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TOPIC

Descriptive epidemiology of hepatitis B and C in the M'sila region

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Dedication

I dedicate this modest work:

To my dear parents, Nassima and Omar.

For all their sacrifice, their love, their tenderness, and above all their support throughout my studies.

To my maternal grandmother Louiza and my late paternal grandmother Hafsia, thank you for inspiring my path in this life.

To my maternal grandfather Amor and in loving memory of my paternal grandfather Abdelaziz.

To my brother Khalil.

To my uncles and aunts, for their constant encouragement and their trust in me.

To my cousins and my friends.

Without forgetting of course my dear colleagues, specifically Amira Wissal, we have formed an unbeatable team.

To all my teachers during 19 years of study, I will always be grateful. Thank you for always being there for me.

Khouloud.

Dedication

To my dearest parents Zouina and Abdel karim whose unwavering support and belief in me have been my greatest strength.

To my soul mother Salima whose spirit continues to be a beacon of inspiration in my life.

To my beloved aunts Malika and Hadda whose love and guidance have been invaluable.

To my cherished sister Lina and my steadfast brother Djamel whose presence in my life has been a constant source of comfort.

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This thesis is a testament to all of you, whose love, support, and belief in me have made this achievement possible.

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ملخص

تعد كل من الفيروسات التهاب الكبد B (HBV) وC (HCV) من الأسباب الأكثر شيوعًا لالتهاب الكبد الفيروسي المزمن في جميع أنحاء العالم وفي الجزائر خاصة وذلك لسرعة انتشارها خاصة في الدول النامية. الهدف من هذه الدراسة وصف وبائي دقيق ومفصل للمرضى الذين أصيبوا بالتهاب الكبد B وC في ولاية المسيلة.

من أجل ذلك قمنا باعتماد المنهج الوصفي التحليلي الرجعي سواء للمعطيات على مستوى مديرية الصحة والسكان الفترة 2013- 2022 وعلى مستوى وحدة الأمراض المعدية لمستشفى الزهراوي لعام 2023 ولتحليل المعطيات ورسمها استخدمنا2021 Excel.

سجلت الاحصائيات أن بلدية مقرة تملك أكثر انتشار لHBV بأعلى بنسبة %79,54 في عام 2020 تليها بلدية برهوم وعين الخضراء بالنسب التالية على التوالي %47,17 و %35,89. أما بالنسبة الى انتشار HCV كانت بلدية مقرة الأعلى بنسبة %58,3، عام 2020. تعتبر الفئة العمرية الأكبر من 65 سنة أكثر إصابة بالنسبة إلى HCV وبين 20 و44 سنة إلى HBV. على الرغم من عدم توفر معلومات كافية بهذا الصدد إلا أن الدراسة أظهرت أن سبب العدوى الرئيسي للالتهاب الكبدي الفيروسي B هو علاج الأسنان بنسبة %17 وسبب العدوى للالتهاب الكبدي الفيروسي C هو العمليات الجراحية بنسبة 18%.

يمكن **استغلال هذه النتائج الأولية من أجل توجيه البحوث المستقبلية و سياسيات الصحة العمومية الهادفة للحد من آثار هذه العدوى في منطقة المسيلة** كما يمكن التقليل من مشكلة عدوى التهاب الكبد الفيروسي المزمنة وذلك بإتباع الإجراءات الوقائية اللازمة ونشر التوعية.

Résumé

Les virus de l'hépatite B (VHB) et de l'hépatite C (VHC) sont parmi les causes les plus courantes de l'hépatite virale chronique dans le monde, en particulier en Algérie, en raison de leur propagation rapide notamment dans les pays en développement. Le but de cette étude est de fournir une description épidémiologique détaillée des patients ayant contracté l'hépatite B et C dans la Wilaya de M'Sila.

Pour cela, nous avons adopté une approche descriptive, analytique et rétrospective en utilisant les données de la Direction de la Santé et de la Population pour la période 2013-2022, et du service des Maladies Infectieuses de l'Hôpital Zahrawi pour l'année 2023. Pour l'analyse et la visualisation des données, nous avons utilisé Excel 2021.

Les statistiques ont enregistré que la commune de Magra avait la plus forte prévalence de VHB avec un taux de 79,54 % en 2020, suivie des communes de Berhoum et Ain Khadra avec des taux respectifs de 47,17 % et 35,89 %. Quant à la prévalence du VHC, la commune de Magra avait le taux le plus élevé à 58,3 % en 2020. Le groupe d'âge de plus de 65 ans était le plus touché par le VHC, tandis que le groupe d'âge de 20 à 44 ans était le plus touché par le VHB. Bien qu'il y ait des informations insuffisantes à cet égard, l'étude a montré que la principale cause d'infection par le VHB était le traitement dentaire à 17 %, et la principale cause d'infection par le VHC était les interventions chirurgicales à 18 %.

Ces résultats préliminaires peuvent être utilisés pour orienter les recherches futures et les politiques de santé publique visant à réduire l'impact de ces infections dans la région de M'Sila. De plus, le problème des infections chroniques par l'hépatite virale peut être atténué en suivant les mesures préventives nécessaires et en sensibilisant la population.

Abstract

Hepatitis B (HBV) and Hepatitis C (HCV) viruses are among the most common causes of chronic viral hepatitis worldwide, particularly in Algeria, due to their rapid spread and especially in developing countries. The aim of this study is to provide a detailed epidemiological description of patients who contracted hepatitis B and C in the Wilaya of M'Sila.

For this purpose, we adopted a descriptive, analytical, and retrospective approach using data from the Health and People's Directorate for the period 2013-2022, and from the Infectious Diseases Departement of Zahrawi Hospital for the year 2023. For data analysis and visualization, we used Excel 2021.

Statistics recorded that the region of Magra had the highest prevalence of HBV with a rate of 79.54% in 2020, followed by the regions of Berhoum and Ain Khadra with rates of 47.17% and 35.89% respectively. As for the prevalence of HCV, Magra had the highest rate at 58.3% in 2020. The age group over 65 years old was the most affected by HCV, while the 20-44 age group was most affected by HBV. Although there is insufficient information in this regard, the study showed that the main cause of HBV infection was dental treatment at 17%, and the main cause of HCV infection was surgical procedures at 18%.

These preliminary results can be used to guide future research and public health policies aimed at reducing the impact of these infections in the M'Sila region. Additionally, the problem of chronic viral hepatitis infections can be mitigated by following necessary preventive measures and raising awareness.

List of abbreviations

ALT: Alanine Aminotransferase.
Anti-HBc (IgM): Hepatitis B core Antibody (Immunoglobulin M).
Anti-HBs: Hepatitis B surface Antibody.
APOBEC3: Apolipoprotein B editing Complex 3.
AST: Aspartate Amino-transaminase.
AuAg: Australian Antigen.
bDNA: Branched deoxyribonucleic acid.
cccDNA: Covalently closed circular deoxyribonucleic acid.
CD81: Cluster of Differentiation 81.
CHB: Chronic Hepatitis B.
COVID-19: Corona Virus Disease 2019.
CRE: Cis-acting RNA elements.
DAA: Direct-acting Antivirals.
DNA: Deoxyribonucleic acid.
DR1: Direct repeat 1.
DR2: Direct Repeat 2.
EGFR: Epidermal growth factor receptor.
eIF3: Eukaryotic translation initiation Factor 3.
EN1: Enhancer 1.
EN2: Enhancer 2.
FEN1: Flap structure-specific endonuclease 1.
HAV: Hepatitis A Virus.
HBcAg: Hepatitis B core Antigen.
HBeAg: Hepatitis B envelope Antigen.
HBsAg: Hepatitis B surface Antigen.
HBV: Hepatitis B Virus.
HBx protein: Hepatitis B x protein.
HCC: Hepatocellular Carcinoma.
HCV: Hepatitis C Virus.
HDV: Hepatitis Delta Virus.
HEV: Hepatitis E Virus.
HIV: Human immunodeficiency Virus.
HSPG: Heparin sulfate proteoglycans.
IgG: Immunoglobulin type G.
IgM: Immunoglobulin type M.
INFa: Interferon Alpha.
INR: International Normalized Ratio.
IRES: Internal Ribosome entry site.
ISG: Interferon-Stimulated genes.
LIG1 and LIG3: Ligases 1 and 3.
mRNA: Messanger ribonucleic acid.
NANBH: Non-A Non-B Hepatitis.
NASH: Non-Alcoholic Steatohepatitis.
NIH: National Institutes of Health.
NK cells: Natural-Killer cells.
NS3 protein: Non-structural 3 protein.
NS4B protein : Non-structural 4B protein.
NS5A protein : Non-structural 5A protein.
NTCP: Sodium Taurocholate Co-Transporting Peptide.
ORF: Open Reading Frames.
PCR: Polymerase Chain Reaction.
pgRNA: Pregenomic ribonucleic acid.
PI: Protease inhibitor.
Pol: polymerase.
RBM24: RNA Binding Motif protein 24.
rcDNA: Relaxed circular Deoxyribonucleic acid.
RNA: Ribonucleic Acid.
ROS: Reactive Oxygen Species.
rRNA: Ribosomal ribonucleic acid.
SFMG: Société Française de médecine générale.
SH: Serum Hepatitis.
SL: Stem loop.
SLC10A1: Solute Carrier Family 10 member 1.
TDP2: Tyrosyl-DNA phosphodiesterase 2.
TOP1 and TOP2: Topoisomerases 1 and 2.
UTR: Untranslated regions.
WHO: World Health Organization.
WHV: Woodchuck Hepatitis Virus.

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Introduction

Introduction

Hepatitis is an ancient and frequent infection that has been known for 5000 years in China and that has affected the human liver in different ways surging from acute and benign inflammations to chronic and more complicated ones. This clinical variation depends on the origin of the infection; viral hepatitis being the most common type (Feinstone, 2019). Various viral entities can cause hepatitis, but the most prominent ones are hepatitis B and C viruses. Both possess a specific endemic character that makes their studying very important. (Damascus University et al., 2016)

On a global scale, the World Health Organization (WHO) has been closely monitoring both diseases by calculating their epidemiological parameters and updating their reports on their situations every few years. The WHO has also established an ambitious worldwide program that hopes to eliminate viral hepatitis by 2030 based on the efficient and continuous distribution of antiviral medications and vaccines that are available now. (WHO, 2023)

The WHO has divided the world into regions based on several properties and Algeria belongs to the African region where viral hepatitis is considered endemic (WHO). In Algeria, specific measures have been taken to help eradicate viral hepatitis by ensuring stable treatment plans and hepatitis b vaccination for those in need. Still, the epidemiological study of those diseases seems very limited (Health Ministry, 2022). Our objective in this study is to put up an epidemiological profile that is precise and detailed in terms of disease disparities for both hepatitis B and C that would help build a more solid ground for future studies as well as control its spread.

Bibliographic section

Chapter I: Epidemiology of the hepatitis infection.

Chapter I. Epidemiology of the hepatitis infection.

I.1. Definition:

Viral hepatitis is an infection that can result in an acute or chronic inflammation of the liver, mainly caused by a variety of viruses A to E (HAV, HBV, HCV, HDV, and HEV) (WHO, 2022), all of them have a tropism towards the liver tissue. Despite the clinical similarities, the pathogens belong to different families and could be distinguished pathogenesis, transmission routes, prevention, and therapy options (Dudareva et al., 2022). The importance of the epidemiological study of this infection stirs from the fact that it is recognized as a public health issue and it deals with a significant global burden (Lanini et al., 2018). The field of epidemiology in general has developed in tandem with social shifts, the advent of novel diseases, and the creation of other epidemiologically related fields, so using this tool to study hepatitis is very critical to understanding it. (Frérot et al., 2018)

I.2. Prevalence:

The World Health Organization estimates that 296 million people were living with chronic hepatitis B infection in 2019, accounting for a global prevalence of approximately 3.8%. While chronic hepatitis C infections are estimated to be around 58 million people, with a prevalence of 0.7%. (WHO, 2021)

The African region seems to be the most affected according to the WHO, with 91 million people living in this region infected with either hepatitis B or C. (WHO, 2022)

In Algeria, hepatitis B prevails in 2.15% of the general population while hepatitis C in 1% of them. (Health ministry, 2022)

I.3. Incidence:

The global incidence rate for hepatitis B and C is around 1.5 million people each, per year. The African region takes the lead with 990 000 new infections of hepatitis B and 210 000 new cases of hepatitis C every year, as we can resume in the illustration below (Figure 01). (WHO, 2021)

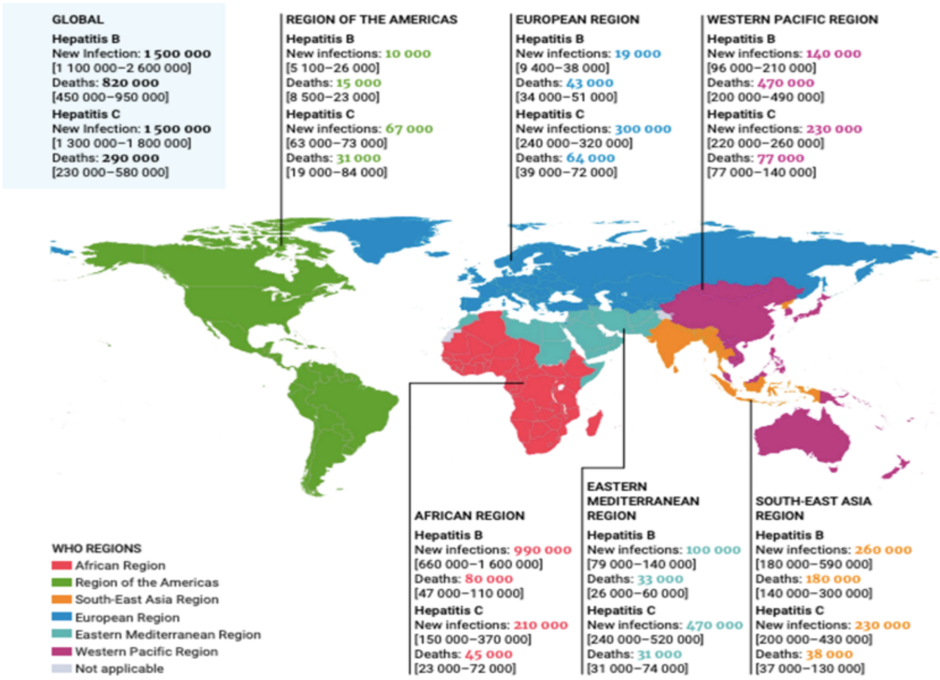

Figure 01: Distribution of global incidence of viral hepatitis B and C. (WHO, 2021)

I.4. Morbidity:

Morbidity deals with the rate of viral hepatitis within a population and viral hepatitis is known for having a major share in global morbidity. (Rísquez et al., 2022)

We notice a serious lack of information concerning Algerian data, apart from a prevalence rate no other ones are declared by the health ministry.

