-HCV prevalence of 2.23% compared to the 0.52% observed in the 1964 birth cohort and 0.46% in the cohort born before 1945. Considering that the estimated seroprevalence of HCV in the entire US population is 1.19%, this means that over 74% of cases fall within the baby boomer cohort. The results of a pilot study carried out in a Spanish municipality were slightly different: with the same HCV seroprevalence (1.14%), the birth cohort at greatest risk of infection was between 1955 and 1970 [8]. As regards Italian data, a recent study

representative of the entire Italian population residing in metropolitan areas [9] shows an overall seroprevalence of HCV of 2.3% in the adult population (1.7% HCV-RNA positive). The regions of central Italy (represented by the city of Rome) show a higher seroprevalence (2.6%). In this case, the authors highlight the broad diffusion of the virus in the older population (birth cohort 1935–1944), where the prevalence reaches 7%. The other birth cohort with the highest prevalence is that between 1965 and 1974 (1.6%). On average, in the age groups between 1964 and 1984, the prevalence is 1.3% [9].

Globally, there are approximately 4–5 million people coinfecting with HIV/HCV. Coinfection with HCV/HIV is common in people who inject drugs [10]. People living with HIV and HCV coinfection suffer a more rapid progression to severe fibrosis and cirrhosis, representing a significant cause of death. According to a systematic review [11] aimed at estimating the prevalence of anti-HCV among injecting drug users, the prevalence of HCV infection in people who inject drugs (PWID) exceeded 80% in 12 countries.

A recent meta-analysis [12] that evaluated viral hepatitis and HIV coinfection among prisoners showed a pooled prevalence rate of HIV/HCV coinfection of 62%. Among HIV-positive prisoners who reported injecting drugs, the HCV prevalence increased to 78%. Several studies on HCV patients treated with DAAs have demonstrated sustained virologic response (SVR) rates in HIV/HCV coinfection comparable to those with HCV mono-infection, which ranged between 95% and 98% and 95% and 99%, respectively [13]. One study assessing treatment efficacy in PWID showed a SVR of 99% in these patients. The factors that contributed positively to adherence included older age and stable housing [14]. Regarding the prison setting, among people who completed treatment, all were cured (SVR12 = 100%). However, the high turnover rate in prisons makes it difficult to ensure completion of the normal course of antiviral treatment [15]. For this reason, the antiviral treatment can be shortened to 8 weeks in particular population groups [16].

Table 2 shows the incidence and prevalence of HCV, HIV/HCV, and HCV in people with substance use disorders globally, in Europe, and in Italy

**Table 2.** Global, European, and Italian incidence and prevalence of HCV.

		Globally	Europe	Italy
<b>Incidence</b>	HCV *	1.5 million [2]	1019 [17]	55 [18]
<b>Incidence</b>	HCV in PWID	12.1/100 person years [19]	12.8/100 person years [19]	5.83/100 person years [20]
	HCV	50,688,000 [21]	6,271,000 [21]	398,610 [22]
	HIV/HCV	2.3 million [23]	66,800 [10]	27.3% HCV-Ab positive; of those tested for HCV-RNA 39.3% were positive [24]
<b>Prevalence</b>				
	HCV in PWID	52.3% are HCV Ab positive [25]	60.64% average of HCVAb positive in 11 countries with recent data [26]	54.1–71% HCV Ab positive [26]

\* Incidence estimated as acute symptomatic cases.

In Tuscany, a study conducted by Stasi et al., 2015 [27], in a cohort of patients with HCV highlighted that 20.7% of the transmission routes were represented by the use of intravenous drugs. In 2018, Shiffman [28] indicated that new HCV cases tripled between 2005 and 2015. Approximately 50% of injecting drug users were exposed to HCV, and 25% of these people were under 25 years old. Despite the observed increase, intravenous drug users are less likely to access healthcare and receive treatment for HCV than the baby boomer cohort. Possible reasons for this include the lack of other medical disorders associated with the infection that require medical treatment and the high prevalence of associated mental disorders, which are both situations that reduce patient compliance.

More recently, an Australian study [29] assessed the progress of HCV elimination among people who inject drugs by examining changes in the prevalence of HCV infection and the treatments provided for patients in the years 2018–2019 and 2019–2021. Of 2395 enrolled subjects, HCV prevalence decreased from 24% to 17% between 2018–2019 and 2019–2021, while antiviral therapy increased from 66% to 74%. Factors associated with infection included homelessness, incarceration, and recent intravenous drug use.

