# Chapter 1

# Introduction

In 2014, the scientific community celebrated the 25th anniversary of the discovery of the hepatitis C virus (HCV). Since the isolation of HCV, extensive progress has been made in the field, and a growing knowledge of the virus life cycle has led to the development of potent drugs.

This handbook will focus on the HCV particle, its life cycle, clinical features of HCV disease, pathophysiology, diagnosis, management and treatment of disease, and future challenges. An overview of current knowledge on hepatitis C and up-to-date advances are covered, with the goal to assist the medical community in the management of this disease.

## Historical perspective

### Discovery of HCV

In the 1970s, Harvey J Alter and his collaborators described a large number of hepatitis cases that occurred after blood transfusion and proved they were due to neither hepatitis A nor hepatitis B viruses [1]. These cases of hepatitis were thus called non-A, non-B hepatitis (NANBH) for more than 10 years. The agent responsible for hepatitis C, HCV, was first isolated and described in 1989 after the extensive screening of bacterial clones derived from experimentally infected chimpanzee samples by researchers from the Chiron Corporation in California [2–4]. Since the isolation of HCV the interest in this field has expanded remarkably, as reflected by the number of publications found in PubMed using 'hepatitis C virus' as a query (Figure 1.1).



N. Goossens et al. (eds.), *Handbook of Hepatitis C*,
DOI 10.1007/978-3-319-28053-0_1

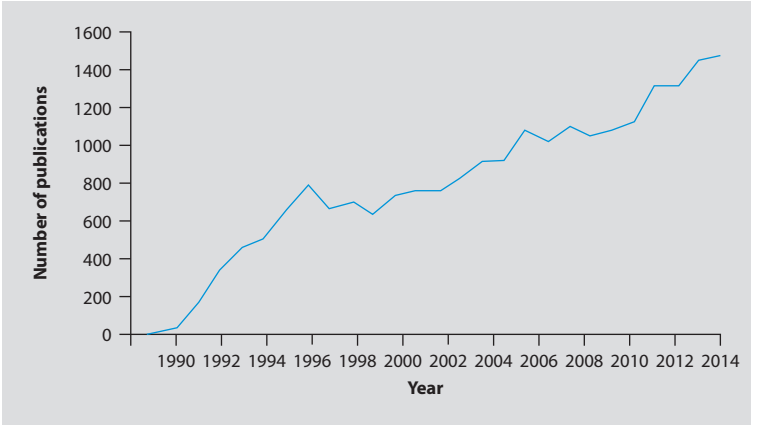



**Figure 1.1 The number of publications obtained in PubMed from 1990 to 2014 when using 'hepatitis C virus' as query in the publication title.**

## Main scientific and medical advances in HCV research

The discovery of HCV led to the development of diagnostic tools and, in the early 1990s, the implementation of systematic screening of blood supplies; in the US this contributed to the reduction of infection via blood transfusion by almost 100% [5]. In 1991, the use of interferon-alpha (IFN-α) as a treatment for hepatitis C disease was approved and in 1998 the combination of IFN-α and ribavirin was approved. In 2001, pegylated IFN-α (peg-IFN-α) (which has improved pharmacokinetics and efficacy compared to IFN-α) was introduced. Despite the potentially severe side effects of this regimen it remained the gold standard for over 10 years; the sustained virological response (SVR) could reach up to 50% [6] in certain subgroups. During this time extensive efforts have been undertaken to develop cell culture systems, which have helped the development of direct acting antiviral (DAA) drugs (Chapter 6). The replicon system, developed in 1999, allowed a better understanding of HCV replication in the human hepatoma cell line Huh-7 [7]. Major advances in the study of HCV entry and neutralizing antibodies were achieved thanks to the establishment of the HCV pseudoparticle system in 2003, which consists of lentiviral particles harboring HCV envelope protein (E)1 and E2 [8]. The major breakthrough in HCV research has undeniably been the development of the JFH1-based cell culture system, which recapitulated the complete HCV life cycle in vitro [9] (Figure 1.2).