I.5. Mortality:

In 2019, according to the WHO, 820,000 people died from hepatitis B-related causes, while 290,000 others died from hepatitis C-related causes. This translates statistically to a rate of 10 deaths per 100,000 for hepatitis B and 4 deaths per 100,000 for hepatitis C. In Africa, hepatitis B was responsible for 80 000 deaths while hepatitis C for 45 000 was deaths. (WHO, 2021)

In Algeria, HBV-related deaths account for a rate of 2.7 while HCV-related mortality is 4.86, both recorded in 2019. (Coalition for Global Hepatitis Elimination, 2019)

I.6. Risk factors:

A risk factor is defined as a physiological or pathological attribute or characteristic leading to a higher risk for the individual in whom it is detected to contract a certain condition or a disease

(SFMG, 2019). In this case, both hepatitis B and C infections are significantly associated with multiple blood transfusions, tattooing/piercing practices, and a history of hospitalization or working in hospitals for healthcare providers. Hepatitis B though had a slightly higher linked risk with dental surgery and immunosuppressive diseases (Baliashvili et al., 2022). Other risk factors that could be general to liver failure are alcohol consumption, tobacco use, and high body mass index. (Kazmi et al., 2022)

I.7. Complications:

Persistent inflammatory processes play a crucial role in the progression of chronic hepatitis infection into its well-known complications. More than 80% of Hepatocellular Carcinoma (HCC) cases develop from chronic inflammation. In chronic HCV infection, HCC typically develops against the backdrop of cirrhosis. HBV-associated HCC occurs in 10-20% of cases without passing through the stage of cirrhosis and chronic inflammatory processes. During the infection, there's an induction of both innate and adaptive immune responses. This leads to the elimination of the pathogen through cytolytic and non-cytolytic processes. In case of unsuccessful pathogen elimination, inflammatory stimuli may persist, leading to permanent inflammation and impaired tissue regeneration. In HBV infection, the transition to chronic hepatitis is characterized by activation of the adaptive immune response, which involves HBV-specific CD8+ T cells and secretion of proinflammatory cytokines. The known regenerative processes no longer fully compensate for the destruction of liver tissue. The immunopathogenesis is further amplified by the release of Reactive Oxygen species (ROS) from CD8+ T cells, infiltrating natural killer cells (NK cells), as well as the release of proinflammatory cytokines. The interplay of these factors inhibits regenerative processes, stimulates genomic instability, and increases the occurrence of genomic mutations. There is milder inflammation in the case of chronic HCV infection, which depends significantly on other factors. HCV infection triggers responses from interferon type I and III, thus inducing the expression of a series of interferon-stimulated genes (ISGs). At the same time, there are HCV-specific CD8+/CD4+ T cell responses and activation of NK cells, leading to the release of proinflammatory cytokines and a significant increase in ROS levels. This, in turn, leads to lipid peroxidation and mitochondrial dysfunction which may contribute to a further increase in ROS levels and DNA damage. The persistent inflammation and incomplete regeneration cause the development of cirrhosis. (Glitscher et al., 2022)

I.7.1. Cirrhosis:

Cirrhosis, a chronic and irreversible scarring of the liver, is usually secondary to many health conditions of which viral hepatitis is a leading one. In 2019, 2.4% of deaths around the world were caused by cirrhosis. Among those 42% had a hepatitis B infection while 21% had a hepatitis C infection. (Figure 02) (Alberts et al., 2022)

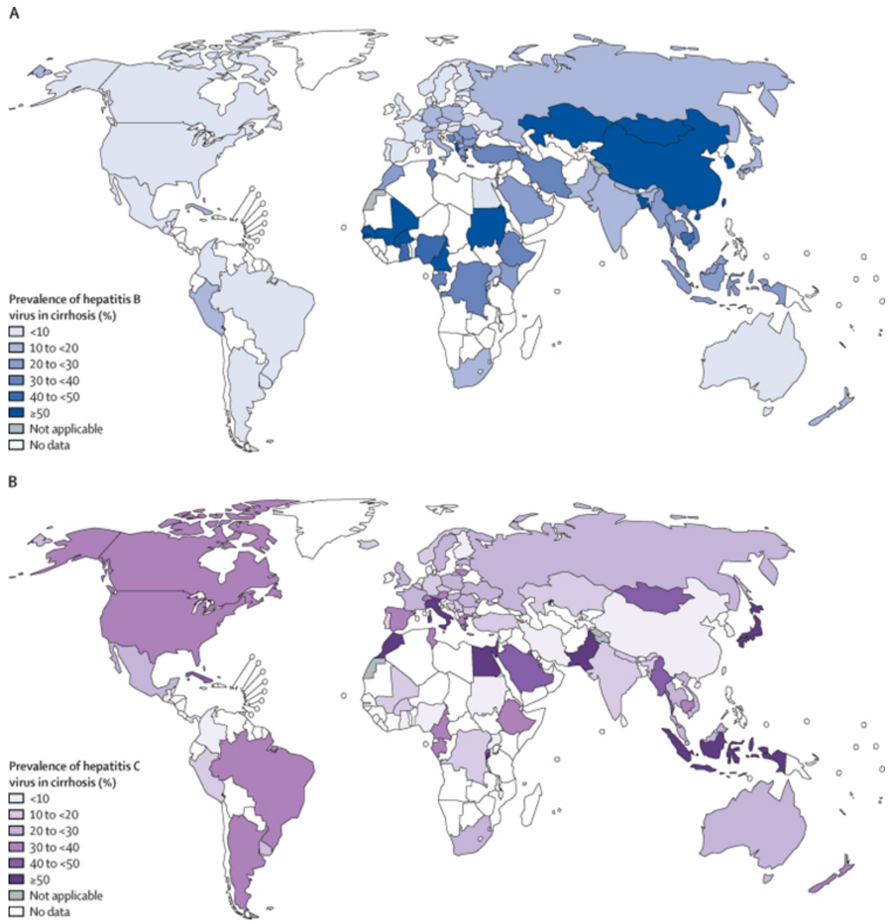

Figure 02: Prevalence of hepatitis B and C in global cirrhosis cases. (Alberts et al., 2022)

I.7.2. Hepatocellular carcinoma:

HCC is a cancer that begins in the hepatocytes, making viral hepatitis a significant risk factor for it. Studies show that persons infected with HBV risk of developing liver cancer is between 10-25%, and those infected with HCV are 10 to 20 times higher than average people with an incidence that ranges from 0.5-10%. (McGlynn et al., 2021)

For hepatitis B-infected patients, HCC can develop through either cirrhotic or non-cirrhotic ways. This means that it is either through the viral pathogenesis of HBV itself, inducing mutagenesis due to viral genome binding with the hepatocyte genome, or by the same mechanism described above of persistent liver inflammation. (Perisetti et al., 2021)

As for hepatitis C, Carcinogenesis might be due to the presence of Non-Structural 3 protein (NS3), Non-Structural 4B protein (NS4B), and Non-Structural 5A protein (NS5A) but the most accepted mechanism is the generation of ROS during a prolonged inflammatory process that will lead eventually to fibrosis, cirrhosis, and liver cancer. (Perisetti et al., 2021)

Chapter II: Hepatitis B.

Chapter II. Hepatitis B.

II.1. History:

The history of the current study on viral hepatitis began in 1963 when Nobel Prize winner Baruch S. Blumberg (1925-2011) published the first public report on the identification of a novel antigen known as Australia antigen. In the years that followed, AuAg (Australia antigen) became the first precise marker of viral hepatitis. (Gerlich, 2013)

Blumberg first assumed that AuAg was a polymorphic serum protein, like the lipoprotein antigen he had previously found. However, evidence quickly collected suggesting it may be related to hepatitis, which Blumberg first highlighted in a 1967 book. Parallel to this, Alfred Prince was hunting for a "serum hepatitis (SH) antigen" in the blood of hepatitis B patients and reported on it in 1968, but he quickly discovered it was like AuAg. Subsequently, multiple researchers established that Au/SH-Ag was a marker for acute or chronic hepatitis B and that Au/SHAg carriers appeared to be healthy. (Gerlich, 2013)

II.2. Virology:

HBV is a tiny, encapsulated, hepatotropic virus with a partially double-stranded, relaxed circular (rc) genome. It is the first member of the Hepadnaviridae family. Although animal hepadnaviruses, such as woodchuck hepatitis virus (WHV), duck hepatitis B virus (HBV), and others, do not cause infections in humans, they serve as model systems for the study of viral replication, pathogenesis, and the assessment of antiviral medicines against HBV. (Datta et al., 2012)

II.2.1. Structure:

The hepatitis B virus structure has been extensively studied, revealing its complex composition. HBV is a hepatotropic DNA virus, belonging to the hepadnavirus family, and shares similarities with hepatitis viruses found in various animal species such as woodchucks, ground squirrels, Pekin ducks, and herons. It is a relatively small virus, approximately 42 nm in diameter, with distinct features including an outer lipid-bilayer envelope and an inner nucleocapsid structure. (BSc, 2019)

The outer envelope of HBV is composed of a surface protein known as the hepatitis B surface antigen (HBsAg). Detection of HBsAg through a simple blood test serves as a primary diagnostic marker for HBV infection. Positive results indicate the presence of the virus within the individual.

Within the virus's inner core lies the hepatitis B core antigen, encapsulating the viral DNA and essential enzymes for replication (Figure 03). This core structure plays a crucial role in the viral lifecycle, which helps to facilitate replication and propagation within the host. Studies have elucidated the intricate relationship between HBV's structural components and its pathogenic mechanisms, offering insights into potential therapeutic targets and diagnostic strategies. (Humans, 1994)

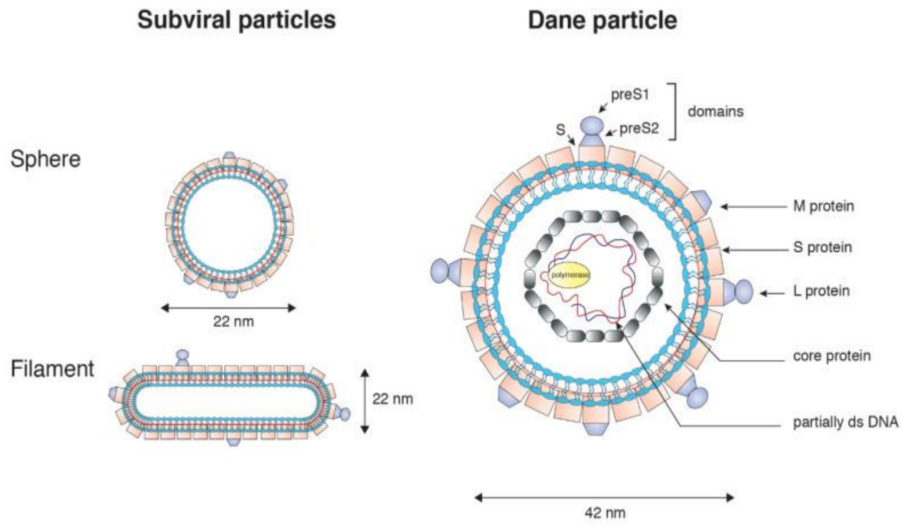

Figure 03: Structure of the HBV infectious particle. (Herrscher et al., 2020)

II.2.2. Genome:

The HBV DNA exhibits a highly compact and evolved organization of coding and regulatory regions, with every nucleotide serving a purpose within the genome. It codes for four overlapping ORFs (open reading frames): P (pol), C (core), S (surface), and X, each contributing to various viral functions. The P ORF encodes the viral polymerase essential for genome replication, while the C gene produces structural proteins and the 'e' antigen. The S region synthesizes envelope glycoproteins, and the X region encodes the multifunctional X protein. Moreover, the genome contains regulatory elements and signals for polyadenylation and encapsidation. (Datta et al., 2012)