The other population group considered at greater risk of HCV infection is prison inmates. A recent meta-analysis [30] investigated the seroprevalence of HCV in the global prisoner population. The meta-analysis showed that in the 93 studies considered (22 in Asia, 26 in Europe, 7 in Africa, 29 in the US, and 9 in Australia and Oceania) with a total sample size of 145,823 subjects, the prevalence of HCV infection in prisoners globally is 17.7% (95% CI, 15–20.7%). Specifically, the highest HCV prevalence was reported in prisoners in Australia and Oceania, reaching 28.4% (95% CI: 21.6–36.4), and in Europe, reaching 25.1% (95% CI: 19.4–31.8) [30].

Given these premises, HCV screening may be an important strategy for identifying cases of infection where the subjects are unaware and untreated.

Back in 2016, the Centers for Disease Control and Prevention (CDC) recommended that adults born between 1945 and 1965 ('baby boomers') should be screened regardless of prior assessment of risk factors for HCV [31]. In 2017, recommendations from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America—recognizing the 1945–1965 birth cohort to be at greatest risk of infection—recommended one-time HCV testing (regardless of country of birth) without risk assessment, as well as for all other people with behaviors, exposures, and conditions associated with an increased risk of HCV infection. In this regard, in 2019, the US Preventive Services Task Force established the moderate to substantial (Grade B) recommendation of screening for HCV infection in all adults aged 18 to 79 years [32].

Therefore, this review highlights the most recent changes in the epidemiological scenario at the global, European, Italian, and regional (Tuscany) levels.

## 2. Epidemiology of Chronic HCV in Europe

The European Centre for Disease Prevention and Control, based on recent modelling, has estimated that there are 2.4 million individuals with chronic HCV infection in the EU/EEA [33]. In 2019, the Global Burden of Disease (GBD) in Europe reported 11.87 million prevalent cases, 52,920 incident cases, and 36,890 deaths by cirrhosis without significant changes from 2010 to 2019. However, when standardized by age, the prevalence (−6.4%), incidence (−5.9%), and mortality (−11.1%) rates decreased. In 2019, approximately 32,000 prevalent and 24,000 incident cases of HCV-related hepatocellular carcinoma (HCC) and 23,000 HCV-related deaths were reported, with a significant increase from 2010 to 2019. However, when considering age-standardized rates, the HCV-related caseload remained stable from 2010 to 2019 [34].

In Europe, the total burden of disability-adjusted life years (DALYs) associated with cirrhosis was 1.09 million, and 416,000 were due to HCC. Between 2010 and 2019, DALYs due to cirrhosis decreased, while those due to HCC increased by 10.4% [34].

At the level of European regions, in 2010, the age-standardized incidence rate of acute hepatitis C was higher in Eastern European countries, with values that saw a slight decrease in the period examined (2010–2019). Similar values were observed in Central and Western Europe, with a decline in cases in 2019 [34].

With the SARS-CoV-2 epidemic, all member states are out of line with the WHO targets, but they were already behind before the epidemic.

In fact, in 2017, there were only nine countries in line with the WHO objectives of viral hepatitis elimination by 2030 [35]. It should also be considered that over 40% of national plans did not have dedicated budget lines to support efforts to achieve elimination [36].

### 3. The Chronic HCV Burden in Italy

Specialists have been able to prescribe DAAs since 2014 (free-of-charge) through a monitoring system established by the Italian Medicines Agency, which has introduced criteria for prioritizing treatment for individuals with advanced liver disease (Metavir F3 and F4) and broadened access to treatment from 2017 [37].

Although Italy is among the countries capable of achieving the WHO objectives, unfortunately, it ranks among the European countries with a high percentage of deaths registered with the cause of HCV. According to estimates recently published by Kondili et al. [22], as of 1 January 2021, there are approximately 398,610 people with active HCV infection (prevalence of 0.66%), of whom 287,730 have a stage of fibrosis from none to severe (F0–F3) and are, therefore, potentially asymptomatic (prevalence 0.48%). The same authors reported a difference in prevalence within Italy that varies from 0.54% recorded in the northern regions to 0.88% in the regions of central Italy (south: 0.72%; islands: 0.67%). Subjects with a past or current history of intravenous drug use represented 48.6% of all individuals with chronic HCV infection [22].

There are no epidemiological studies carried out on the whole of Italy that estimate the number of subjects that qualify for eradication therapy, although the cumulative trend of treatments started has increased, reaching around 260,872 to date (March 2024) [37].

An epidemiological research article by Andriulli found an anti-HCV prevalence of 2.6% in central Italy, of which 74.1% were HCV RNA positive [9]. If the literature data are applied, in particular Andriulli's prevalence estimates, in Tuscany, there are 80,762 HCV positive subjects and 60,975 subjects with chronic infection (1.96% of the population > 20 years).