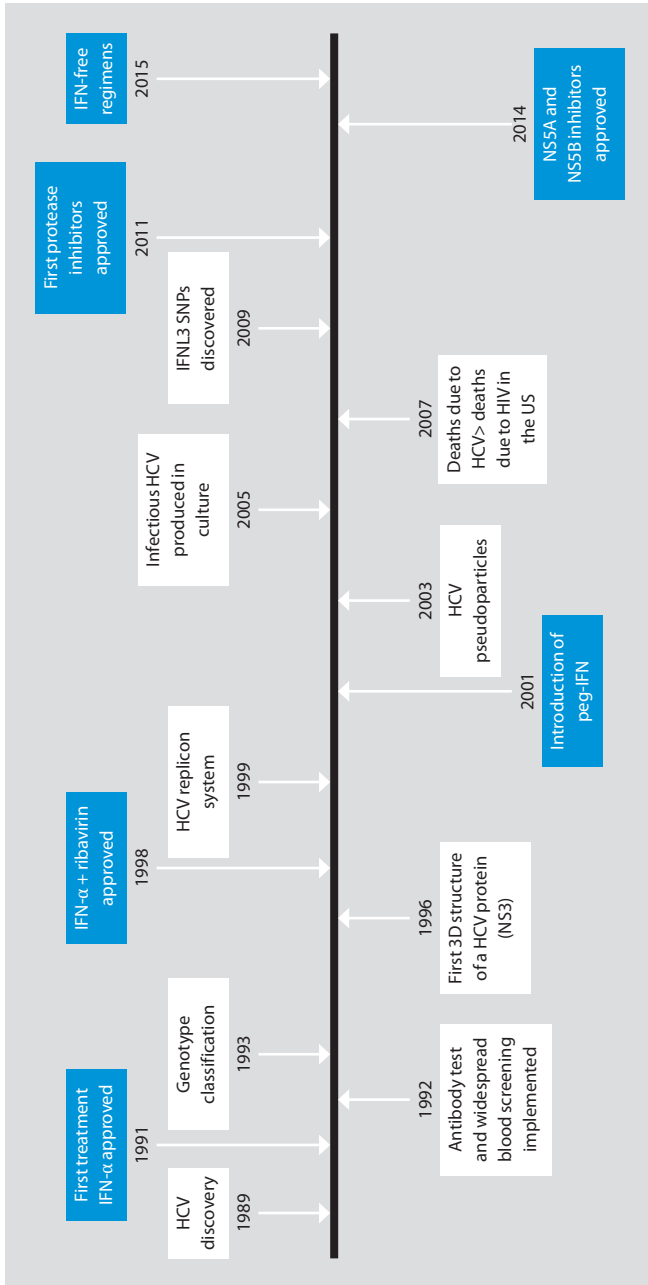



**Figure 1.2 Timeline of hepatitis C virus research and treatment advances.** HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN-α, interferon-alpha; IL, interleukin; NS, non-structural; peg-IFN, pegylated interferon; SNPs, single nucleotide polymorphisms.

## Epidemiology

HCV infection is a major health problem worldwide. A recent study based on anti-HCV seroprevalence data estimated that 185 million people, corresponding to 2.8% of the world's population, have been infected with HCV [10]. Among those infected with HCV, the World Health Organization estimates that 130–150 million individuals worldwide are chronically infected [11]. The Centers for Disease Control and Prevention (CDC) estimates that in the US alone approximately 29,700 new cases are diagnosed per year, a number that is steadily increasing [12]. Global mortality due to hepatitis C infection is approximately 700,000 individuals per year [13]. In the US, the number of deaths from HCV was 19,368 in 2013 [12] and a large study reviewing the death certificates of 22 million deceased people demonstrated that the number of deaths due to HCV (15,106) surpassed those due to human immunodeficiency virus (HIV) infection (12,734) in 2007 [14].

HCV infection is prevalent worldwide and its geographical distribution varies (Figure 1.3). North Africa, East Asia, and the Middle East have the highest prevalence of HCV [15], estimated at more than 3.5%. Within North Africa prevalence is highest in Egypt (approximately 15%); this is thought to be a consequence of a prophylaxis campaign against schistosomiasis carried out between 1961 and 1986 [16]. By contrast,