Utilizing multiple in-frame initiation codons allows the production of different virion proteins from the same ORF, synthesizing diverse surface molecules. The preS1, preS2, and classical HBsAg proteins are products of the preS/S ORF, each initiated at distinct start codons. Similarly, the core protein gene produces HBcAg and HBeAg from different start codons, contributing to the virus's adaptability. (Datta et al., 2012)

HBV possesses a distinctive genome structure characterized by circular, relaxed, and partially double-stranded DNA. The asymmetry of the two strands, along with cohesive termini and direct repeats, facilitates viral replication. The minus strand contains a single 'nick,' while the long strand is incomplete, the twice featuring direct repeats crucial for replication initiation. Additionally, the negative strand carries a terminal protein linked to its 5′ end, while the plus strand begins with a capped oligoribonucleotide, highlighting the complexity of HBV replication mechanisms. (Figure 04) (Datta et al., 2012)

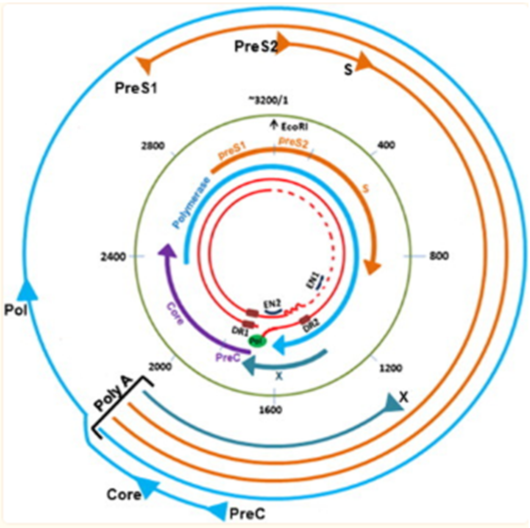

Figure 04: The diagram illustrates the genome and translational layout of HBV. Inside, the red circles represent the rcDNA, displaying the reverse transcriptase/polymerase (Pol) attached to the 5′ end of the complete minus strand DNA and a capped RNA oligomer linked to the 5′ end of the incomplete plus strand DNA. Direct repeats (DR1 and DR2) and enhancers (EN1 and EN2) are marked. The green line indicates viral genome positions in nucleotides. Protein-coding regions, including precore (PC) and core genes (violet), polymerase gene (blue), X gene (aqua), and envelope genes preS1, preS2, and S (orange), are depicted between the green and red circles. Genome positions vary based on HBV genotype. Outer semi-circular lines represent the four RNAs (genomic and subgenomic) corresponding to the ORFs, with arrowheads indicating initiation codon positions within each ORF. (Datta et al., 2012)

II.2.3. HBV replicative cycle:

Understanding the mechanism of action of direct-acting antiviral agents in development requires reviewing the HBV viral life cycle. HBV infection begins with loose attachment to heparan sulfate proteoglycans (HSPGs) on hepatocyte membranes, followed by binding to its entry receptor, Sodium Taurocholate Co-Transporting Peptide (NTCP), via interaction with the pre-S1 lipopeptide of the L envelope protein. Subsequently, fusion of the HBV envelope with the endosomal membrane occurs, leading to endocytosis. Uncoating releases the rcDNA genome, transported into the hepatocyte nucleus, where host enzymes repair it into covalently closed circular DNA (cccDNA). This cccDNA acts as the transcriptional template for viral mRNAs and pregenomic RNA (pgRNA), facilitating viral replication. Four viral transcripts—polymerase, core, surface, and X—are translated into 7 viral proteins in the cytoplasm. Core proteins self-assemble into a viral nucleocapsid, while pgRNA and viral polymerase are packaged into it through encapsidation. Viral replication proceeds through an RNA intermediate step within the nucleocapsid. Mature viral capsids containing rcDNA are enveloped with S, M, and L surface proteins in the endoplasmic reticulum and secreted as intact virions or transported back to the nucleus to replenish the cccDNA pool. (Spyrou et al., 2020)

II.2.3.1. HBV entry:

HBV entry into hepatocytes involves several sequential steps. Initially, the virus loosely attaches to the host cell surface through interactions with molecules like HSPGs, such as glypican 5. Subsequently, it engages more specifically and strongly with its primary receptor, the NTCP/SLC10A1, which is uniquely expressed in the liver and normally facilitates the uptake of bile salts. NTCP binds to a specific region (aa 2-48) of the preS1 protein, known to be crucial for receptor binding. This interaction triggers the internalization of the virus into the cell via endocytosis, likely facilitated by the involvement of a receptor tyrosine kinase, epidermal growth factor receptor (EGFR), which directly interacts with NTCP. Recent findings suggest that the oligomerization of NTCP can impact its ability to mediate viral internalization. Once internalized, the viral envelope fuses with cellular vesicles, though the exact mechanism remains unclear. The viral nucleocapsid is then directed towards the nucleus along microtubules and imported into the nucleus through the nuclear pore complex in a process dependent on importin. (Figure 05)

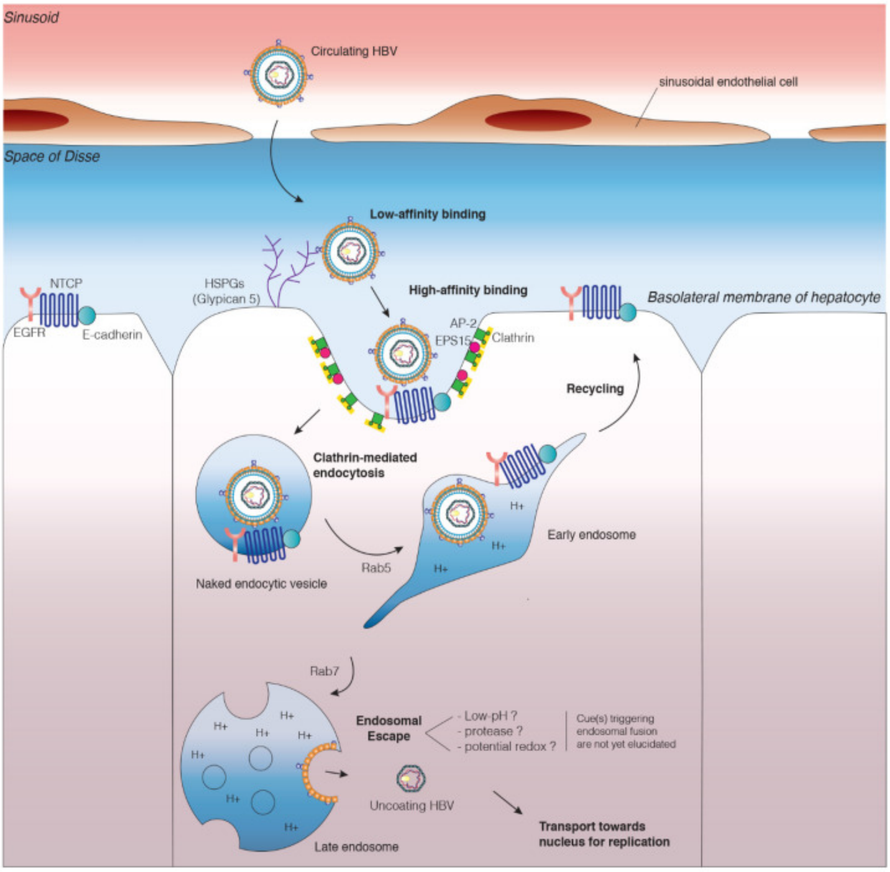

Figure 05: Early events in the life cycle of hepatitis B virus. HBV interacts with heparan sulfate proteoglycans (HSPGs), including glypican 5, on the hepatocyte cell membrane. HBV binds its receptor sodium taurocholate co-transporting polypeptide (NTCP) and its coreceptor epidermal growth factor receptor (EGFR). This internalization complex is associated with E-cadherin linked to N-glycosylated NTCP. This association permits the relocalization of NTCP to the plasma membrane. The HBV–NTCP–EGFR complex is taken up into the cell by clathrin-mediated endocytosis. The EGFR sorting machinery coordinates HBV transport in the endosomal network. Endosomal escape remains incompletely understood, but it has been suggested that the localization of HBV to late endosomes is crucial for productive infection and that fusion may occur in this compartment. The cues triggering endosomal fusion have yet to be clearly elucidated. Following endosomal escape, the free nucleocapsid is thought to use the microtubule network for transit to the nucleus, where it dissociates at the nuclear pore complex. Once within the nucleus, the relaxed circular DNA is converted into cccDNA, which acts as a template for transcription. (Herrscher et al., 2020)

II.2.3.2. cccDNA formation:

In the nucleus, HBV genetic material undergoes modifications facilitated by cellular factors. Initially, the Pol-linked terminal redundant sequence at the 5'-end of the minus strand DNA and the RNA oligonucleotide attached to the 5' end of the long strand DNA is excised from the rcDNA. This process, described by various studies, generates cccDNA, a key component for viral replication. Several factors contribute to cccDNA formation, including tyrosyl-DNA phosphodiesterase 2 (TDP2) and flap structure-specific endonuclease 1 (FEN1), involved in removing Pol and RNA primers, respectively. (Cui et al., 2015) (Ni et al., 2014) (Kitamura et al., 2018)

Subsequently, DNA polymerases (Pol κ and Pol α), DNA ligases (LIG1 and LIG3), and topoisomerases (TOP1 and TOP2) participate in filling the gaps in rcDNA. Despite uncertainties about the precise mechanisms and localization of cccDNA maintenance in the nucleus, it persists episomally and serves as a stable template for viral replication over time. Studies indicate varying half-lives for cccDNA, ranging from approximately 40 days in laboratory settings to potentially over 9 months in clinical observations (Ko et al., 2018) (Boyd et al., 2016). Factors influencing cccDNA stability include immune responses and cytokine stimulation, with proteins like apolipoprotein B editing complex 3 (APOBEC3) playing a role in modulating cccDNA stability. (Lucifora et al., 2014)

Moreover, integration of HBV DNA into the host genome occurs alongside cccDNA formation, potentially within a week of infection, according to recent cell culture studies. Although integrated HBV DNA is replication incompetent, it can contribute to the production of HBs antigen, impacting HBV-specific immune tolerance and disease progression. (Tu et al., 2018)

II.2.3.3. HBV transcription:

cccDNA functions as a minichromosome, associating with both viral proteins and host factors. The transcriptional activity of cccDNA is regulated by post-translational modifications of histones, such as trimethylation or acetylation of lysine residues, which influence transcriptional activity. Additionally, various histone modification enzymes and other factors are recruited to cccDNA to modulate viral transcription. These modifications can be targeted by interferon to suppress HBV transcription.

Transcription of HBV RNAs is regulated by the recruitment of cellular transcription factors to the viral promoter and enhancer regions on cccDNA. These factors include liver-specific nuclear receptors. Some factors activate transcription, while others suppress it.

Hepatitis Bx or HBx, an essential protein for HBV replication, plays a multifaceted role in regulating viral transcription. It associates with cccDNA and modulates the recruitment of chromatin-modifying enzymes to control the epigenetic status of cccDNA-associated histones.

HBx also affects the activity of the Smc5/6 complex, which suppresses HBV transcription, by inducing its degradation. (Figure 05) (Cui et al., 2015)

II.2.3.4. HBV RNAs stability:

Recent studies have highlighted the significance of HBV RNA stability in regulating viral replication. The presence of stem-loops called epsilon, at both 3' and 5' termini of HBV pgRNA is crucial for RNA packaging into capsids. Zinc finger antiviral protein (ZAP), RNA helicase super killer viralicidic activity 2-like, and IFN-induced exoribonuclease gene of 20 kDa (ISG20) have been identified as cellular factors that interact with HBV RNAs, promoting their decay. Additionally, non-canonical poly(A) RNA polymerase-associated domains containing proteins 5 and 7 have been implicated in stabilizing HBV RNA. Post-transcriptional modifications, such as N6-methyladenosine, at the epsilon stem-loop structures, can regulate HBV RNA stability. These findings underscore the intricate regulation of HBV RNA stability by various cellular factors. (Tsukuda & Watashi, 2020)

II.2.3.5. Encapsidation and DNA synthesis:

RNA encapsidation is a crucial step in HBV replication, requiring the involvement of HBc, Pol, and viral RNA. HBc monomers initially form dimers, which then self-assemble into icosahedral capsids. Concurrently, Pol interacts with the epsilon stem-loop of pgRNA at the 5’ terminus, forming a ribonucleoprotein complex incorporated into the capsid. Host chaperones aid in this process by interacting with Pol and optimizing its conformation. RBM24 mediates encapsidation by interacting with both Pol and epsilon RNA. Nucleophosmin B23 interaction with HBc also enhances capsid assembly. Several host factors are incorporated into the capsid. Following RNA incorporation, viral genome synthesis occurs within the nucleocapsid. The epsilon in pgRNA serves as a template for priming, initiated by a tyrosine residue in the Pol TP domain. The resulting complex is translocate to the DR1 sequence at the 3’ end of pgRNA for minus-strand DNA synthesis. The pgRNA template is degraded during this process, leaving a short RNA fragment translocated to DR2 and extended to the 5’ terminus of the minus strand DNA (Figure 06). Extension of the plus strand DNA eventually produces rcDNA. (Tsukuda & Watashi, 2020)