Since the arrival of DAAs on the market, numerous regional decrees have followed, the first of which (to our knowledge) was in Tuscany. The goal of eradication can certainly be achieved by creating treatment opportunities for those diagnosed but not yet treated. In Italy, the submerged HCV population (those diagnosed but not treated and those still undiagnosed) amounts to around 300,000 people [22], many more than those who have already benefited from the treatment.

### 4. An Overview of Chronic HCV in Tuscany

One of the first studies we carried out on a cohort of patients in Prato (serological database of 22,404 subjects, of whom 508 cases were HBV (50.5%), defined by the presence of HBsAg, and 496 positives for HCV antibodies) who showed a prevalence of HBV of 2.3% and anti-HCV of 2.2% [38]. These data are in line with the prevalence found by Andriulli et al. [9].

Based on current health data, as of 31 December 2022, 30,228 patients with chronic HCV infection were known to the regional healthcare system, of whom 4707 were subjects who had never been treated with therapies based on interferon and ribavirin, nor with DAAs [39].

In consideration of the high rate of chronicity, and given the small proportion of symptomatic cases in the acute phase, it is particularly complicated to identify, without screening, the infected subjects who have contributed year after year to the increase in cases of chronic liver disease in the general population. The introduction of DAAs has given rise to the need to identify subjects who have not yet been diagnosed or treated for chronic HCV in order to reduce the spread of the infection and its complications. For this reason, in 2015, the Tuscany Regional Authority launched a program (Regional Gov. Decree No 647 [40]) aimed at eradicating HCV in the regional population through the treatment of people with chronic infection, which was renewed in 2018 (Regional Gov. Decree No 397 [41]). To facilitate access to DAA prescription centers, an information campaign targeting the general population was launched and, at the same time, the Tuscan health authorities undertook a call-to-action campaign targeting people with medical exemption for HCV-related chronic liver disease registered as having undergone the old interferon-based therapy. The constant increase in the emergence of people with HCV who were previously undiagnosed or



untreated people that has been observed over the years seems to confirm the successful outcome of the ongoing campaign.

Following the national screening [42], the entry into force of Legislative Decree No 162 of 30 December 2019 (converted with Law No 8 of 28 February 2020), established, for the period 2020–2021 (extended), the activation of free HCV screening for people born between 1968 and 1989 and for subjects in the care of addiction services (Ser.D) and prison inmates. The Tuscany Regional Authority undertook reviewing of the existing situation (Ser.D, approximately 16,000 subjects and approximately 3000 prisoners), encouraging the implementation of screening for the general population (birth cohort 1969–1989). The proposal, approved with Resolution No 1538 of 27 December 2022 [43], is developed along four central lines:

- activation of an information campaign aimed at the target population;
- organization of an HCV program;
- consolidation of the linkage to the care system for subjects with active HCV (HCV RNA positive);
- computerization of data from screening activities through the use of platforms already operational in the region.

This national screening program, currently underway in all Italian regions, is monitored every six months by examining the results recorded and sent by the different regional health authorities. The experimental phase was completed on 31 December 2023.

Having activated free screening among two of the groups envisaged by the ministerial decree (persons in the care of addiction services and prisoners), on 4 September 2023 Tuscany started the screening campaign aimed at the other cohort of the population, i.e., all persons resident in the region born between 1969 and 1989.

The screening is available from local health authorities and voluntary associations, with direct access and without reservation, with prescriptions being issued by GPs for screening and HCV RNA tests. If the HCV RNA test is also positive, the GP will refer the patient to a liver clinic to start the treatment process.

In 2015, the region also activated numerous local research projects aimed at estimating the number of people with active HCV infection potentially treatable with DAAs or already in the care of the hepatology services in Tuscany [27].

The research is currently underway through the regional study “Optimization of diagnosis and treatment pathways for chronic HCV in Tuscany—OPT-HepaC”, which involves the strengthening of diagnosis activities carried out at specialist clinics and the regional monitoring of patients with HCV infection [44].

Pending the results of the OPT-HepaC study, the Tuscany Regional Health Agency (ARS) is continuing to monitor existing health data flows. The trend analysis shows an increase in the number of people with HCV infection who have accessed the regional health services (SSR), confirming the success of the policies implemented in identifying new cases of the disease. Regarding the treatment uptake, a retrospective analysis of administrative data of the ARS [45] was carried out for the period 2015 to 2020. Data linkage was performed using data on patient medical exemptions, hospital admission codes, and hospital pharmacy drug dispensing codes. All individuals with a known diagnosis of HCV, including prevalent and newly diagnosed cases, were recorded. Treatment uptake over time and the size of the population in need of treatment were assessed by assuming 49.5% and 95% SVR with DAAs and previous treatments, respectively. At the end of 2014, there were 26,993 HCV diagnoses in Tuscany, including 1215 new diagnoses, corresponding to  $33 \times 100,000$  inhabitants. A total of 24,014 were estimated to be still in need of treatment. From 2015 to 2019, an average of 1631 (range 1462–2046) new HCV diagnoses were reported, dropping to 742 in 2020. At the end of 2020, there were 30,338 individuals with a previous diagnosis of HCV. Since 2015, a total of 13,908 patients have been treated with DAAs. On average, 2555 patients have started DAA treatment each year during the period 2015–2019, with a peak of 4118 in 2018. The estimated number of subjects needed to be treated with

