This article presents an overview of the historical timeline of the gradual discovery of various hepatitis viruses and the pivotal roles of epidemiological observations, human experimentations, and laboratory research in their discovery and containment.

**ABSTRACT**

Viral hepatitis is an ongoing global infectious public health problem and a major cause of chronic liver diseases, including liver cancer. Previously described as “epidemic jaundice,” viral hepatitis has been known to exist since ancient civilizations. The contagious nature of the illness was suspected even in the eighth century CE. Records from major military campaigns in different continents from the 18th to 20th centuries, including the American Civil War and the First and Second World Wars, reported that “campaign jaundice” caused significant morbidity of the troops and impacted war strategies. Epidemiological observations from late 19th century and research, including human experimentation in the 20th century, led to the gradual identification of a distinct “infectious hepatitis” agent transmitted by oral-fecal transmission, known later as hepatitis A virus (HAV), and a “serum hepatitis” agent transmitted by inoculation or transfusion of serum, blood or plasma, or sexual contact. Experiments that involved feeding and injecting infected feces, urine, and serum into volunteered military personnel, prisoners, and mentally retarded children raised issues of informed consent and mental competency of the retarded children. Only until the 1960s was one of the causative agents of “serum hepatitis,” the hepatitis B virus (HBV), discovered. Further research led to the discovery of additional hepatitis viruses (HCV, HDV, HEV, and HGV). Breakthroughs in the containment of the hepatitis epidemic included development of hepatitis vaccines and recent therapeutic successes for hepatitis C. This paper presents an overview of the historical timeline of the gradual discovery of the causative agents of viral hepatitis.

**INTRODUCTION**

Viral hepatitis refers to inflammation of the liver caused by viral infection. Most cases of viral hepatitis are caused by HAV, the causative agent of viral hepatitis A (previously called infectious hepatitis, infectious jaundice, or campaign jaundice); hepatitis B virus (HBV), the causative agent of viral hepatitis B (previously called serum hepatitis); hepatitis C virus (HCV), the causative agent of viral hepatitis C (previously called Non-A, Non-B hepatitis); or hepatitis E virus (HEV), the causative agent of enter-
Historical Path of Discovery of Viral Hepatitis

According to the World Health Organization (WHO), viral hepatitis is one of the most common infectious diseases and a global public health problem. About 1 in 12, or 500 million people, are chronically infected with HBV or HCV, with millions more at risk. One million deaths each year can be attributed to viral hepatitis infections and its complications. The majority of the global burden of viral hepatitis is in the Asia-Pacific region.

The path to various discoveries in this field showcases scientific ingenuity but is also full of controversies, especially related to human experimentation. Modern medicine has come a long way since the earliest documentation of jaundice as a manifestation of viral hepatitis, but surprisingly, there are no good reviews in the recent literature highlighting this incredible journey. This review traces various discoveries that eventually led to our current understanding of various hepatotropic viruses and viral hepatitis.

Ancient Period

Early epidemics of jaundice were reported in the time of Babylonia and ancient China over thousands of years ago [1]. Hippocrates documented an epidemic of jaundice occurring on the island of Thassos in the fifth century BCE [2]. A description of liver disease including jaundice can be found in the Babylonian Talmud of the fifth century BCE as a cause of fever, malaise, lassitude, stomach problems, and sometimes death [3]. The contagious nature of “jaundice” was first mentioned in a letter from Pope Zacharis to Saint Boniface in 751 CE, in which Pope Zacharis instructed Saint Boniface, Archbishop of Mainz, to hold off serving Holy Communion to persons with jaundice until all the rest had been served and to bury horses infected with the same condition [4]. Throughout history, hepatitis caused frequent pandemics in Europe, ranking only behind cholera and plague [3].

Epidemic Jaundice or Infectious Hepatitis

Disease outbreaks called “Epidemic Jaundice,” or “Campaign Jaundice” (hepatitis A infection) plagued armies and civilians during medieval wars and impacted militaries for centuries [3]. The French called the disease jauniesse des camps; to the Germans it was Soldatengelbschüt; scientists called it icterus, in reference to a yellow bird from Greek mythology [3]. Similar conditions were described as infectious hepatitis in the United States, infective hepatitis in England, and Botkin’s disease in Russia [5]. Epidemics of jaundice occurred in Europe in the 17th, 18th, and 19th centuries, likely due to the growing and increasingly crowded populations.

The Military records from the British Military Hospitals in Germany from 1761 to 1763 documented epidemics of illness among the troops with fever, jaundice, vomiting, diarrhea, abdominal pain, and occasional fatalities [6]. Similar epidemics were reported among British troops in India and may have been caused by “bad water,” “change of diet,” and “great repletion after long fasting” [7]. Fatal cases of hepatitis following dysentery were reported in Bengal in 1796 [8]. Jaundice also decimated Napoleon’s army during his Egyptian campaign in 1798 [3]. Epidemics of jaundice involving a French army in Pavia during the Italian war coincide with a similar epidemic in the town of Pavia [9]. Army surgeons described similar “epidemic jaundice” in almost all parts of the world, including Europe, Asia, and America, caused by small parasites, denominated germs that were “the producers of serious and even fatal forms of hepatic complaint” [10]. An epidemic of jaundice also inflicted the military and civilian populations in Paris during the Franco-Prussian War in 1870 [3]. In retrospect, we feel that these “epidemic jaundice” or “campaign jaundice” were likely the result of HAV, HEV, or other virus outbreaks.

A misconception of hepatitis as “catarrhal jaundice” by Virchow, who misunderstood the cause of jaundice as the consequence of blockage of the common bile duct by mucus plug, delayed the discovery of the true infectious nature of hepatitis [1,11]. In his
lecture series in 1874, Murchison discussed cases of jaundice independent of obstruction of the bile duct [12]. He described “Epidemic Jaundice” in children in Essen in 1772 with high fatality, in Rotherham in 1862 associated with bad drainage and preceded by fatal outbreak of enteric fever, and London in 1846 after a prevalence of extremely hot weather and outbreaks of enteric fever, and fatal cases resembling those of “acute yellow atrophy of the liver” [12]. Other physicians described an epidemic in the island of Martinique that inflicted 30 pregnant women, 20 of whom died after suffering an abortion of premature labor [9]. We believe it is very likely that these fatal cases represent outbreaks of viral hepatitis with fulminant hepatitis from HBV, HCV, HEV, or other viruses.

During the American Civil War, over 71,000 cases of jaundice were reported among both Union and Confederate troops, with outbreaks of sporadic cases and local epidemics of jaundice with fever and diarrhea, largely attributed to the insanitary conditions of the battlefield [13]. However, the mortality from jaundice was low [1]. In Africa, approximately 6,000 cases of jaundice were reported among the British and Dominion troops in the Boer War in South Africa [1].