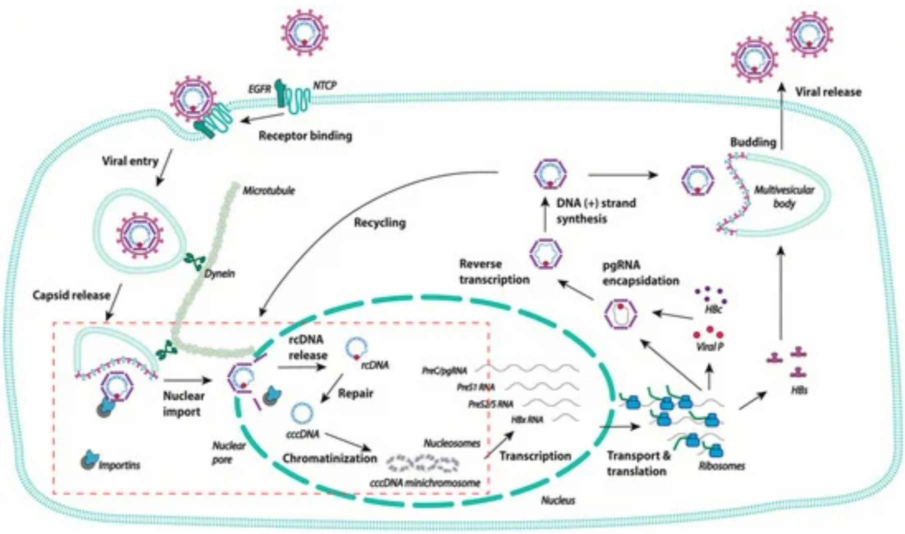

Figure 06: Diagram outlining the human hepatitis B virus (HBV) life cycle: Upon binding to the sodium taurocholate co-transporting polypeptide (NTCP) receptor, HBV is internalized via endocytosis, releasing the viral capsid into the cytoplasm. Utilizing the microtubule network, the capsid travels to the nuclear pore. Inside the nucleus, the relaxed circular DNA (rcDNA) is released and converted into covalently closed circular DNA (cccDNA), which undergoes chromatinization. This cccDNA acts as the template for transcribing all HBV RNAs. In the cytoplasm, the pregenomic RNA (pgRNA) is encapsidated and reverse transcribed into rcDNA. These capsids are then either enveloped in multivesicular bodies (MVB) and secreted as new virions or transported back to the nuclear pore to replenish the cccDNA pool. The stages of the viral life cycle discussed in the review are highlighted in the red box. (Diogo Dias et al., 2021)

II.3. Transmission and clinical manifestation:

II.3.1. Transmission:

The hepatitis B virus can spread through various routes, including vertical and horizontal transmission. Vertical transmission is commonly reported in regions with high endemicity, while horizontal transmission is prevalent in many other areas. Factors such as close contact with carriers and sharing personal items can contribute to intrafamilial transmission (Athalye et al., 2023). It spreads primarily through direct contact with infected blood or specific bodily fluids. The most common transmission route is from an infected mother to her baby during childbirth due to blood exchange. Other transmission routes include unsterile medical equipment, unprotected sex, and sharing unsterile needles. Fluid from cuts or sores is highly infectious, so it's important to keep them covered. However, the virus is not casually transmitted through activities like sneezing, coughing, shaking hands, hugging, or sharing meals. Daily activities like using the same utensils or hugging pose minimal risk unless there are bleeding gums or open sores. Infection risk is primarily associated with trace amounts of infected blood, rather than saliva or other bodily fluids.

For instance, while saliva on a toothbrush isn't a significant concern, the potential exchange of blood through shared toothbrushes is. (WHO)

II.3.2. Clinical manifestation: acute infection

During the initial six-month period of acute hepatitis B infection, individuals may experience symptoms such as loss of appetite, joint and muscle pain, low-grade fever, and possible stomach pain. Some may also develop more severe symptoms like nausea, vomiting, jaundice (yellowing of the eyes and skin), or a bloated stomach. Seeking medical attention is crucial, as treatment focuses on managing symptoms and preventing complications such as fulminant hepatitis, which can lead to sudden liver failure. It's important to avoid alcohol, limit smoking, eat healthily, and discuss medications with healthcare providers. While recovery from acute infection generally has few lasting effects, individuals should inform all healthcare providers of their past infection to prevent virus reactivation when taking immune-suppressing medications in the future. (Hepatitis B foundation)

II.3.3. Clinical manifestation: chronic infection

Chronic hepatitis B infection occurs when the virus remains in the blood and liver for more than six months after initial diagnosis. The risk of chronic infection is higher if exposure to the virus occurs at a young age. While being diagnosed with chronic hepatitis B can be distressing, most people can live a long and healthy life with proper management. Treatment options are available to control the virus and prevent liver damage, with promising new therapies on the horizon. Though the risk of liver disease or cancer is elevated, lifestyle changes can help reduce these risks. (Hepatitis B foundation)

II.4. Diagnosis:

II.4.1. Acute HBV infection:

Acute hepatitis B is diagnosed clinically through the presence of HBsAg, symptoms, and elevated serum aminotransferases. Chronic infection is identified by the persistence of HBsAg for over 6 months. Past infection is indicated by the presence of anti-HBs and IgG anti-HBc antibodies.

Occult HBV infection is characterized by low levels of intrahepatic HBV DNA without detectable HBsAg. It is diagnosed serologically by isolated anti-HBc antibodies without HBsAg or anti-HBs antibodies. Real-time PCR for serum HBV DNA detection is commonly used to diagnose occult HBV infection due to its sensitivity. (Song & Kim, 2016)

Table 01: Hepatitis B tests.

Resource level	Testing
High	• HBsAg • Anti-HBc (IgM) & Anti-HBs • HBV DNA • ALT • INR • Bilirubin
Medium	• HBsAg • Anti-HBc (IgM) • ALT • INR • Bilirubin
Low	• HBsAg • Anti-HBc (IgM) • ALT • INR • Bilirubin

HBsAg: Hepatitis B surface Antigen. Anti-HBc (IgM): Hepatitis B core Antibody (Immunoglobulin M). Anti-HBs: Hepatitis B surface Antibody. HBV DNA: Hepatitis B virus DNA. ALT: Alanine Aminotransferase. INR: International Normalized Ratio.

II.4.2. Chronic HBV infection:

Diagnosing chronic HBV infection involves identifying HBsAg persistence for over 6 months, followed by determining the individual's phase of infection, either HBeAg-positive or HBeAg-negative. Subsequent testing for HBV replication markers, including HBeAg and serial serum HBV DNA measurements alongside ALT (Alanine Aminotransferase), aids in decision-making regarding HBV therapy eligibility. Regardless of serum ALT levels and HBV DNA detectability, lifelong monitoring is essential as the infection's status may evolve. Individuals with chronic HBsAg persistence, especially those with elevated serum ALT, require closer monitoring, with consideration for antiviral therapy if HBV DNA levels consistently exceed 2000 IU/mL. Therapy initiation depends on various factors beyond HBV DNA and ALT levels, including liver disease progression indicated by liver biopsy or noninvasive markers. Furthermore, testing for hepatitis C and hepatitis D is necessary to rule out superinfection, especially in patients with elevated ALT but low HBV DNA. Other considerations encompass drug-induced liver injury, nonalcoholic steatohepatitis (NASH), and iron overload. (*World Gastroenterology Organisation (WGO)*)

II.5. Stages of HBV infection:

Significant advancements have been achieved in comprehending the four distinct phases of chronic hepatitis B (CHB): immune tolerance, immune clearance, inactive HBsAg carrier, and reactivation stages. Nevertheless, not all individuals with CHB experience each of these stages.(Shi & Shi, 2009)

II.5.1 Immune clearance stage:

As the immune system matures, changes in hepatic inflammation or HBeAg levels may activate specific T-cell responses against HBV. This transition from tolerance to activation leads to immune-mediated liver injury, known as the clearance phase of CHB infection. During this phase, cytokines like IL-2, INF, and tumor necrosis factor are released, contributing to inflammation. The active phase of CHB is marked by elevated ALT levels, liver inflammation, and increased HBV-DNA replication. HBeAg seroconversion, associated with reduced HBV replication, often leads to biochemical and histological remission. However, some patients experience symptomatic flare-ups resembling acute hepatitis, which may precede HBeAg disappearance and hepatitis remission. The duration and severity of these flare-ups correlate with the risk of progressing to cirrhosis and HCC. (Shi & Shi, 2009)

II.5.2. immune tolerance stage:

Patients with perinatal or early childhood-acquired HBV infection enter an initial tolerance stage characterized by HBeAg presence, high serum DNA levels, and normal liver enzyme levels. This stage is rare in those infected later in life. HBeAg may promote chronic HBV infection by inducing immune tolerance, particularly in infants infected by HBeAg-positive mothers. This mechanism involves HBeAg-specific Th2-like cells and anti-inflammatory cytokines. Patients in the immune tolerance phase have a low risk of liver disease progression. Although antiviral therapy is not typically recommended during this phase, close monitoring is essential for potential progression to the immune clearance phase, where therapy may be considered if HBeAg seroconversion does not occur. (Shi & Shi, 2009)

II.5.3. Inactive HBsAg carrier stage:

During the inflammatory phase of HBV infection, HBeAg seroconversion occurs, leading to inactive HBsAg carrier status, the largest group of chronic HBV patients. After seroconversion, most patients have undetectable or low viral loads and mild liver inflammation, with a small risk of liver cancer development. However, approximately 20%-30% may experience spontaneous hepatitis B reactivation, potentially causing liver damage or decompensation. Some carriers eventually clear HBsAg and develop anti-HBs, with a low but persistent risk of liver complications, including HCC, especially in patients with cirrhosis. (Shi & Shi, 2009)

II.5.4. Reactivation stage:

Chronic HBeAg-negative patients can be categorized into two groups: chronic inactive HBsAg carriers and those with ongoing liver inflammation and intermittent viral activity. Inactive carriers may experience HBeAg-negative chronic hepatitis, primarily caused by mutations in the pre-core and core promoter regions, leading to loss of HBeAg synthesis. These mutations can result in a shift from HBeAg-specific Th2 cell activity to inflammatory Th1-like cells, exacerbating liver injury. The occurrence of HBeAg-negative mutants is associated with a worse prognosis, including severe liver injury and a higher risk of cirrhosis and liver cancer compared to HBeAg-positive patients. Progression to this phase typically occurs spontaneously or during immune suppression. HBeAg-negative chronic hepatitis occurs after HBeAg seroconversion, with older age and lower ALT and HBV DNA levels observed compared to HBeAg-positive patients. However, spontaneous recovery is rare, and the long-term prognosis is poorer, with a higher incidence of cirrhosis and fibrosis. Antiviral treatment may alleviate chronic HBV infection by reducing viral load and shifting the cytokine profile. (Shi & Shi, 2009)

II.6. Treatment:

Currently, there are five drugs approved for treating HBV infection: interferon D2b (IFND2b), peginterferon D2a (PEG-IFND2a), lamivudine, adefovir dipivoxil, and entecavir. Telbivudine is a more recent addition. These drugs, except for interferon, are nucleoside/nucleotide analogs taken orally, which inhibit reverse transcription during the viral replication cycle in hepatocytes. Several new antiviral agents and immunomodulatory therapies are being investigated but are not yet commercially available. (Ferreira & Borges, 2007)

It would take many years of treatment with nucleoside/nucleotide analogs to achieve the eradication of cccDNA from liver cell nuclei. Each antiviral drug will be analyzed separately, showing the results of the studies that proved the activity of each one of them in chronic hepatitis B. Table 3 shows the antiviral activity of all drugs effective in treating AgHbe-positive chronic hepatitis B, with data collected from several studies in the literature. (Ferreira & Borges, 2007)

Table 02: Some drugs used in chronic hepatitis B treatment. (Hepatitis B foundation)

Drug	Development Stage	Anti-HIV Activity	YMDD Mutation
Lamivudine	Approved	Yes	No
Adefovir	Approved	No	Yes
Entecavir	Approved	No	No
Tenofovir	Approved	Yes	-

YMDD: Tyrosine-Methionine-Aspartate-Aspartate, a mutation in the HBV polymerase gene associated with resistance to nucleoside/nucleotide analogs.

II.7. Prevention:

Since its introduction in 1982, hepatitis B vaccination has significantly reduced the incidence of acute viral hepatitis B, leading to a decline in chronic hepatitis B cases and a notable decrease in hepatitis D infections, which rely on HBV for replication. Universal vaccination of children is now widespread globally. In adults, high-risk individuals should be identified, screened, and vaccinated if they lack immunity. (Bhat et al., 2014)

Pregnant women with active HBV replication should start antiviral therapy during the third trimester to prevent vertical transmission. Newborns should receive hepatitis B immunoglobulin and vaccination at birth to prevent infection. Recent evidence suggests potential mother-to-child transmission, underscoring the importance of universal vaccination. (Bhat et al., 2014)

For patients with established chronic liver disease, vaccination against hepatitis A and B is recommended unless immunity is already present. The efficacy of the HBV vaccine may be reduced in various chronic liver diseases, except for fatty liver and liver transplant patients. Additionally, pneumococcal and influenza vaccines are strongly advised for patients with chronic liver disease or post-liver transplant, although their efficacy may be slightly diminished in this population. (Bhat et al., 2014)

Chapter III: Hepatitis C.

Chapter III. Hepatitis C.