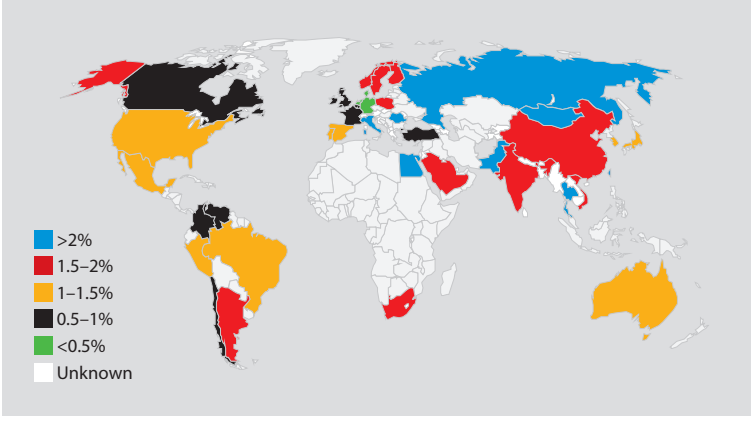



**Figure 1.3 Hepatitis C virus prevalence worldwide** [14]. Reproduced with permission from © John Wiley and Sons.

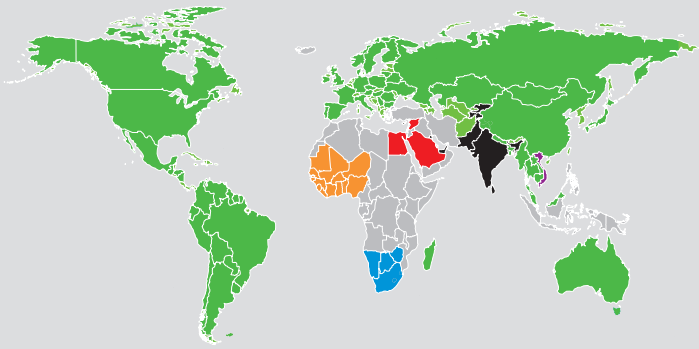
prevalence in industrialized countries in Europe, America, and Australia has been reported to be significantly lower, with the exception of Spain and Russia, where prevalence is 1.5 [17] and 2.9% [18], respectively, and central and south Italy and Romania where it is higher than 3% [19]. However, it should be noted that most of the prevalence data are based on specific person subgroups that are not necessarily representative of the overall population of one country. Additionally, epidemiologic data are not available in all countries. For example, in Africa robust data are only available for Egypt and South Africa.

## HCV genotypes

HCV has a high capability to generate mutations and exists as seven different genotypes, subdivided into more than 60 subtypes [20]. HCV circulates within a single patient as closely related variants named 'quasispecies'. This constant variation of the HCV genome is the major reason for the difficulties encountered in the development of a vaccine against HCV. Based on nucleotide homology analysis of the non-structural (NS)5 region of the HCV genome, it has been estimated that strains from different genotypes share a similarity of between 67 and 69%. Within subtypes of HCV only 20–25% of nucleotides are different [21]. In 2015 Messina et al [22] carried out a large retrospective literature analysis combining epidemiologic data from 1217 studies published between 1989 and 2013, representing 117 countries. The study demonstrated that genotype 1 is the most predominant (42%), followed by genotype 3 (30%). The sum of genotype 2, 4, and 6 corresponds to approximately 23%, while genotype 5 represents less than 1% of the total number of HCV cases. HCV genotype 7 was first described in 2014 [20] and has been reported so far in only a few patients [23,24].

Genotype 1 is widely spread throughout the world; however, the other genotypes have more restricted geographical distributions. Genotype 2 predominates in West Africa, genotype 4 in the Middle East, genotype 5 in South Africa, and genotype 6 in East and South East Asia, and is the main genotype in Vietnam [15,22]. Although genotype 3 is widely distributed, its prevalence is particularly high in South Asia (Figure 1.4). The prevalence of genotypes and subtypes is different depending on

the transmission route. For example, genotypes 1a and 3a are more frequent among intravenous drug users (63% and 33%, respectively) while genotype 1b has a high prevalence among patients who were infected through blood transfusions [25]. Although all genotypes can establish chronic infection, there are specific clinical disease features associated with genotypes; steatosis, for example, is more prevalent in genotype 3 infections [26] (see Chapter 4). The response to therapy is also dependent on HCV genotype; genotype 1 and 4 infections are the most difficult to cure with peg-IFN-α and ribavirin combination therapy as compared to genotypes 2 and 3 [27], whereas chances of SVR to IFN-free regimens appear to be lower in genotype 3-infected patients (see Chapter 6).



**Genotype 1**

Highest prevalence worldwide. Two main subtypes, 1a and 1b.

**Genotype 2**

Main genotype found in West Africa and also found throughout the world.

**Genotype 3**

Predominant in South India and can be found at high prevalence in some other countries throughout the world (eg, Germany, UK, Greece).

**Genotype 4**

Mainly found in the Middle East and Egypt.

**Genotype 5**

Mostly restricted to South Africa.

**Genotype 6**

Mainly found in Asia.