During WWI, highly contagious epidemics of “infectious jaundice” were reported in British troops in the Middle East Campaign at Gallipoli and Egypt, affecting up to 25% of the units [14]. No parasites or bacteria were identified, and the condition was thought to be more consistent with hepatitis following a systemic infection rather than catarrhal jaundice from plugging of the bile duct, as postulated by Virchow [14]. The possibility of “blood infection” through person-to-person transmission closely associated with dysentery, enterocolitis, or diarrhea was suggested as a cause of “epidemic jaundice of campaign” in Alexandria, Gallipoli, Mudros, Salonika, and Mesopotamia, with involvement of a third or more of some units [15].

During WWII, 200,000 cases of “epidemic jaundice” occurred among US troops alone from 1942 to 1945 [16]. In total, the German army and citizens suffered over 5 million cases of jaundice [1,17]. Major outbreaks often occurred around the Mediterranean shores, including Palestine, Egypt, and Syria [18]. Investigations of fatal cases revealed no evidence of duodenal catarrh or obstruction of the common bile duct by mucus [18]. Interestingly, military officers were more susceptible to the conditions than other ranks [19]. Potential causes for this phenomenon include the officers’ congregation in isolated communities and segregation from civilian population with their own lodgings, social clubs, swimming pools, and improvised portable bathing facilities to conserve water [19].

Facing the need to achieve military success during the Second World War, both the US and Britain intensified their research of the understanding of the cause and transmission of the “campaign jaundice” that had significantly impacted the fighting forces.

**DISCOVERY OF HEPATITIS A VIRUS, IMMUNOGLOBULIN, AND VACCINE**

In 1945, Stokes and Neefe showed that immune globulin (concentrated antibodies obtained from pooled human plasma) provided protection against illness among children at a summer camp who had been exposed to hepatitis A by either preventing or attenuating the hepatitis A infection [20,21]. “Since then, immune globulin has been used widely for post-exposure prophylaxis.” Currently, it “remains an effective intervention for preventing the transmission of hepatitis A to family members and other close contacts of patients who have recently become ill” [21].

In 1973, with the use of immune electron microscopy, Feinstone el al. identified a “spherical 27-nanometer particles” in stool obtained from the feces of hepatitis A patients in the acute stage of the disease [22]. The authors concluded that “the particle was serologically specific for this disease, and every hepatitis A patient tested demonstrated a serological response to this antigen,” thus suggesting “that it is the etiologic agent of hepatitis A” [22].
In 1996, Hilleman at Merck developed a hepatitis A vaccine with attenuated HAV. With the development of a childhood vaccination for hepatitis A virus infection, the incidence in the United States has decreased significantly, although “the majority of the world’s population is still at moderate-to-high risk for hepatitis A virus infection” [23]. In 2001, more than 10,000 cases were reported in the United States, but “the actual number of cases of hepatitis was probably 5 times that reported, and the number of new asymptomatic infections was probably 10 times the number of reported symptomatic cases” [21]. According to Craig, “[one] third of the US population has serologic evidence of previous hepatitis A infection, with a prevalence ranging from 9 percent among children 6 to 11 years of age to 75 percent among persons 70 years of age or older” [21]. Nevertheless, “the rates of hepatitis A infection in the United States have been decreasing gradually during the past several decades” [21]. The decrease is likely due to the “use of hepatitis A vaccine since 1995 in many communities where the rate of infection had been high,” combined with “advances in hygiene, including improved water supplies, enhanced sewage disposal, reduced crowding, augmented food safety, and other factors” [21]. In developing countries, where the hepatitis A vaccine is not readily available, “nearly all people have had hepatitis A infection by early adulthood” [21].

**Serum Hepatitis or Serum Jaundice**

In 2012, Bar-Gal et al. reported the discovery of the full viral genome of ancient HBV (aHBV) extracted from the liver of a 16th century Korean mummy [24]. The authors concluded that “[t]he calculated time of most recent common ancestor suggests that the Korean HBV sequence origin dates back at least 3,000 years and possibly as long as 100,000 years” [24]. The proven existence of HBV in ancient times corroborated Blumberg’s landmark discovery of Australian antigen in an aborigine who had never received blood transfusion, which was subsequently confirmed to be Hepatitis B surface antigen (HBsAg) [25]. We agree with Dr. Krugman’s opinion that “[i]n retrospect, it was obvious that the Australian aborigine [reported by Dr. Blumberg was] a hepatitis B carrier” with HBsAg [5].

Most authors credited Lurmen with reporting the first epidemic of serum hepatitis in 1883 to 1884 in a Bremen shipyard where the workers received vaccine against smallpox derived from human lymph of cases of Vaccinia (cowpox) [26]. 191 of 1,289 workers developed jaundice within 1 to 7 months after receiving the same lot of lymph, whereas 500 workers in the same shipyard vaccinated with a different lot of lymph were unaffected [26]. Lurmen concluded that “Considering the distribution of cases [accordingly], one must take into account the [vaccination] … as the etiological source of icterus epidemic” [3].

Subsequent outbreaks of injection-associated hepatitis were described. In 1908, McDonald discovered that acute yellow atrophy of liver tends to occur in groups and recognized the possibility of a virus as an infectious cause of the disease [27]. He reported an acute, subacute, and chronic phase of yellow atrophy of the liver with cirrhosis in the chronic cases [27]. He also described the development of jaundice in some patients being treated for syphilis [27].

Observations by Stokes in 1920 reported a dramatic increase of 1,000 percent of patients who developed severe jaundice and arthritis after receiving injections of arsphenamin for syphilis at the Mayo Clinic from August 1917 to July 1920 [28]. After ruling out syphilis or arsphenamin as a cause of the jaundice outbreak, the authors suggested a systemic infection of hematogenous source as the possible cause [28]. Similarly, in 1943, McCallum reported a high percentage of jaundice outbreaks in venereal disease centers after being injected with arsphenamine [29]. He suspected that infectious agents were being transmitted from patient to patient by sharing unsterilized and contaminated syringes and needles containing small amounts of infected blood [29].

In 1937, Findlay reported a total of 52 cases of “acute hepatitis” 2 to 7 months after yellow fever immunization of British troops, featured by malaise, loss of appetite, nausea, vomiting, jaundice, dark
urine, pale stool, and weakness [30]. The authors concluded that the post-vaccinal hepatitis could be due to some virus injected with the serum because the vaccine was filtered and treated to be “bacteriologically sterile” [30]. The clinical presentation of post-vaccinal hepatitis was analogous to outbreak of jaundice following antisyphilitic treatment [30]. Similar clinical observations were described in horses with jaundice and acute necrosis of liver approximately 62 to 78 days after inoculation against horse-sickness virus with serum from previously infected horses [30]. In 1938, Propert reported seven cases of hepatitis in children after an injection of convalescent measles serum; three children died of acute necrosis of liver [31].