III.1. History:

❝ *The 2020 Nobel Prize in Physiology or Medicine is awarded to Harvey J. Alter, Michael Houghton and Charles M. Rice for the discovery of Hepatitis C virus.* ❞

The Nobel Prize Assembly, 2020.

Hepatitis, in general, is a disease that has been associated with many symptoms and different occurrence circumstances throughout the centuries, mainly related to jaundice and fatigue symptomatology. However, it wasn't until the second half of the 20th century that researchers' interest was picked by this new virus causing hepatitis but one that was essentially related to post-transfusion cases, this virus was initially called non-A non-B hepatitis virus (NANBH) in relation to these two viruses having been already studied. Three researchers' combined efforts, beginning with Dr. Alter H of the National Institutes of Health (NIH), were able to establish that most of the post-transfusion hepatitis was caused by a novel virus. Houghton M. replicated the virus and created a blood test to single out people who were infected with it after that. Lastly, Rice C showed that a cloned hepatitis C virus, created through the application of molecular biology techniques, may result in persistent infection and cause the same illness that has been seen in humans (Figure 07), these three were awarded The Nobel Prize for this specific discovery in 2020. (Campollo et al., 2022)

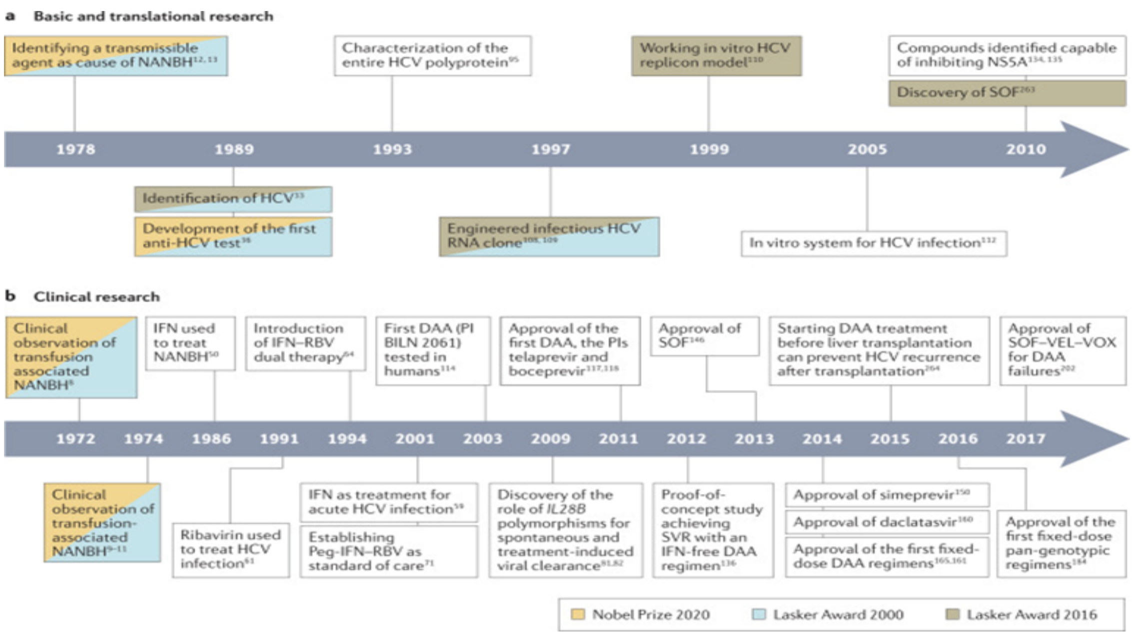

Figure 07: Important breakouts in HCV history. (Manns & Maasoumy, 2022)

III.2. Virology:

HCV is a type member of the genus Hepacivirus in the family Flaviviridae. It is an enveloped, positive-strand RNA virus. The arrangement of the genomes and the overlapping components of viral replication are common to all viruses in the Flaviviridae family. (Lindenbach & Rice, 2013)

III.2.1. Structure and genome:

HCV particle measures around 40 to 100 nm, it is represented by three basic structural elements: The envelope which is the anchoring site for the E1 and E2 glycoproteins. The icosahedral viral capsid is formed from the assembly of numerous copies of the capsid protein and finally the genome is formed by approximately 9600 nucleotides. (Moradpour et al., 2007)

The envelope glycoproteins E1 and E2, as well as the core protein, which is found inside the virus particle, are examples of viral structural proteins. HCV RNA replication and particle assembly involve non-structural (NS) proteins. The first NS protein is a viroporin called p7, which has an assembly-related function. Protease NS2 participates in assembly as a cofactor. NS3 works as a helicase and a protease; its protease activity is what cleaves the downstream NS protein precursor cleavage sites. While NS4B is involved in the membrane rearrangement of replication complex formation, NS4A is a cofactor for NS3. RNA-dependent RNA polymerase, or RdRp, is the viral replicase; NS5A is involved in RNA replication and assembly. (Figure 08) (Niepmann & Gerresheim, 2020)

The 5′ and 3′ untranslated regions (UTRs), which are highly organized, encircle the single big open reading frame found in the hepatitis C virus RNA genome. The protein-coding region and the UTRs contain cis-acting RNA elements (CREs) that support RNA translation and/or genome replication. Different components in the 3′UTR and CREs in the protein-coding region aid in the synthesis of the HCV proteins, which is mediated by the internal ribosome entry site (IRES) in the 5′UTR. There are three stem-loop (SL) domains that make up the IRES. SLIV overlaps with the 5′ end of the core coding region and creates a short, relatively unstable stem that includes the start codon of the HCV ORF. Of them, SLII and SLIII lie in the 5′UTR and assume an expanded structure. Mechanistically, SLIII is crucial to IRES function because it promotes the interaction between the IRES and 40S ribosomal subunit by using a conserved base pairing between the 18S rRNA and a SLIII sequence. Furthermore, SLIII pushes eIF3 aside to make room for the formation of a translation-competent ribosome, while SLII forms a strong association with the head of the 40S subunit. Several components downstream of the IRES, including SL47 and SL87 (also known as SLV and SLVI, respectively) in the core coding region, have an impact on RNA translation in addition to the SL domains in the 5′UTR. The liver-specific microRNA (miR)-122, which binds to several locations throughout the viral genome, also regulates RNA translation. (Tabata et al., 2020)

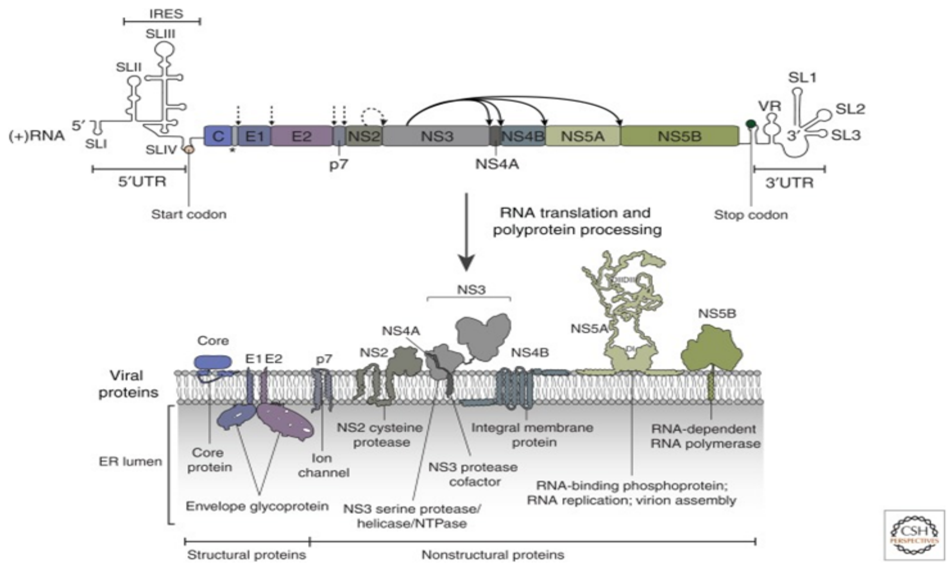

Figure 08: Hepatitis C virus genome organization and membrane topology of viral proteins. (Tabata et al., 2020)

Using phylogenetic research, HCV may be divided into 67 subtypes and 7 main genotypes. The two most common genotypes, 1 and 3, account for about 30% of infections. Less than 10% of infections are caused by genotypes 2, 4, 5, and 6, correspondingly. Few individuals from Central Africa have been identified as having genotype 7. (Figure 09) (Roger et al., 2021)

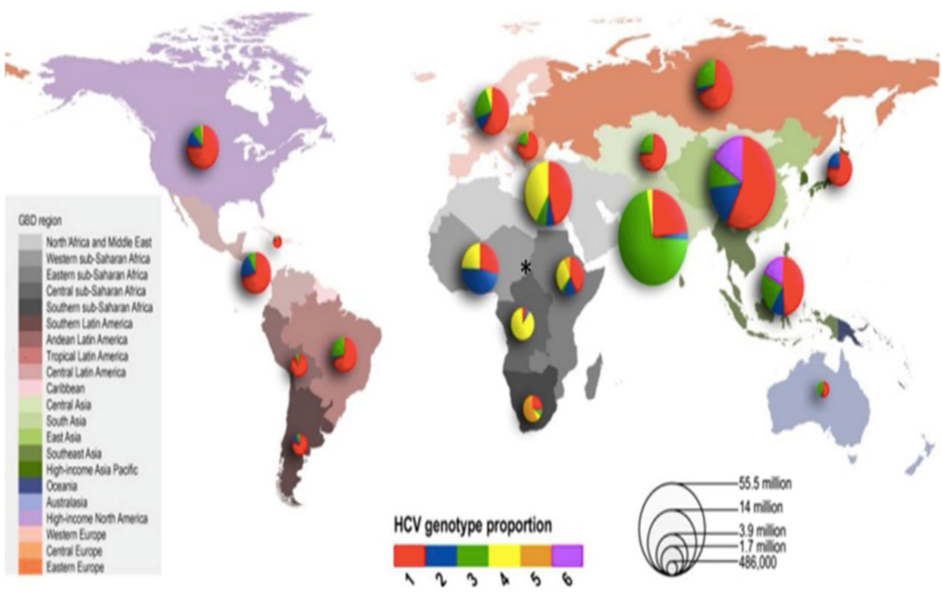

Figure 09: Prevalence of each HCV genotype in the world. (Roger et al., 2021)

III.2.2. Replicative cycle:

HCV starts its life cycle when it binds to a hepatocyte. Proteins, lipids, and glycans are among the several biological components that facilitate HCV particle entrance into hepatocytes. HCV first binds to tetraspanin CD81 and surface proteoglycans, such as the scavenger receptor BI. The HCV entrance process requires the presence of claudin-1 and occludin proteins following lateral translocation to tight junctions. In low pH environments, clathrin-mediated endocytosis engulfs HCV particles, which are then united with endosomal membranes. The cytoplasm is then exposed to viral genomic RNA. Then, both protein translation and viral RNA replication employ the HCV genomic RNA. Within the replication organelles of the endoplasmic reticulum, HCV RNA replication occurs. Lastly, HCV assembles the viral particles and leaves the cells by using the very low-density lipoprotein biosynthesis pathway. (Figure 10) (Li et al., 2021)

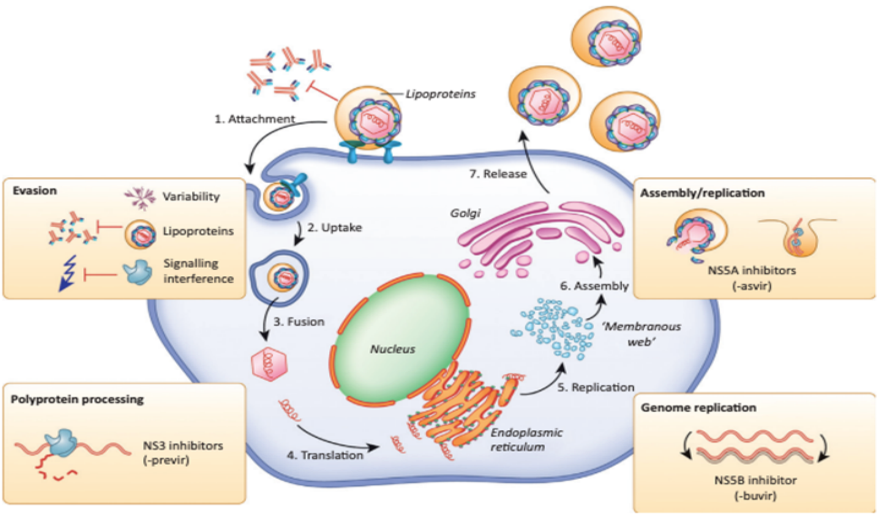

Figure 10: Replicative cycle of hepatitis C virus. (Pietschmann & Brown, 2019)

III.3. Transmission and clinical manifestation:

III.3.1. Transmission:

The hepatitis C virus is transmitted through blood. This mode most often takes place by either reuse or ineffective sterilization of medical equipment, in particular syringes and needles in healthcare settings, or transfusion of blood and/or blood products that have not been screened and analyzed. This can also apply to drug use including sharing needles and infected blood. HCV can be passed as well from an infected mother to her child and through sexual practices involving exposure to blood but not through semen or other bodily fluids. It is crucial to note that Hepatitis