DAA in Tuscany dropped steadily during the period 2015–2020 (average annual percentage change −8%) and stood at 14,266 in 2020.

As is widely known, the prevalence of chronic viral hepatitis is particularly high in migrants compared to the general population, since they have a greater exposure to environmental risk factors, in addition to a greater probability of encountering barriers (linguistic, cultural, etc.) in the diagnostic–therapeutic pathway.

Screening strategies in these at-risk populations are therefore essential to achieving the WHO goal of HCV and HBV eradication by 2030.

Most studies conducted in disadvantaged populations [46–48] highlight a greater prevalence of HCV and HBV compared to those recorded in the general population.

The ARS conducted a national study on prisoners [46] involving 57 prisons from five Italian regions and the Salerno local health authority (ASL), covering 28% of all inmates in Italian prisons. All prisoners registered as of midnight on 3 February 2014 in the detention facilities enrolled in the study—corresponding to 17,086 subjects—were considered eligible. Of these inmates considered, 92.2% (15,751 subjects, including 14,835 men and 869 women) agreed to take part in the study, which was conducted between 4 February 2014 and 4 June 2014. The prevalence of chronic HCV (7.4%) was found to be approximately three-times higher than that of the general population, with an overall higher prevalence in the age group > 45 years.

Another study [47] was conducted in prisons, but at a regional level, to examine the prevalence of people with a substance/alcohol use disorder and the prevalence of viral hepatitis in this cohort of patients; it highlighted that out of a total of 3100 prisoners, 29.4% had at least one psychiatric disorder, of which 17.8% had a substance/alcohol use disorder. In these subjects, the prevalence of chronic HCV infection was 19.8%.

A study in Tuscany conducted over 5 years of HIV surveillance [48], aimed at identifying coinfection with HBV and/or HCV in this cohort of subjects, found that, of a total of 1354 new HIV diagnoses, 7.8% ( $n = 106$ ) were coinfecting with HCV, 4.1% with HBV ( $n = 56$ ) and 0.33% with HCV/HBV ( $n = 4$ ).

Research to define the burden and characteristics of patients with HCV attending the liver clinics in Tuscany, after the advent of DAAs, enrolled 4015 patients with chronic viral infection, of whom 27.3% were chronically infected with HBV, while 72.7%—with a mean age of  $57.44 \pm 15.15$  (SD)—were infected with HCV (54% male, 46% female). In this cohort of patients with HCV, genotype 1 was prevalent; specifically, genotype 1b had a prevalence of 47.4%, while genotype 2 had a prevalence of 16.5%. The major routes of transmission were the use of intravenous drugs (20.7%); hospital/dental care (20.6%); and clotting factors/blood transfusions (13.3%). Among the comorbidities that were investigated, diabetes was found in 20.8%, metabolic syndrome in 15.5%, and ischemic heart disease in 6.2%. In this HCV cohort, 32.8% were frankly cirrhotic, of whom 40 were on the list for liver transplant. In cirrhotic patients, the signs of hypertension were present especially in the over-45 age group, with a frequency of 92.3%. Systemic HCV manifestations were found in 13.3% of cases, with a higher prevalence of cryoglobulinemic syndrome (58.3%) and B-cell non-Hodgkin lymphoma (10.5%) [27].

## 5. Conclusions

In conclusion, there is still a lot to be achieved both at global and local levels, through the support of public authorities, policymakers, and individual hepatologists, in order to achieve the hepatitis C virus eradication objective set by the WHO.

A global HCV elimination strategy and national and regional plans in some countries have been applied with some success, though the COVID-19 pandemic hindered progress in 2020. In Italy, DAA treatment uptake has been rapidly scaled-up since 2015, although the number of new diagnoses has remained constant over time.

International collaborations certainly help countries with fewer economic resources to implement plans for the eradication of HCV, but national networks are needed also in high-

and middle-income countries to overcome barriers that in some cases are still present in these countries.

The finish line is still a long way off; however, the first steps towards the eradication of HCV show that screening is an essential part of achieving this objective.

The expansion of the screening population cohort to people over 55 years could facilitate this mission set by the WHO.

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