In 1942, the US Secretary of War reported that 28,585 cases of jaundice had developed among army personnel between January 1 and July 4, apparently from the use of vaccination against yellow fever [32]. The total number of deaths was 62, with a ratio of one death for every 461 cases [32]. In 1944, Turner described an outbreak of hepatitis affecting 4,083 military persons at Camp Polk, Louisiana, from May 1942 to September 1942, after the use of only one lot of yellow fever vaccine [33]. As a result of the high infection rate in Camp Polk, the entire unit was unable to go abroad [3].

Seefe et al. reported a follow-up of the 1942 hepatitis outbreak linked to the receipt of specific lots of yellow-fever vaccine involving approximately 50,000 US Army servicemen [34]. Follow-up of the veterans who had received the implicated vaccine showed 97% of the group of veterans who received the yellow-fever vaccine and developed jaundice tested positive for antibodies to HBV; 76% of the group of veterans who received the yellow-fever vaccine but remained well tested positive for antibodies to HBV; and only one subject had hepatitis B surface antigen, for a carrier state of 0.26% among recipients of the implicated vaccine [34]. The authors concluded that HBV caused the outbreak with about 330,000 military persons possibly infected, and resultant rare occasions of a Hepatitis B carrier state, but induced Hepatitis B antibodies that persisted for life [34].

In 1943, the British Ministry of Health published a memorandum on “Homologous Serum Jaundice” describing an outbreak of jaundice involving 86 of the 266 soldiers inoculated with convalescent plasma from mump patients and 12 cases of jaundice in persons who received transfusion of plasma or whole blood [19]. In addition, based on the reported cases of “Syringe-Transmission Hepatitis,” researchers believed that an icterogenic agent was present in apparently normal individuals [19]. Outbreaks of jaundice occurred in patients receiving injections or venepunctures in clinics for various reasons, including arsenotherapy in syphilitic clinics, diabetic clinics, sanatoria, and arthritis clinics [19]. Potential causes for these outbreaks included the following: a limited number of available syringes that was unable to meet the high demand, thus requiring the sharing of syringes and needles between patients; the common practice during venipuncture of aspirating small amounts of blood into the syringe to ensure insertion of the needle in the vein; and simply washing the syringes, without sterilizing or boiling them (to avoid potentially breaking them) [19]. The incidence rate of hepatitis in syphilitic clinics that did not sterilize used needles and syringes ranged from 30% to 60% of all patients, whereas there was no jaundice in groups receiving injections by sterilized apparatus [19]. The authors concluded: “Hepatitis was being transmitted in the course of venipuncture and intravenous injections” [19].

Importantly, the authors observed that the “incidence of hepatitis tended to be low in clinics where syringes were sterilized between patients, and high in clinics where the syringes were “merely washed” [19]. In addition, the “[high] infectivity of blood during the long incubation period resulted in continuous contamination of needles and transmission to almost all the patients” [19]. Based on these observations, researchers suspected that an infectious agent carried in human blood was being transmitted
from patient to patient by means of syringes and needles that had been inadequately sterilized and was causing the serum hepatitis [19].

At that time, two distinctive clinical forms of hepatitis were recognized based on clinical and epidemiological features. One form of hepatitis had short incubation period, transmitted by oral-fecal route, and occurred as epidemics named “infectious hepatitis” or “campaign jaundice” (now designated as HAV). Another form of hepatitis had a longer incubation period and was transmitted by parental injections or blood transfusion, hence the name “serum hepatitis” (now designated as HBV). Patients with infectious hepatitis were immune to the same type of hepatitis, and patients with serum hepatitis were not immune to the infectious type. In 1947, MacCallum suggested the names of hepatitis A and hepatitis B for these two forms, respectively [35].

**ROLE OF HUMAN EXPERIMENTATIONS**

Over the past century, human experimentations played a significant role in the discovery of viral hepatitis and led to many controversies. Many of these experiments that were pivotal in the discoveries of HAV and HBV cannot be conducted today due to ethical considerations. One of the key issues prior to the discovery of HBV by Dr. Blumberg in mid-1960s was the inability of the researchers to isolate and propagate the infectious agents that caused the two main types of hepatitis: that is, infectious hepatitis (HAV) and serum hepatitis (HBV). In the 1940s, humans were the only known susceptible host for hepatitis virus proliferation, and attempts to isolate and propagate the viruses in a laboratory by using cell cultures, guinea pigs, hamsters, rabbits, mice and rats, and even non-human primates failed. A series of experiments in humans established the differences in mode of transmission of HAV (infectious hepatitis) and HBV (serum jaundice), demonstrated protective immunity, and established these as clearly separate disorders.

In 1942, Voegt fed volunteers with duodenal fluid obtained from patients with hepatitis, with one in four patients becoming infected [36]. From 1941 to 1942, Cameron injected serum from jaundiced soldiers with infectious hepatitis from Palestine into soldier volunteers, infecting them with hepatitis [37]. In 1944, MacCallum injected serum and sprayed feces from patients with infectious hepatitis into the nose of volunteers [38].

In 1945, Havens fed volunteers with feces and serum, and he injected serum from patients with infectious hepatitis into volunteers, who became infected with hepatitis [39]. The authors also injected the serum of patients with serum jaundice into volunteers, who also became infected with hepatitis [39]. Accordingly, the authors concluded that hepatitis could be caused by oral feeding of stool and serum and by injection of serum from patients with infectious hepatitis [39].

Neefe et al. fed pooled feces from patients with active serum hepatitis to volunteers [40]. None of the patients showed evidence of hepatitis during a 4- to 6-month period, suggesting that the causative agent either was not present in the feces or was not active when administered by the gastro-intestinal route [40]. By contrast, volunteers fed with pooled feces of patients with infectious hepatitis developed hepatitis within 26 days, confirming the observation of other authors that the causative agent is present in feces of patients with active disease [40].

In 1945, Neefe et al. described an outbreak of infectious hepatitis in a summer camp at Poconos Mountains [41]. Volunteers were inoculated with serum, feces, nasopharyngeal washings, and urine from infected camp patients [41]. Research findings indicated that the causative agent responsible for this epidemic of infectious hepatitis was water borne, excreted in the feces of persons infected with the disease [41]. Anything subject to direct or indirect contamination with feces could provide a potential means of transmission [41].