C is not spread through breast milk, food, or water or through casual contact such as hugging or kissing, or sharing food, or drinks with an infected person. (WHO, 2023)

III.3.2. Clinical manifestation: Acute Infection

There is a window of one to three weeks following HCV exposure before serum HCV RNA is detectable. The incubation period between exposure and the onset of symptoms varies from 2 to 12 weeks for those who experience symptoms. 80% of patients with acute HCV infection do not show any symptoms. Fever, exhaustion, nausea, vomiting, diarrhea, stomach discomfort, dark urine, and jaundice may be present in the remaining 20%. Due to the low occurrence rate of those symptoms, and along with the fact that they are non-specific and mostly mild, the suspicion of hepatitis C in its acute stage is rare to non-existent. (Liu & Kao, 2023)

III.3.3. Clinical manifestation: Chronic Infection

Chronic infection is translated clinically by a long-term inflammation of the liver that affects the latter mainly and may lead to cirrhosis, fibrosis, and HCC. In three-quarters of patients chronically infected with hepatitis C, the inflammation is responsible for extrahepatic manifestations such as neurocognitive disorders, insulin resistance, and an elevated risk of cardio-, cerebro- or reno-vascular diseases. However, there are many treatment options accommodated to each stage of the disease that are less and less scary through the fact that it is considered the first cured viral infection in terms of a sustained response represented essentially by undetectable HCV-RNA after the end of therapy. (Pol & Lagaye, 2019)

III.4. Biological diagnosis:

III.4.1. Detection of anti-HCV antibodies:

As of right now, recombinant antigens from the NS3, NS4, and NS5 sections are employed sparingly, and the antibodies identified are those generated in the immune response against antigens from the core. Anti-HCV Immunoglobulin M (IgM) tests were developed to have an assay that could distinguish between acute and chronic HCV infection. The assays are not employed in clinical practice, and the attempts have been thwarted by the presence of anti-HCV IgM antibodies in both acute and chronic infection, but in varying percentages. As a result, their significance is frequently ambiguous. (Ansaldi, 2014)

Rapid immuno-chromatographic techniques based on recombinant antigens from the core, NS3, NS4, and NS5 regions have been tested recently and have demonstrated > 99% specificity and sensitivity for the detection of anti-HCV antibodies (Ansaldi, 2014). Its foundation lies in the immunoaffinity partitioning of the sample into a restricted "affinity zone" created by immobilizing an antibody on the membrane, and a laterally migrating sample across a porous membrane. (Vuento, 2009)

III.4.2. Detection of HCV antigen:

Assays for detecting the HCV core antigen were created. It is currently offered as an automated quantitative chemiluminescence immunoassay with sensitivity and specificity reported to be between 80% - 99%, and 96% - 99% respectively.

Numerous investigations revealed that the test is capable of accurately identifying and measuring every genotype and that there is a strong association between the levels of HCV-RNA and the quantification of the core HCV antigen. Furthermore, because it can identify core antigens, it can be used to track the effectiveness of treatment for HCV as well as confirm acute infection. The major test restriction is the lower limit of detection, which varies depending on the HCV genotype from 500 to 3000 IU/mL of HCV-RNA. Even with this limitation, HCV antigen assay can serve as a helpful diagnostic marker in labs that are unable to do HCV-RNA molecular testing. (Ansaldi, 2014)

III.4.3. Detection of HCV-RNA:

One to three weeks after infection and around one month prior to the formation of anti-HCV antibodies, HCV-RNA can be detected in plasma and serum using transcription-mediated amplification, branched DNA signal amplification (bDNA), and polymerase chain reaction (PCR) (Ansaldi, 2014). These methods focus on amplifying the RNA sequence that would make the detection and other purposes such as sequencing and analyzing easier. (Khehra et al., 2024)

III.5. Treatment:

The first treatment option for HCV infection was Interferon α (INFα), it was used even before the full discovery of the virus due to its popularity among researchers in the 1980s after showing results with hepatitis B, as it was clear that NANBH was of a viral origin. The first outcome was very promising in the face of a yet unknown disease and virus even though the efficacy among patients was limited to 40%, monitored by the decreasing levels of Alanine Amino-Transaminase (ALT) and Aspartate Amino-Transaminase (AST) and later those of HCV-RNA.

The next option was introducing the first antiviral: Ribavirin. In monotherapy, it was barely effective but with association to the INFα, the results conducted showed a better response than it was to the interferon alone. This therapy plan became the standard for HCV infection in 1998 but soon INFα was replaced by long-acting pegylated INFs officially beginning the standard treatment for the next decade (2001-2011).

A major step forward in the study of the viral replicative cycle later resulted in the initiation of the use of Direct-acting antiviral medicines (DAAs); they precisely and directly obstruct several viral proteins that are necessary for HCV replication. The first DAAs to be created belonged to the protease inhibitor (PI) class, which stops the corresponding HCV NS3 or NS4A protease from splicing the HCV polyprotein between NS3 and NS4A. Boceprevir and Telaprevir are two PIs that have been licensed for the antiviral treatment of HCV. (Figure 11) (Manns & Maasoumy, 2022)

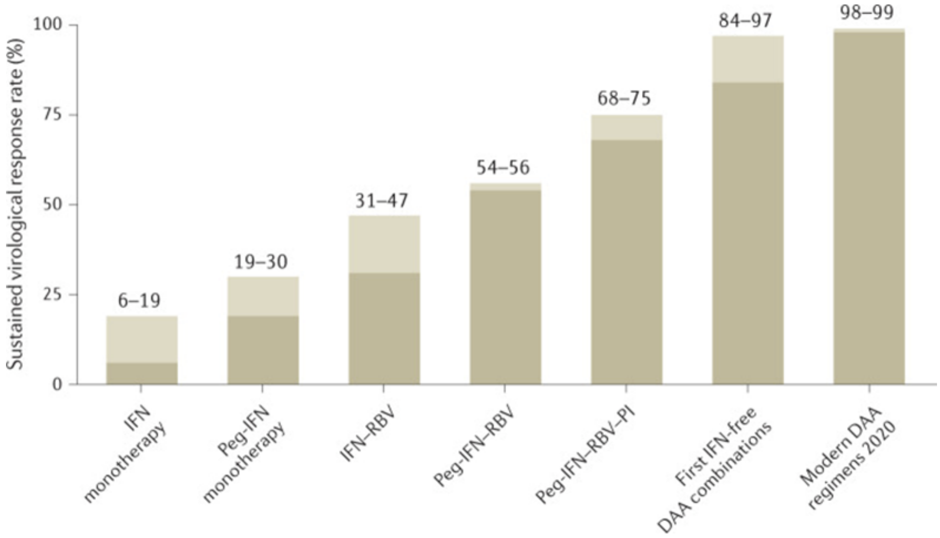

Figure 11: Evolution of HCV infection therapy. (Manns & Maasoumy, 2022)

III.6. Prevention:

With antiviral regimens that successfully treat practically all chronic infections, the necessity for vaccination to stop the spread of HCV may be questioned. Theoretically, direct-acting antivirals might take the role of vaccination as a means of treating chronic hepatitis C. This would stop the virus from spreading and possibly eradicate it from human populations, which has slowed down research on the disease. It is possible to avoid persistent infection in HCV-naïve persons with immunization, according to two observations. First, the emergence of HCV-specific T cells and antibody responses corresponds with the first control of virus replication during acute primary infection. Resolving infections are characterized by persistent adaptive immune responses, especially with the assistance of CD4+ T cells. Second, in humans and chimpanzees re-exposed to the virus, spontaneous remission of acute hepatitis C leads to long-lasting immunity and a significantly lower risk of chronic infection. This naturally occurring immunity frequently offers a defense against HCV genotype challenges.

While some of these vaccines concentrated on the expression of non-structural proteins like NS3, NS4a, NS4b, NS5a, and NS5b that are prominent targets of the T cell response, others were composed of the HCV E1 and E2 envelope glycoproteins, which are targeted by neutralizing antibodies. (Walker, 2017)

The focus of current preventative efforts is limiting viral exposure. The majority of iatrogenic HCV acquisition has been eliminated in high-income countries by standard infection control methods for blood-borne infections, and rates have decreased in many countries with inadequate resources. However, iatrogenic transmission persists in many endemic places. Although intrusive fetal monitoring during labor is discouraged due to links between its use and increased transmission, obstetric procedures like cesarean sections do not seem to hinder vertical transmission. (Ohmer & Honegger, 2016)

Experimental section
Chapter IV: Material and methods.

Chapter IV. Material and Methods.

IV.1. Zone of the study:

The study was carried out in the Wilaya of M'sila, central Algeria. The study covers a large geographic region consisting of Wilaya that harbors 990,591 inhabitants on a ground area of 18,718 km2, which allows for a better understanding of the epidemiological situation of viral hepatitis B and C in this population and environment.

The data were collected from the people and health directorate of the Wilaya and the infectious diseases department of the public hospital. This approach was chosen to benefit from the expertise and resources available in this department, which is responsible for monitoring and studying infectious diseases, including viral hepatitis B and C.

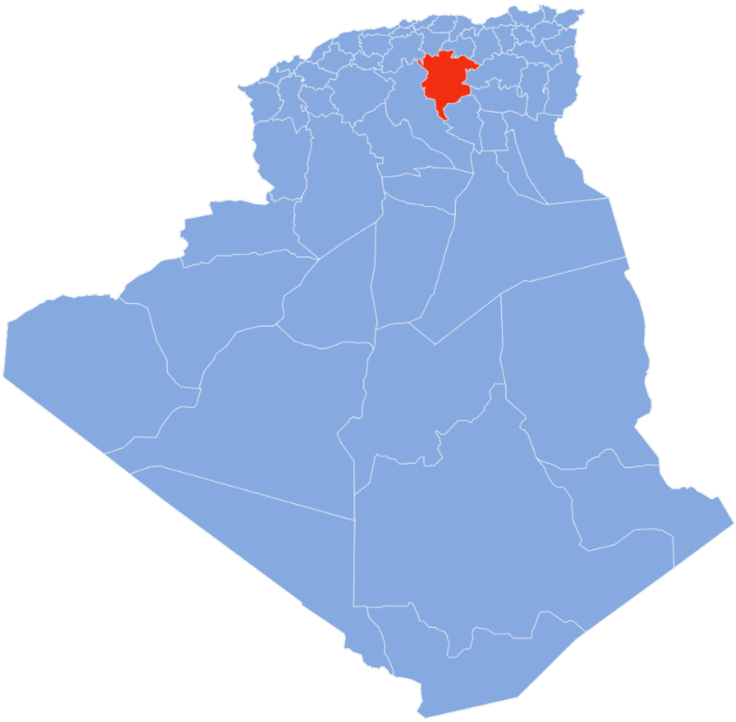

Figure 12: The Wilaya of M'sila geographic region in central Algeria.

IV.2. Period of the study:

This is a retrospective descriptive study carried out over ten years, from January 1, 2013, to December 31, 2023, in the Wilaya of M'sila. The year 2023 was more detailed due to the availability of data.

IV.3. Population of the study:

The study population included all patients with viral hepatitis B and C who were hospitalized and treated in the relevant health facilities. The data relating to these patients was collected from both medical registers and patient folders, which contain the researched data. The inclusion of all subjects with viral hepatitis B and C ensures a complete representation of the study population.

This will enable an in-depth analysis of the epidemiological characteristics, risk factors, and clinical outcomes associated with these infections.

IV.4. Epidemiological data:

As part of this study, epidemiological data are collected in detail for each patient with viral hepatitis B or C. Information collected includes the type of hepatitis (B or C), age, gender, and marital status of each patient. A key aspect of this data collection is the identification of contamination modes. This involves collecting information on various aspects such as dental care, blood transfusions, dialysis, surgical interventions, unprotected sexual intercourse, the practices of El Hidjama (an alternative medicine technique involving blood extraction), and intra-family transmission. Additionally, we also record medical management for each patient (Show annex 01).

IV.5. Statistics analysis:

We used descriptive statistical techniques: table and graphical presentations, produced by the following software: EXCEL 2021.

Chapter V: Results and discussion.

Chapter V. Results and discussion.

V.1. Results:

V.1.1. Data collected from the health and people directorate:

V.1.1.1. Hepatitis B:

V.1.1.1.1. Case distribution of HBV according to regions of the wilaya:

The data revealed that the wilaya of M'sila has four regions that represent the most affected ones of the hepatitis B infection. The Magra region is by far the most touched with a percentage of 74,57% of the total cases reported in the wilaya during the year 2020 while the lowest was 21,4% in 2018 which is still relatively high. The M'sila region comes second with a steady rate throughout the years, its peak was in 2021 with 39% of the total cases and it fell to 3% in 2016. Ouled derraj as well is considered steadily endemic with rates ranging from 6,5% to 17,3%. Chellal has recorded fewer alarming numbers during our study period (2013-2022) but a huge rise was noted in 2018 with a total of 29,31% of the wilaya cases, the unprecedented rate for the region.