**Figure 1.4 Hepatitis C virus genotype distribution and prevalence around the world.** Adapted from Negro and Alberti [15] and Messina et al [22].

## Modes of disease transmission and risk factors

The principal route of transmission of HCV is via the blood. In developed countries, since the systematic screening of blood donors, the risk of HCV infection consecutive to transfusion or organ transplant has dramatically decreased to less than 1 per 100,000 [28]. In some countries, however, HCV can still be transmitted via the transfusion of unscreened blood. HCV was also identified to be highly present among patients receiving long-term dialysis, with a prevalence of anti-HCV positive patients in this population ranging from 1 to 70% (depending on the country) [29]. Of course, the risk of HCV transmission in patients on dialysis is largely increased by the number of transfusions and the time spent on dialysis, but once again, transmission of HCV by blood transfusions is now very rare in dialysis units of developed countries thanks to the introduction of systematic screening of blood donors and the extensive implementation of safety procedures [29]. Organ transplantation is another route of HCV transmission [30]; even though the screening of donors has been implemented in developed countries, some cases of HCV transmission due to organ transplantation are still reported [31].

Any source of blood is able to transmit the virus, even if it is indirect (such as soiled material). Tattooing, body piercing, or even acupuncture have also probably contributed to the spread of HCV, even in developed countries. In health care settings, needle-stick injuries, unsafe injections, and reuse or improper sterilization of contaminated medical equipment are also responsible for some cases of HCV infection in developed countries and still represent a major route of transmission in resource-poor areas of the world. During the year 2000, it has been estimated that 16,000 health care workers worldwide were infected by HCV following percutaneous injuries [32]. In developed countries, however, the most significant risk for HCV infection is related to intravenous drug use through the sharing of contaminated needles and other paraphernalia. This mode of transmission accounts for more than 60% of newly diagnosed cases of hepatitis C [33]. Cocaine users have also been shown to transmit the virus by sharing snorting straws [34]. HCV can be transmitted sexually, although this route of transmission is uncommon. In groups of people with high-risk sexual behavior, such as HIV-positive

men who have sex with men, the incidence of HCV is higher than in the general population and has increased in recent years [35]. By contrast, in monogamous serodiscordant couples the risk of transmission is very low and has been estimated to be <0.25% per year [36–38]. One explanation for this low rate of transmission may be that seronegative partners somehow develop immune defenses against HCV via regular contact with small amounts of virus.

The vertical (mother-to-child) transmission rate is around 4% [39] and can occur both during pregnancy and at the time of the delivery. The type of delivery (vaginal versus cesarean) does not appear to impact on the risk of transmission [39]. Importantly, reports have shown that co-infection with HIV increases the risk of maternal-fetal transmission of HCV [35].

## Economic and social burden

HCV infection is a major health concern worldwide due to its high prevalence and the fact that HCV-associated disease has long-term consequences. The latter is of great importance considering that over 75% of infected adults are 'baby-boomers' (a term that refers to those born between 1945 and 1965) [40] and that the burden of HCV will significantly increase over the next decade with increased projected cases of cirrhosis and hepatocellular carcinoma (HCC), despite improved cure rates for HCV. Another important issue is the low diagnosis rate, which potentially leads to an underestimation of the overall number of patients. The US CDC run a national campaign, Know More Hepatitis™, which provides information about hepatitis C and encourages people born between 1945 and 1965 to get tested [40]. With the arrival of IFN-free regimens expected SVR rates are greater than 90% but barriers to treatment access remain significant (eg, inadequate screening, poor linkage to care, and high cost of treatment) and many people remain untreated [41]. If we take into account the indirect costs of untreated chronic HCV (absenteeism and lower work productivity of HCV-infected individuals [42]), treating HCV with efficacious drugs is certainly cost-effective in most subgroups of patients [43].

*Key points*

- Between 130 and 180 million people are infected with HCV worldwide and there are around 700,000 deaths related to HCV per year.
- Prevalence is highest in Africa and Asia and lowest in North America, Europe, and Australia.
- Risk factors include intravenous drug use, co-infection with HIV, history of blood transfusion or organ transplant before 1992, history of long-term hemodialysis, history of detention, and tattoos or body piercings.
- Route of transmission is mainly via blood (syringe exchange between drug users, transfusion of unscreened blood, tattoos, piercing, reuse or improper sterilization of contaminated medical equipment, and needle-stick injuries).
- Mother-to-baby transmission can occur (especially if the mother is co-infected with HIV).
- Sexual transmission is rare.

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