Subsequent human experimentations demonstrated homologous immunity in serum jaundice (or serum hepatitis) and infectious hepatitis, and protective effect of normal human globulin when administered
during the incubation period of epidemic infectious hepatitis. In 1945, Haven et al. confirmed that volunteers convalescing from experimentally induced infectious hepatitis were resistant to re-inoculation with the same strain of virus 6 to 9 months later [42].

In 1946, Neefe et al. orally fed and parenterally injected infected feces and serum into different groups of volunteers [43]. The findings revealed that virus from patients with serum hepatitis (or serum jaundice) is present in pooled plasma and induced hepatitis in normal volunteers after being inoculated parenterally but not orally; feces from patients with serum hepatitis failed to induce hepatitis when administered orally or parenterally (Seitz filtrate) to volunteers; onset of hepatitis in serum hepatitis was relatively insidious; and volunteers who had serum hepatitis after inoculation were resistant to re-infection with serum hepatitis virus but susceptible to infection with virus of infectious hepatitis [43]. For infectious hepatitis, virus-induced active hepatitis developed after 17 to 37 days in 73% of volunteers who were inoculated orally but in only 11% of volunteers who were inoculated parenterally [43]. The interval from inoculation with infectious hepatitis virus to the onset of hepatitis did not exceed 37 days [43]. Infectious hepatitis virus was present in the blood and feces of patients with active hepatitis due to oral administration of the virus [43]. Volunteers who developed infectious hepatitis were resistant to reinfection to infectious hepatitis virus but were susceptible to parentally injected serum hepatitis virus [43]. The authors observed that after so-called “catarrhal jaundice,” patients were resistant to infectious hepatitis virus but not resistant to serum hepatitis virus for 4 to 10 years [43]. These observations suggest an antigenic similarity of the causative agent of so-called “catarrhal jaundice” and infectious hepatitis, and a difference in antigenic properties of the causative agent of “catarrhal jaundice” and serum hepatitis (or serum jaundice) [43].

In 1951, Stokes et al. conducted human experiments at different institutions, such as institutions for the mentally retarded, prisons, student nurses from orphanage, and state training schools, using subjects such as mentally retarded children and adults, prison inmates, student nurses, “boys and girls,” and “adult employees” [44]. The authors concluded that gamma globulin was “highly protective in passive immunization against viral (infectious) hepatitis,” even at a dosage of “0.01 ml per pound of body weight” [44]. Stokes showed that “injection of gamma globulin, an antibody-rich distillate of human serum, could modulate the clinical course of infectious hepatitis by means of ‘passive’ immunity” [44]. He predicted that if hepatitis infection occurred during the period of passive immunity induced by the gamma globulin, the “clinical disease would be mild and long-lasting immunity to future infection might result” and accordingly named this theory “passive-active” immunity [44].

Subsequent studies on the natural history, epidemiology, and transmission of viral hepatitis were conducted from 1956 through 1971 at Willowbrook State School (WSS), a state-funded residential facility for mentally disabled persons in Staten Island, NY, on institutionalized mentally disabled children. Hepatitis was endemic at WSS and Saul Krugman, MD, a pediatrician, was asked to investigate and research for ways to prevent and control its spread at WSS. Krugman’s experiments on mentally retarded children raised issues of informed consent and mental competency and generated intense ethical debates among researchers and bioethics scholars [45-47].

**DISCOVERY OF HBV**

HBV was serendipitously discovered by Baruch Blumberg who was interested in studying the role of blood antigen polymorphisms, inherited differences in specific blood proteins, in genetics of disease susceptibility [5,48]. The discovery of HBV led to a blood-screening campaign that significantly reduced the incidence of post-transfusion hepatitis from HBV [48]. More importantly, this discovery led to the development of a highly effective hepatitis B vaccine, which over the next several decades protected hundreds of millions of people from HBV infection and led to a decrease in the incidence of
HBV-associated hepatocellular carcinoma, thus constituting the first effective vaccine in preventing any cancer [48]. Dr. Blumberg was awarded the Noble prize for his contribution in 1976 [1].

In the 1950s, Blumberg obtained blood samples from native populations from remote areas of the planet in order to investigate their genetic differences and how that might impact their susceptibility to different diseases. He also obtained blood samples from hemophiliac patients who had received blood transfusions from multiple donors and, hence, produced antibodies against antigens from donors. In 1965, Blumberg reported the discovery of the “Australian antigen” in the sera of an Australian aborigine, which reacted immunologically with a panel of sera from hemophiliac patients by forming a precipitin line in agar gel immunodiffusion [25]. He speculated that the “antigen” is present in the “normal” sera of the Australian aborigine because the aborigine never received blood transfusion, and the “antibody” is present in the sera of patients with hemophilia because they have previously received multiple blood transfusions, and tentatively called the protein as “Australia antigen” [25].

In 1968, Prince and Okochi established that the Australian antigen was found in most patients with serum hepatitis but not infectious hepatitis, and he established that blood containing Australian antigen was more likely to cause post-transfusion hepatitis [49,50].

In 1969, after further research, Blumberg et al. reported the presence of “Australian antigen” in the sera of 20% of 125 patients with acute viral hepatitis in the United States [51]. Other patients showing increased frequencies of “Australian antigen” included patients with Down syndrome who have abnormal liver function tests and evidence of hepatitis in liver biopsy, patients with post-transfusion hepatitis, and leukemic patients [51]. Based on these observations, Blumberg concluded that “the antigen is selectively associated with viral hepatitis,” and “intimately associated with a virus causing hepatitis,” demonstrated by its presence in infected serum [51]. He discovered that the “Isolated Australian antigen is a particle 20μm in diameter with an appearance compatible with that of a virus” [51].

Subsequent studies suggested that the Australian antigen may be the infective virus of serum hepatitis itself and reported the existence of a carrier state of the Australian antigen for nearly 20 years [52]. A technologist at Dr. Blumberg’s laboratory and a patient with Down’s syndrome, who were previously negative for Australian antigen, both developed hepatitis and became seropositive for Australian antigen, indicating that the latter was the etiological agent of “serum hepatitis” [1].

In 1970, with the use of immune electron microscopy, Dane et al. reported the identification of HBV with “virus-like particles about 42 nm,” which “may be complete virus of Australian-Antigen-Associated Hepatitis,” and “that the much more numerous 22 nm particles and long forms of Australian antigen are surplus virus-coat material” [53]. These were subsequently called “Dane particles.” Subsequent studies in 1971 by Almeida et al. reported the use of detergent on Dane particles and observed there were two particles, surface and core [54]. It was revealed that the Australian antigen was a surface protein of the HBV particle (i.e. the Hepatitis B Surface Antigen [HBsAg]). The latter was shown to be noninfectious but tremendously useful as a screening tool for hepatitis B infection in blood donors and infected individuals who were likely at risk of transmitting HBV to others, such as pregnant women, health care workers, homosexuals, and drug abusers. HBsAg also served as the immunogen for Blumberg’s subsequent development of hepatitis B vaccine.