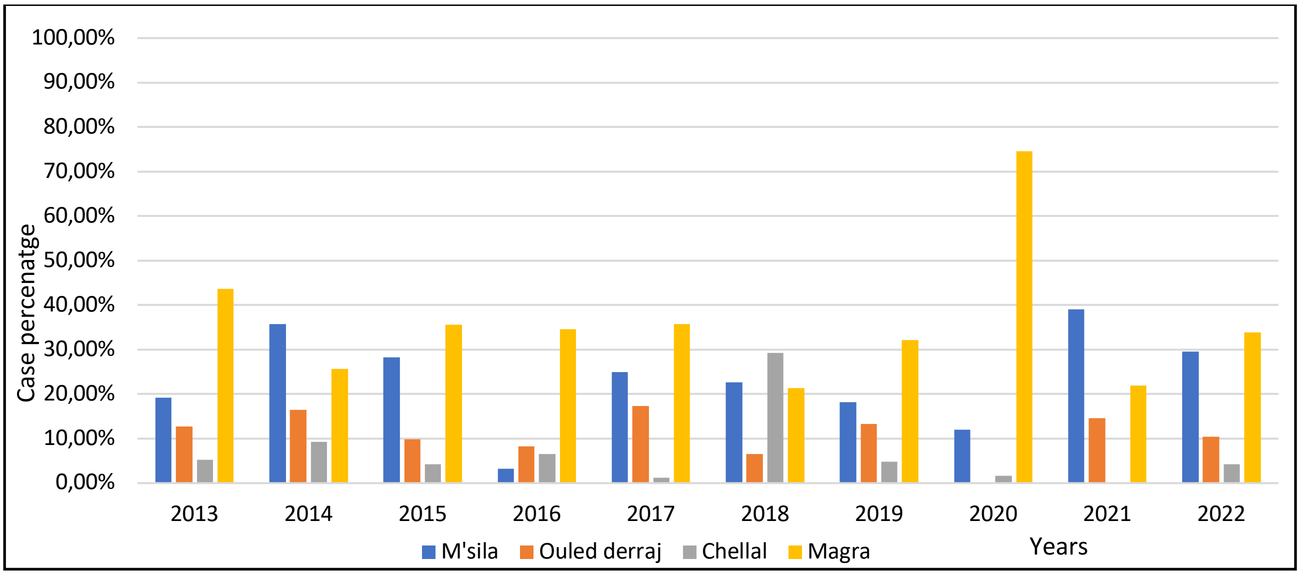

Figure 13: Hepatitis B case distribution according to regions.

V.1.1.1.2. Case distribution of HBV in the Magra region:

According to previous data, Magra has the highest percentage of HBV cases, and for that, this region needs in-depth analysis. The histogram below (figure 14) shows that the town of Magra mostly scored the highest rates surpassing 60% many times over the period (2013-2022), while we note that the second score is alternated between the towns of Ain Khadra and Berhoum recording between 10% and 40% cases each year.

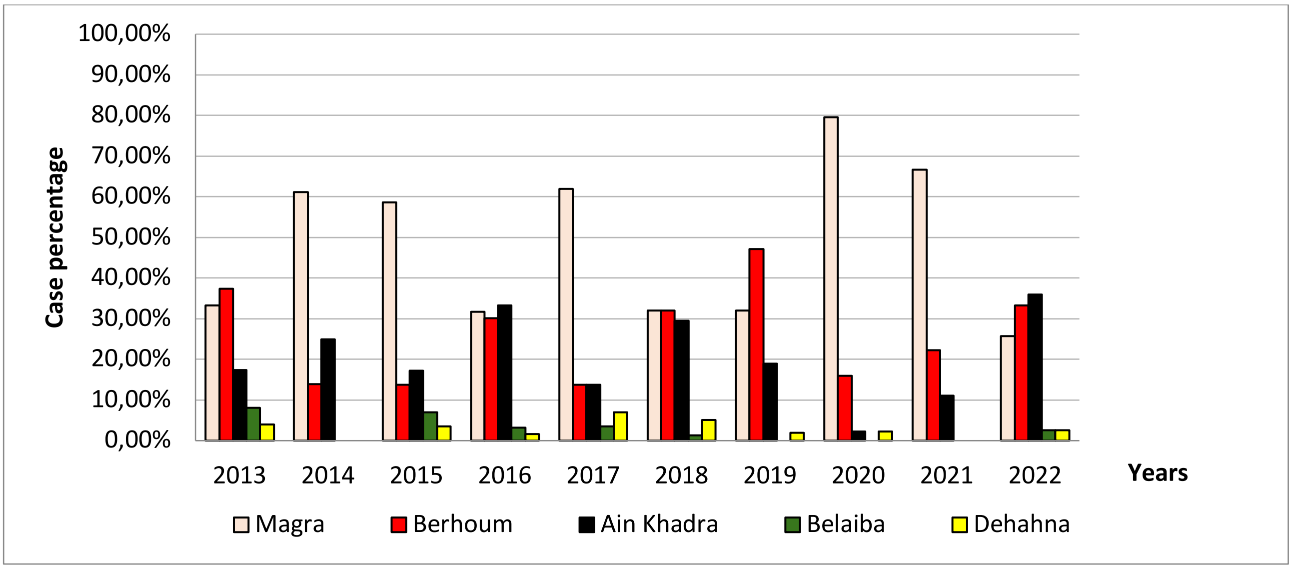

Figure 14: Hepatitis B case distribution in the Magra region.

V.1.1.1.3. Case distribution of HBV according to age and sex:

Concerning the age of hepatitis B infected subjects, we notice that the age group (20 to 40 years) is by far the most touched (62,1%) followed by the age group (45 to 65 years) scoring (24%). Both age groups of people younger than 20 years and older than 65 years are considered the least impacted with rates of 6,2% and 8% respectively.

The human male is, at most ages, more vulnerable than the female in HBV, except for the patients younger than 20 years where 3,1% of each gender is touched. In the age interval between 20- and 44 years old, males represent 35,3% of the contaminated cases while females account for 26,28% of them. Within the age group of (45-65 years), men showed an infection rate of 14,7% while women of 9,3%. In the last group, people aged older than 65 years, 4,4% of them were men while 3,6% were women.

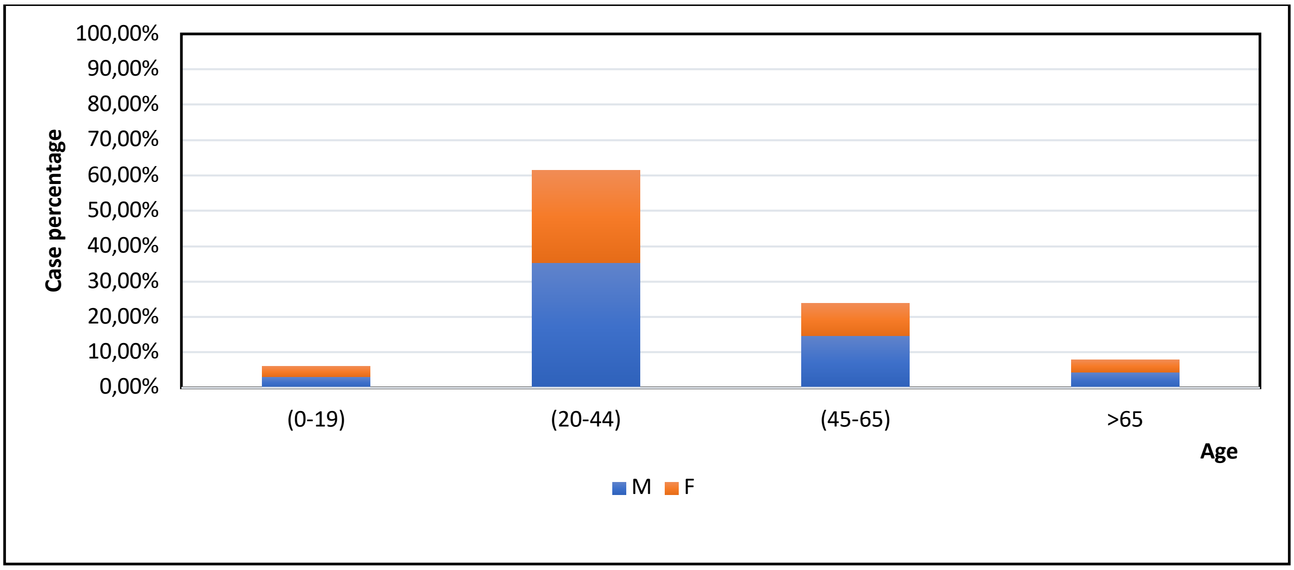

Figure 15: Hepatitis B case distribution according to sex and age.

V.1.1.1.4. Sex ratio of HBV:

The sex ratio data were only assembled by the health and people's directorate for the years of 2020, 2021 and 2022, it reveals a correlation with previously analyzed data. In 2020, 2.8 men were infected with hepatitis B to 1 woman only. Later in 2021, the ratio jumped to 4.5 infected men for 1 woman, but it fell in the year after (2022) with 1.1 infected men for 1 infected woman.

Table 03: Hepatitis B cases sex ratio.

years	sex ratio M/F
2020	2.8:1
2021	4.5:1
2022	1.1:1

V.1.1.2. Hepatitis C:

V.1.1.2.1. Case distribution of HCV according to regions of the wilaya:

During the study period (2013-2022), we see similarity between the cases of HBV et HCV in the distribution (figure 16), where the Magra region was undoubtedly the most affected, with the infection rate meeting 80% in 3 different years; 2016, 2017, and 2020 respectively while the lowest rate was in 2018 with 59,3%. Whereas the other 3 regions namely M'sila, Ouled Derraj, and Chellal had never surpassed the 17,5% recorded in 2014.

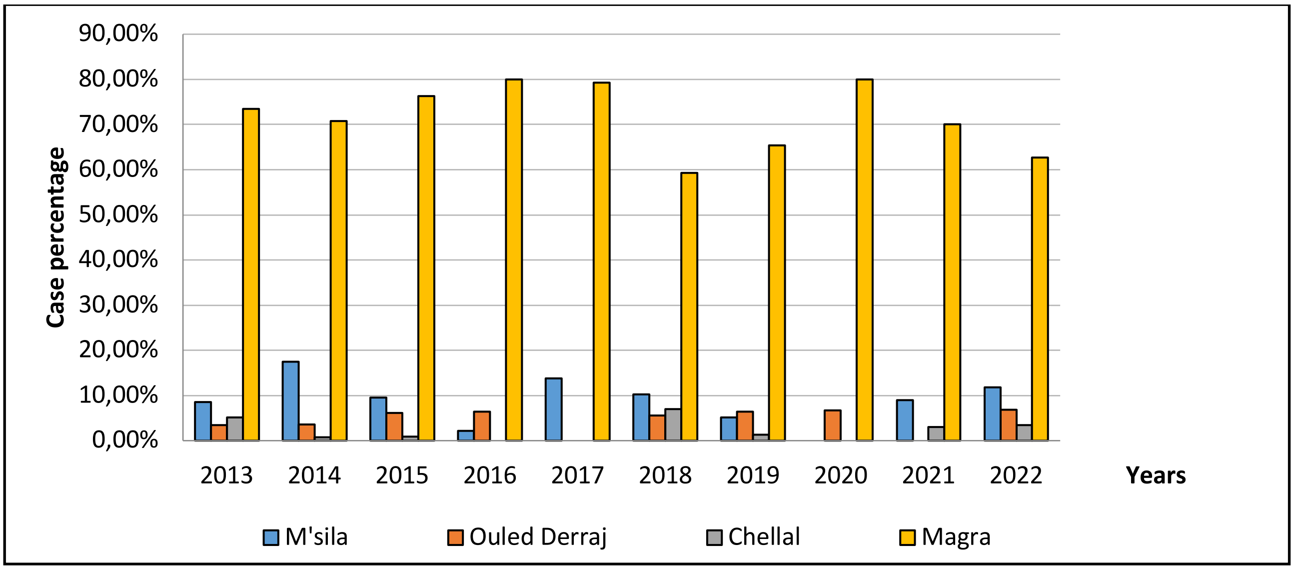

Figure 16: Hepatitis C case distribution according to regions.

V.1.1.2.2. Case distribution of HCV in the Magra region:

Magra town continues to proclaim the highest scores starting from 33,7% in 2018 and peaking at 58,3% in 2020 before dropping to 26% in the following year. Berhoum and Ain Khadra towns come next where the first took the lead in 2021 to attend 43,5% of total cases, and the second reached 28,73% in 2015 as its highest rate. Belaiba's peak was recorded in 2021 with 17,4% cases while Dehahna hadn't surpassed 8% up until 2022 with 10,8%.