After the identification of the HBV as the causative agent of serum hepatitis, subsequent hepatitis research direction was guided by several new objectives: (1) the need to develop a vaccine to protect the population against hepatitis infection, (2) the need to screen for HBsAg on blood donors to prevent post-transfusion hepatitis, and (3) the need to create a new screening test, as the method of agar gel diffusion was inadequate [48].
Hepatitis B immune globulin is used to prevent hepatitis B infection in persons without demonstrated immunity to HBV who have been exposed to the virus perinatally (i.e., infants born to HBsAg-positive mothers), by cutaneous or mucosal contact with HBsAg-positive blood or bodily fluids, or by sexual contact with a person who is positive for HBsAg (or in the case of infants younger than 12 months, by exposure to a primary caregiver in whom acute hepatitis B infection has been diagnosed) [55].

The first Hepatitis B vaccine was developed in 1969 by Blumberg and Millman, based on the understanding that the presence of antibody (anti-HBs) against the HBsAg is protective against hepatitis B infection [48]. Large amounts of HBsAg, a subunit of HBV, were extracted from sera of hepatitis B carriers [48]. Through a unique method of purifying the HBsAg and separating it from the infectious particles, Blumberg and Millman isolated HBsAg from infected blood and produced a prototype HBV vaccine for which they received a patent [48]. In 1970, Krugman also attempted to develop a hepatitis B vaccine by boiling serum containing HBsAg for 1 min and using it as a vaccine to inoculate mentally retarded children at Willowbrook. However, the boiled serum appeared to provide some but not complete protection against subsequent hepatitis exposure [48].

Based on Blumberg and Millman’s concept of utilizing HBsAg purified from infected blood, Merck and its executive scientist, Maurice Hilleman, were able to manufacture sufficient quantity of hepatitis B vaccine (Heptavax B) for field trials. In 1981, the field trials conducted by Wolf-Szumness showed that this highly purified formalin-inactivated vaccine (Heptavax B) prepared from HBsAg-positive plasma was safe, immunogenic, and highly efficacious with 95% of vaccinated subjects developing antibody against HBsAg [56]. The vaccine protected against acute hepatitis B infection, asymptomatic infection, and chronic antigenemia. Within the next 2 years, FDA approved the Heptavax B.

Large-scale production of the hepatitis subunit vaccine was limited by the available supply of infected blood from hepatitis B carrier and the potential risk of transmitting other viruses present in the infected blood. In 1982, William Rutter and his colleagues were successful in synthesizing HBsAg in genetically altered yeast [57]. In 1984, Maurice Hillemen reported their success in producing this second generation of hepatitis B vaccine by recombinant monoclonal DNA techniques that allowed the expression of HBsAg in yeast cells, the first example of a vaccine produced from recombinant cells that is effective against a human infection [58]. By using recombinant yeast, the production of the hepatitis B vaccine eliminated the need for infected blood from hepatitis B carrier, and thus the potential risk of infection from HBV and other unknown infectious agents that might be present in the infected blood and the limitation of available supply of infected blood from hepatitis B carriers [58]. This recombinant vaccine was the first vaccine produced by genetic engineering for use in humans and was licensed by the FDA in 1986.

In 1991, “the Advisory Committee on Immunization Practices (ACIP) recommended a comprehensive strategy to eliminate HBV transmission in the United States, including universal vaccination of infants” using recombinant hepatitis vaccine on all newborn infants and children in the United States [55]. In 1995, the ACIP added “routine immunization of adolescents,” and in 1999, “immunization of all persons up to 18 years of age” [55]. This strategy has reduced the overall annual incidence of acute HBV infections in the United States by 67%, “from 8.5 cases per 100,000 persons in 1990 to 2.8 per 100,000 in 2002” [55]. Based on data showing “a decrease in the burden of acute (and hence chronic) HBV infection as a result of immunization programs for infants, children, and adolescents,” the WHO “recommended that all countries provide universal HBV immunization programs for infants and adolescents” [55]. By 2003, “79 percent of the 192 WHO member states had adopted policies of universal childhood immunization against HBV” [55]. Those countries benefited as a result of the policies; Taiwan, for example, experienced “dra-
matic decline in the incidence of neonatal HBV infections and subsequent sequelae in Taiwan after the introduction and widespread use of hepatitis B vaccine” [55]. There have also been efforts to spread the vaccine to healthcare workers: “since 1991, the Occupational Safety and Health Administration has mandated that health care workers be educated about the vaccine and that employers offer it free of charge” [55]. In 2000, it was estimated that a billion doses of the vaccine had been administered making it one of the most commonly used vaccine in the world [48].

Notably, the HBV vaccine is also a first “cancer vaccine” that can prevent hepatocellular carcinoma, the primary cancer of the liver and one of the most common cancers in the world [48]. Most of the primary liver cancer is associated with HBV or HCV infection. In addition to providing protection against HBV infection, the hepatitis B vaccine also prevents the development of the deadly hepatocellular carcinoma caused by HBV infection [48]. “The apparent success of the HBV vaccine in the prevention of primary cancer of the liver has encouraged the search of other vaccines for cancer prevention” [48].

Furthermore, over the decades since the implementation of the hepatitis B vaccine, significant drop in hepatitis B carriers in Asian countries has been observed. The current Hepatitis B vaccine demonstrates “protective serum anti-HBs antibody concentrations” in “90 percent of healthy adults and 95 percent of infants, children, and adolescents” after completion of the vaccine series [55]. For “immunocompetent persons in whom antibody levels of at least 10 mIU per millimeter develop, the efficacy of the vaccine is nearly 100 percent” [55].

POST-TRANSFUSION HEPATITIS/ TRANSFUSION-ASSOCIATED HEPATITIS

In 1943, Beeson reported seven patients who developed jaundice between 1 to 4 months after receiving whole blood or plasma transfusion [59]. Based on the fact that four of the seven patients received four or more transfusions with relatively large volumes of blood plasma, the authors suggested that the “risk of receiving a jaundice producing substance in a transfusion may be increased in proportion to the number of donors from whom blood or plasma is received” [59]. An explanation for this phenomenon is that “jaundice is caused by a virus which happened to be present in the body fluids of donors, and which, after a long incubation period, produced a hepatitis in the recipient” [59]. Unlike “campaign jaundice,” these post-transfusion outbreaks of jaundice had “a long incubation period, varying from one to seven months” [59].

In the 1960s, a large percentage of donated blood originated from paid donors, who are at a higher risk to be infected with hepatitis virus than volunteer donors. Consequently, the incidence of post-transfusion hepatitis was high. In 1964, 1 year before Blumberg discovered Australian antigen, Grady et al. reported that “the apparently lower incidence of post-transfusion hepatitis in Boston can be related to the type of blood donors used,” finding that “the lowest incidence of post-transfusion hepatitis was seen when commercially supplied blood was avoided” [60]. The authors recommended blood bank personnel to “exclude potential carriers of hepatitis virus by rejecting prospective blood donors with jaundice or signs or symptoms of any infectious disease” [60]. Such donors include “those having previously donated blood to persons in whom hepatitis subsequently developed, those with signs of excess exposure to potentially contaminated needles (e.g., narcotic addicts), those giving a history of infectious hepatitis and those whose appearance suggest unreliability” [60]. The authors stated that “it is not a new idea that alcoholic patients, drug addicts and other unreliable persons who deny disease for fear of rejection are attracted to any receptive and remunerative blood procurement center” [60].

The direct relationship between post-transfusion hepatitis and HBV was confirmed by Gocke et al. who, in 1970, reported, “Transfusion of blood containing Australia antigen was associated with development of hepatitis or an antibody response in 74% (31 of 42) recipients” [61]. Based on the findings,
the authors concluded that “a positive correlation does exist, and that transfusion of blood containing Australia antigen is hazardous” [61]. However, the authors cautioned that “some cases of post-transfusion hepatitis occur in recipients of antigen-negative donor blood” [61]. At the time, further work was required “to determine whether the latter observation reflects a lack of sensitivity in the test system or the existence of other infectious agents” [61]. Since then, the hepatitis B surface antigen has been used as a marker for post-transfusion hepatitis.

In 1970, Roselyn Yalow and Solomon Berson developed a serologic test called radioimmunoassay that can detect the presence of minute quantities of the HBsAg and antibody (anti-HBs) in blood [62]. This method is simpler and more sensitive than the agar gel diffusion method used by Blumberg in the discovery of Australia antigen. The ability to detect the infectious virus in the blood represented the first available method to screen the blood supply for infectious hepatitis virus.

In 1972, the FDA mandated screening of all blood donations for HBsAg. In 1976, FDA further mandated the use of an all-voluntary donor system [63]. These measures by FDA led to a substantial reduction in post-transfusion hepatitis caused by HBV [63]. HAV was determined to not be a causative agent of post-transfusion hepatitis. However, up to 10% of blood transfusion recipients continued to develop post-transfusion hepatitis, of which most cases were attributed to an unknown “non-A, non-B hepatitis” [63]. Accordingly, a “Non-A Non-B hepatitis (NANBH)” was defined as a cause of post-transfusion hepatitis after exclusion of HAV and HBV [63]. In 1986, FDA implemented the use of surrogate marker testing for NANBH and reduced the per unit risk of post-transfusion hepatitis from 1 in 200 to about 1 in 400 [63]. HCV was discovered in 1989 and was established as the causative agent of over 90% of non-A, non-B post-transfusion hepatitis [63].

**DISCOVERY OF HCV**

Globally, 130 to 170 million people, or about 3% of the global population, have chronic hepatitis C, a “major cause of liver cirrhosis and hepatocellular carcinoma” and “the most common cause of liver-related death and reason for liver transplantation” [64]. About 3.2 million Americans, or 1% of the US population, are infected with HCV [65]. In the United States, hepatitis C recently surpassed human immunodeficiency virus (HIV) infection as a cause of death [64].

In 1988, HCV was discovered by Michael Houghton working at a California biotechnology company, Chiron, in collaboration with the CDC [66,67]. The discovery of HCV is unique, as all other methods that led to the discovery of HAV and HBV had failed to identify the causative agent of NANBH, and novel molecular methods were used to identify the viral genome, much before visualization of the actual virus. Houghton identified a cDNA clone using sera of chimpanzees and humans with NANBH that hybridized with a single-stranded RNA made of about 10,000 nucleotides only from sera from NANBH patients. The RNA was homologous to genome of flaviviruses and was subsequently recognized as the “hepatitis C virus.”

Later in 1989, Alter et al. measured the antibody (anti-HCV) to HCV, which causes non-A, non-B hepatitis, by radioimmunoassay in prospectively followed transfusion recipients and their donors [68]. Of 15 patients with chronic non-A, non-B hepatitis documented by liver biopsy, all seroconverted for the antibody; of five with acute resolving non-A, non-B hepatitis, three (60%) seroconverted [68]. The authors concluded that HCV is the predominant agent of transfusion-associated non-A, non-B hepatitis, and screening of donors for anti-HCV could prevent the majority of disease cases [68]. “Surrogate” assays for HCV infection “would have detected approximately half the anti-HCV-positive donors involved in the transmission of hepatitis that we identified” [68]. The authors also acknowledged the possibility of “a second non-A, non-B hepatitis virus” causing the absence of anti-
HCV in cases clinically diagnosed as non-A, non-B hepatitis and “estimated that the routine application of this assay in donor screening would detect approximately 85 percent of those capable of transmitting non-A, non-B hepatitis” [68]. In summary, “[m]easures taken to exclude donors who are at risk for exposure to the human immunodeficiency virus, the increased use of autologous blood, and the introduction of surrogate assays have all served to diminish the risk of transfusion-transmitted hepatitis” and “[t]he coming introduction of anti-HCV assay should bring a further reduction in this risk, and most important, a reduction in the long-term consequences of this common blood-borne infection” [68].

In 1990, blood screening for hepatitis C began. The missing piece to the post-transfusion hepatitis puzzle was provided by Donahue et al. in 1992 who wrote, “The most common serious complication of blood transfusion is post-transfusion hepatitis from hepatitis C virus (HCV)” [69]. This observation is supported by the sharp decrease “in the incidence of post-transfusion hepatitis C,” since the “implementation of donor screening for surrogate markers (liver function tests) and antibodies to HCV” with a rate of about 3 per 10,000 units transfused [69].

The introduction of more sensitive nucleic acid amplification testing (NAT) for HCV further decreased the risk of HCV transmission through blood transfusion to approximately 1 in 2 million [70]. The risk of HCV transmission through blood transfusion is far less than that of HBV risk, “which remains at 1 in 200,000 to 500,000 using a combination of anti-hepatitis B core and hepatitis B surface antigen testing” [70].

**Hepatitis C Therapy**

Antiviral therapy for chronic hepatitis C first began almost 30 years ago with alpha interferon-based treatment [71]. The side effects of cytokine, the need for up to a year of therapy, and the limited response rate of 50% or less, even among carefully selected patients, limited the impact of this early therapy [71]. The recent development of direct-acting antiviral agents (DAAs) has revolutionized HCV treatment, offering prospects for the first comprehensive cure of a chronic viral infection in humans [64]. These new regimens include the combination of ledipasvir and sofosbuvir, two new direct-acting anti-viral agents with potent activity against HCV yield rates of sustained virologic response of 93% to 99% [71].

Unfortunately, challenges in combating HCV infection effectively and comprehensively remain [64]. First, patients with HCV often are diagnosed at a late stage (in high-income countries) or seldom diagnosed at all (in low- or middle-income countries) due to a lack of effective screening programs [64]. Most Americans with HCV became infected decades ago and are unaware of their status, since the symptoms have not yet manifested [72]. Half of the estimated 3.2 million Americans infected with HCV may not be aware that they are infected [71]. Rich et al. projects that in the absence of large-scale efforts at diagnosis and treatment, the burden of HCV-associated disease is expected to increase dramatically in the near future, and more than 1 million people are expected to die from HCV by 2060 in the United States [72].

Second, the high cost of DAAs hampers the effort to fight HCV [64]. A 12-week regimen of sofosbuvir alone currently costs $84,000, or $1,000 per tablet [71]. Adding ledipasvir to the treatment will further increase the cost, not to mention the expenses for diagnostic assays, monitoring, and physician visits [71]. With the current estimates of costs, treating even half of the estimated 3.2 million US residents currently infected with HCV “would add billions of dollars to an already overburdened medical care system” [71]. The high cost will limit their use in most infected patients in low- or middle-income countries and may lead to the “selective use of DAAs for certain patient subgroup” in high-income countries [64].

Third, reinfection remains a possibility even after successful curative therapy [64]. The “extraordinary sequence heterogeneity and ability to evade host immune responses” makes developing a “broadly
protective vaccine” that could potentially eradicate HCV difficult [64].

Another significant challenge stems from “poor global advocacy, perhaps due in part to a false perception of the indolent course of HCV,” resulting in most patients with HCV infection in low- or middle-income counties remaining untreated [73]. Despite the fact that the “global mortality burden of viral hepatitis (A, B, C, and E) is similar to that of HIV and higher than that of tuberculosis or malaria,” viral hepatitis lacks the political support, national and global policymaking and funding, and social activism in comparison with these other global diseases [73].

In the meantime, there are other ways to control HCV infection on a global scale: developing effective HCV screening programs, including full implementation of birth-cohort screening in the United States, establishing access to affordable treatment in low- and middle-income countries, and developing strategies for reducing the risk of transmission (e.g., safe injection practices) [64].

Another possibility is to target and engage “higher-prevalence countries,” such as those with low-and middle-incomes, and to prioritize “higher-risk groups, such as patients with advanced liver fibrosis, and HIV or hepatitis B co-infection” for therapy [73]. Jayasekera et al. advocated “efforts toward equitable access” for the “definitive, curative therapies” to treat HCV, and urged “[listing] DAAs as essential medicine,” “[creating] novel international funding streams,” “[allowing] legal pathways for generic-agent manufacture,” “[differential] pricing of branded originator drugs,” and “[task] shifting of testing and treatment from physicians” [73].

According to Holmberg et al., “there are many points of intervention” in identification and care of patients with HCV infection which will improve the identification and care of patients with HCV and mitigate the increase in hospitalization and deaths resulting from HCV infection [65]. One example is to implement a one-time HCV screening test as recommended by the CDC for those born between 1945 and 1965, which can “help identify the many infected people who would not be targeted for testing as the result of established risk-based testing strategies” [65]. In addition, “a better job of getting HCV-infected persons who know their HCV status into care, evaluated, and, as appropriate, treated” is required [65].

Notably, an increased focus on screening and treatment for HCV in the criminal justice system is needed [72]. According to Rich et al., it is the “best place to efficiently identify and cure the greatest number of HCV-infected people,” with more than 10 million Americans entering and leaving prisons and jails each year, “including nearly one of every three HCV-infected Americans” [72]. The war of drugs has led to the highest per capita incarceration rate in the world; as a result, Rich et al. reasoned, “most Americans who injected drugs have been incarcerated at some point in their lives” [72]. The rate of HCV infection in the incarcerated population has reached epidemic proportions, with one in six prisoners infected with HCV [72]. The prevalence of HCV in prisons, combined with the fact that most HCV infection in the United States is the result of past use of injection drugs and that more than 95% of prisoners are eventually released, demonstrates the effect of the incarcerated population on HCV in the community [72]. As a result, screening and treatment in the criminal justice system represents a critical opportunity to have a substantial effect on the epidemic of HCV [72]. With the low cost of screening and the high prevalence of HCV in the incarcerated population, Rich et al. advocated that everyone in that population should be screened [72]. Furthermore, early detection and treatment in correctional settings could prevent future need for treatment, which, along with its attendant costs, would occur predominantly in the community while also preventing the spread of HCV [72].

**DISCOVERY OF HEPATITIS D VIRUS**

In 1977, Rizzetto et al. described a new antigen, termed δ (delta), detected by direct immunofluorescence in the liver cell nuclei and in the blood of patients with HBsAg-positive chronic liver disease
[74]. They also reported that δ antibody was found only in the serum of chronic HBsAg-positive carriers, with a high prevalence in patients with liver damage [74]. Subsequently, it was determined that delta antigen was not part of HBV but of a separate defective virus that requires the presence of HBV for infection and was named the hepatitis D virus (HDV) to conform to the nomenclature of hepatitis viruses and classified within the genus of Deltavirus [75].

The superinfection of the delta virus in patients with hepatitis B resulted in an increased level of inflammation and necrosis of liver cells, and hence a more rapidly progressive form of HBV-related chronic liver disease, including liver cirrhosis, liver decompensation, and death [76]. Currently, HDV infection is distributed worldwide, involving approximately 5% of HBsAg carriers amounting to 15 to 20 million HDV-infected individuals [76]. It is highly endemic in Mediterranean countries, northern parts of South America, and Central Africa [76]. The virus is transmitted through the parental route and is associated with intravenous drug use, multiple sexual partners, tattooing, and piercing [76]. However, currently there is no efficient therapy except for prolonged treatment with recombinant interferons, which is the only therapy that has shown antiviral activity against HDV, but with only 20–40% efficiency [76].

**DISCOVERY OF HEV**

In 1980, a “common source waterborne epidemic of viral hepatitis” associated with gross fecal contamination of water was reported in Kashmir valley [77]. The epidemic's waterborne nature established the “nonparenteral mode of spread, i.e. a fecal oral spread of the disease” [77]. However, serologic tests for hepatitis A and hepatitis B failed to “reveal an etiologic agent of hepatitis,” even though “the mode of spread of the epidemic, length of incubation, clinical features and biochemical test results of the patients studied resembled that of hepatitis A” [77]. Therefore, the results suggested the possibility of another human hepatitis virus distinct from hepatitis A or hepatitis B.

Another report in 1980 found similar results and described “one of the first serologically documented reports of epidemic hepatitis transmitted via contaminated water that was not caused by HAV” [78]. The author stated that “a large portion of hepatitis in India seems to be caused by previously unrecognized agents,” signifying “growing evidence that non-A, non-B agents which epidemiologically resemble HAV exist,” and are “responsible for much morbidity and mortality, especially in parts of Asia” [78].

In a study by Balayan, a human volunteer was orally fed “pooled stool extracts from patients with presumed non-A, non-B hepatitis” [79]. The volunteer consequently developed non-A, non-B hepatitis, with symptoms similar to those of hepatitis A, without “serological evidence of recent hepatitis A or hepatitis B infection” [79]. Examining the volunteer’s stool using immune electron microscopy revealed “27- to 30-nm spherical virus-like particles indicating possible causative agent of the fecal-oral non-A, non-B hepatitis” [79]. In 1993, Chauhan et al. reported the presence of HEV in both the stools and sera of one of the authors who deliberately infected himself by orally ingesting stools from a patient infected from the hepatitis E epidemic, hence suggesting the possibility of sporadic transmission of HEV parenterally [80].

Currently, hepatitis E, the fifth known form of human viral hepatitis, is probably “the most common cause of acute hepatitis and jaundice in the world” [81]. It is the second most common form of human viral hepatitis in the United States [81]. It is less common in the United States and other developed nations than in developing countries in Asia and Africa, where it is a “major public health problem” [82]. According to population-based surveys from 1988 to 1994, 21.0% of US adults had anti-HEV antibody, which is “lower than that with anti-HAV antibody (38.3%), but higher than that with antibodies against hepatitis B (5.7%) or hepatitis C (2.0%)” [81]. An estimated one-third of the world’s population has been infected with HEV, based on seroprevalence [82]. The lifetime infection risk is
more than 60% in India, with hundreds of thousands of illnesses every year [82].

The role of hepatitis E in causing liver disease is currently not well known. Hepatitis E is usually self-limited and can occur sporadically and in epidemics [82]. However, for pregnant women, who have “the highest risk of associated hepatic failure,” the case fatality ratio increases from 5% to 25%, and those who survive often have “high rates of spontaneous abortion and stillbirth” [82]. Interestingly, similar epidemiological and clinical presentation was reported in 1863 by Harley on the island of Martinique, where an epidemic “inflicted thirty pregnant women” and resulted in twenty fatalities after “an abortion or premature labor” [9]. Currently, the rHev vaccine is effective in preventing hepatitis E, with a reported efficacy of 95.5% [82].

**DISCOVERY OF HEPATITIS G VIRUS**

Approximately “10 to 15 percent of patients with parenterally transmitted or transfusion-associated non-A, non-B hepatitis have no evidence of hepatitis C virus (HCV) infection” and were “classified as having non-A-E hepatitis” [85,86]. In 1996, a new member of the Flaviviridae family, the hepatitis G virus (HGV), was discovered. This virus was identical to another newly cloned agent designated as GB virus, type C [87,88]. However, additional studies did not substantiate HGV as an etiologic agent of non-A-E hepatitis [85]. Persistent infection with HGV was common, but it did not lead to chronic disease and did not affect the clinical course in patients with hepatitis A, B, or C [85]. Other studies of patients with transfusion-associated hepatitis concluded that “HGV was common in a group of volunteer blood donors, and it [could] be transmitted by transfusion” but “most HGV infections were not associated with hepatitis” and “did not worsen the course of concurrent HCV infection” [86]. The authors found “no causal relation between HGV and hepatitis” [86].

**ONGOING CHALLENGES OF A GLOBAL EPIDEMIC**

The advances in our knowledge of hepatitis are breathtaking and miraculous. Through the work of scientists such as Dr. Baruch Blumberg, we have greatly advanced our knowledge of viral hepatitis. The development of vaccines and cures or other therapies for certain types of viral hepatitis provides hope for the future. As of 2009, 91% of WHO Member States included the HBV vaccine in their infant immunization programs and more than 70% of infants received three doses of this vaccine, which provided them with lifelong protection from HBV [89]. 179 Countries have introduced the HBV vaccine that has prevented approximately 1.3 million deaths worldwide [89].

Despite this progress, hepatitis is still a significant global epidemic infecting 1 in 12 people worldwide with hepatitis B infecting about 2 billion and hepatitis C infecting about 150 million people [89]. It is estimated that about 1.4 million new hepatitis A virus infections and 20 million hepatitis E infections occur globally each year [89]. In many countries, there is a dearth of adequate knowledge and awareness among both the general population and health professionals concerning hepatitis, according to the WHO [89]. Countries without a hepatitis surveillance system have difficulty making evidence-based policy decisions [89]. Another barrier to comprehensive treatment of hepatitis is the failure to screen donated blood for diseases such as HBV, HCV, HIV, and syphilis [89]. Irregular supply of test kits and the high costs of HCV screening tests are among the most commonly reported barriers to screening of donated blood [89]. Furthermore, the lack of access to both clean drinking water and improved sanitation, especially in low-income countries, makes it easy for large portions of a population to contract hepatitis [89]. Although treatment for viral hepatitis B and C exists, it is often inaccessible or too expensive for most people in settings where resources are scarce [89].

In order to fight hepatitis, the WHO advocates raising awareness of viral hepatitis infections in order to educate at-risk populations. Other recommended
measures include hepatitis policy based on accurate data, and prevention of transmission, through immunization policies and protecting high-risk groups [89]. Guidelines for screening, for increasing access to care, for treating patients with chronic HBV or HCV infection, and for managing drug resistance are also critical to fighting hepatitis [89].

CONCLUSIONS

This article summarized the historical milestones in the discovery of viral hepatitis. The combination of knowledge of the history of viral hepatitis with effective policies that raise global awareness; prevent transmission; and provide accessible and affordable screening, care, and treatments to those infected with viral hepatitis will allow us to begin effectively combating this silent global epidemic.

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; NANBH, Non-A, Non-B hepatitis; HDV, hepatitis D virus, HEV, hepatitis E virus, HFV, hepatitis F virus; HGV, hepatitis G virus; HBsAg, hepatitis surface antigen; Anti-HBs antibody, Anti-hepatitis B surface antigen antibody; WHO, World Health Organization; WSS, Willowbrook State School; ACIP, Advisory Committee on Immunization Practices; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus.

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