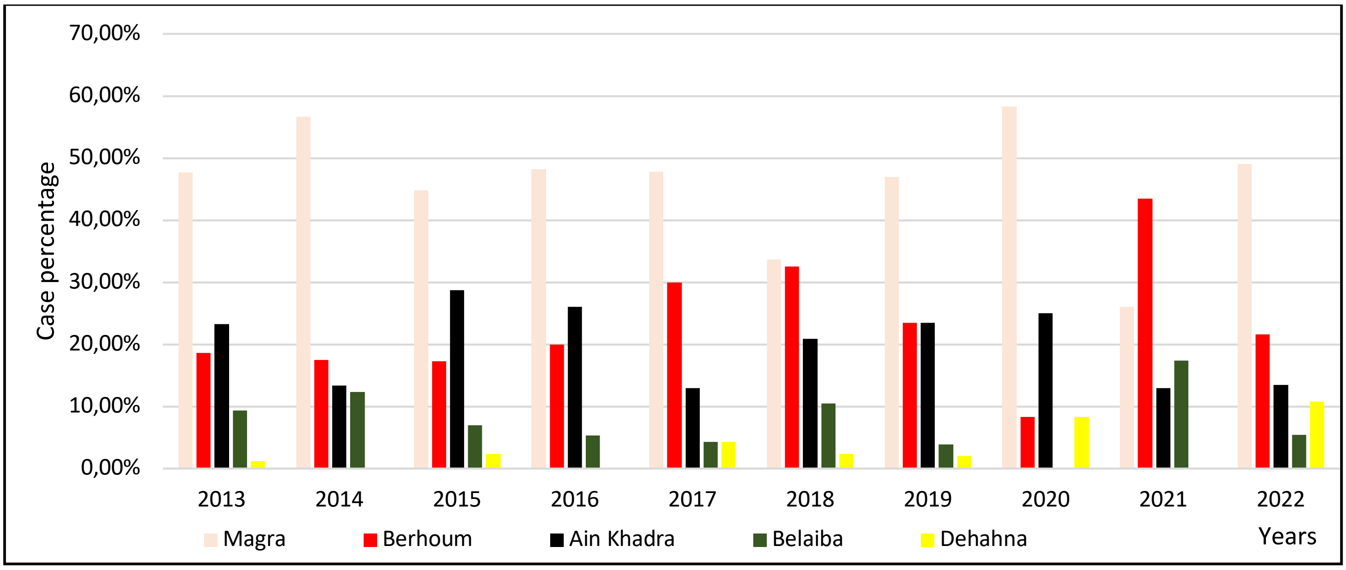

Figure 17: Hepatitis C case distribution in the Magra region.

V.1.1.2.3. Case distribution of HCV according to age and sex:

Hepatitis C infection rates go up along with age, as indicated in the figure 18, people under 20 years old had 5,99% reported cases. For those aged between 20-44 years 14,8%, those aged between 45-65 years old 29%, and those aged older than 65 years 31,19%.

The female gender seems to be more affected by hepatitis C, in three age categories (under 20 years, between 20-44 years, and older than 65 years) more women are infected then men. 4,96%, 10,53%, and 21,12% respectively. For people aged between 45- and 65 years, male gender dominates with 23,8%.

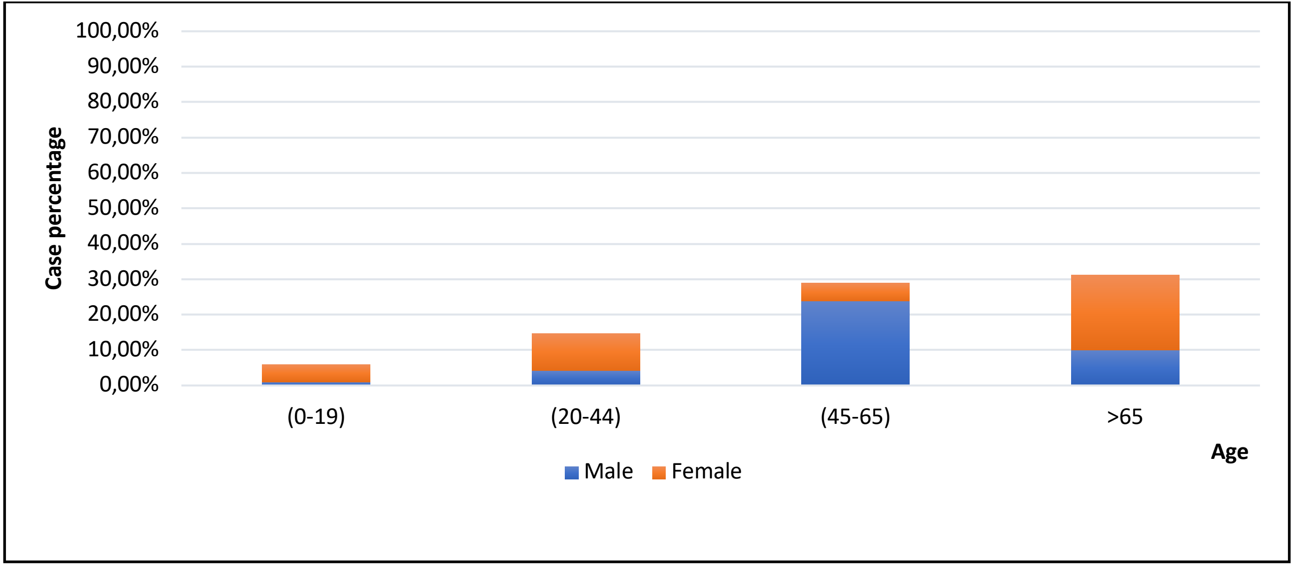

Figure 18: Hepatitis C case distribution according to sex and age.

V.1.2. Data collected from the infectious disease's hospital department:

In 2023, 69% of viral hepatitis cases that were examined by the responsible medical doctors at the infectious disease department were those of hepatitis B. On the other hand, hepatitis C represented 31% of these cases. This means that hepatitis B is more frequent than hepatitis C (Show the figure 19).

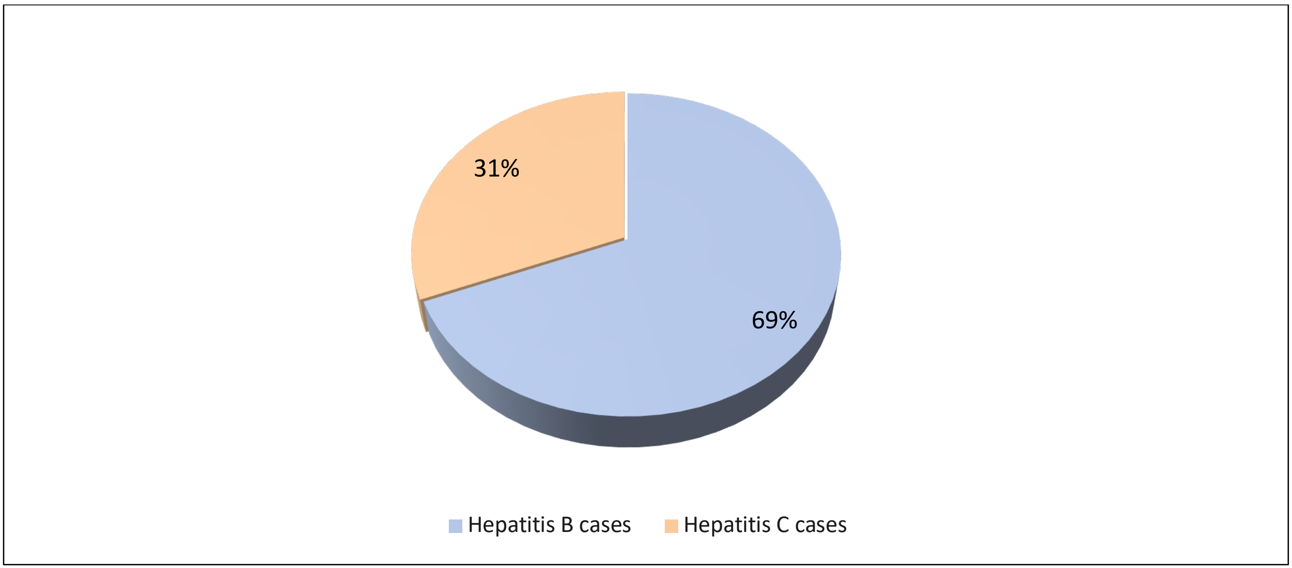

Figure 19: Hepatitis B and C case distribution.

V.1.2.1. Hepatitis B:

V.1.2.1.1. Case distribution of HBV according to sex:

The pie chart visually represents the distribution of Hepatitis B cases based on gender. According to the data extracted from the chart, males account for 56% of the cases, while females represent 44%. This visualization demonstrates that a larger proportion of Hepatitis B cases are found among males compared to females.

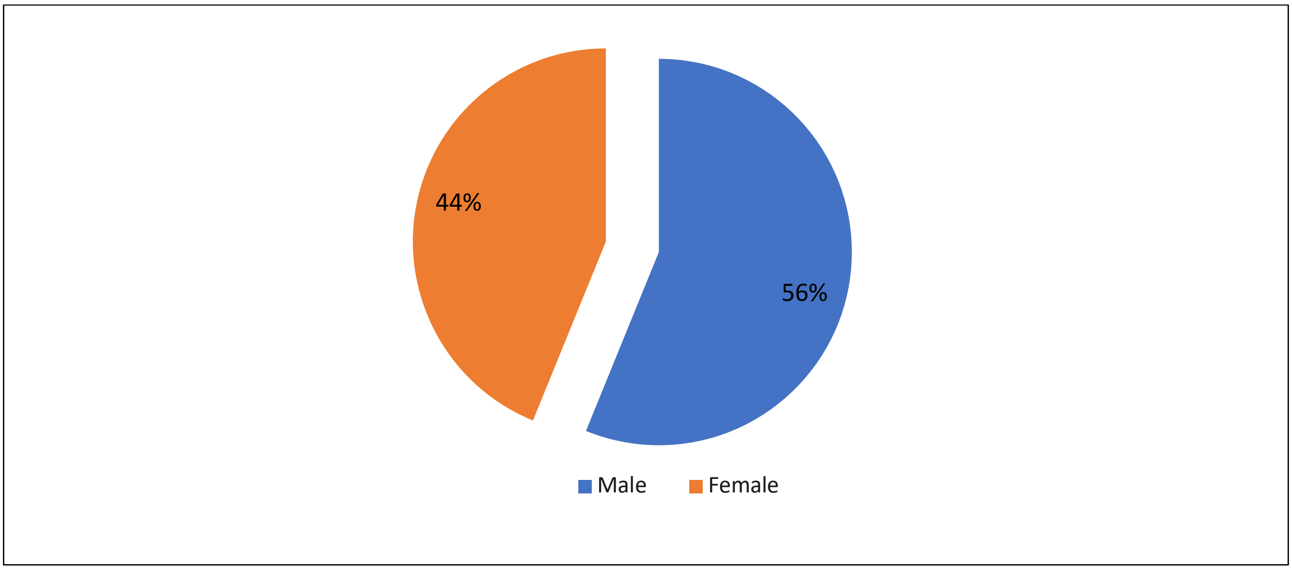

Figure 20: Hepatitis B case distribution according to sex.

V.1.2.1.2. Case distribution of HBV according to age:

The histogram below (figure 21) represents the distribution of Hepatitis B cases across various age groups. Among individuals aged 0 to 19, the percentage of cases is notably low, approximately 1,37%. However, there is a significant increase in prevalence among those aged 20 to 44, where around 41% of cases are observed. In the age group of 45 to 65, the percentage slightly decreases compared to the previous group, accounting for about 30% of cases. Finally, in the oldest age group (>65), the percentage further declines to around 20%. These findings provide insights into how the prevalence of Hepatitis B varies across different age brackets, with the highest rates observed among individuals aged 20 to 44.

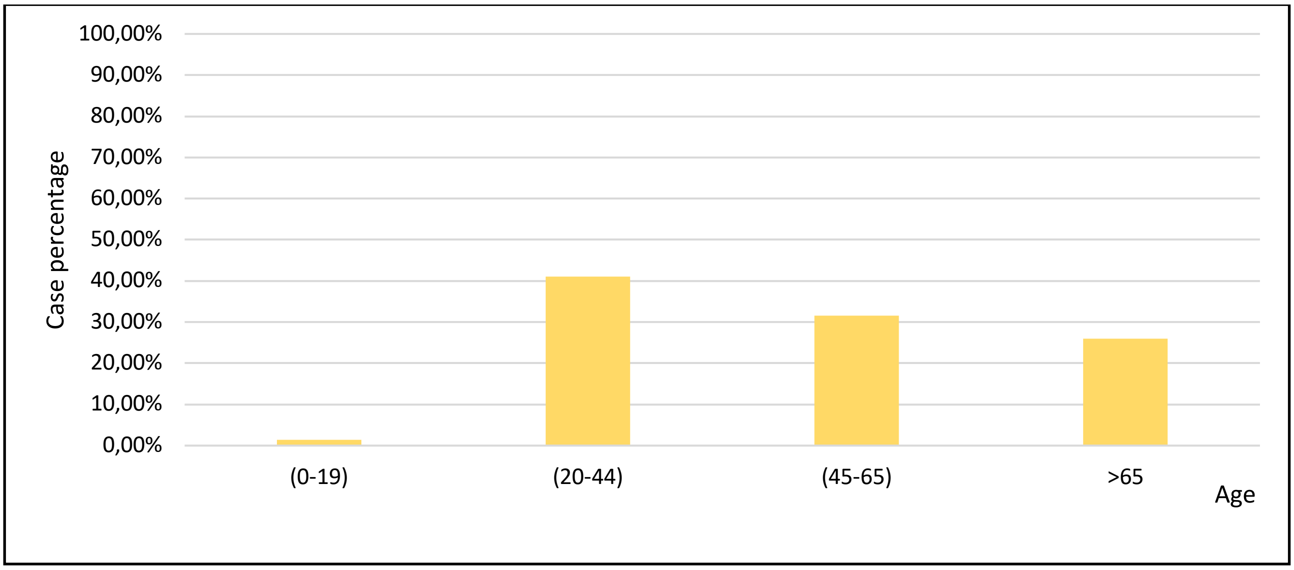

Figure 21: Hepatitis B case distribution according to age.

V.1.2.1.3. Case distribution of HBV according to marital status:

In figure 22, we show the distribution of Hepatitis B cases according to marital status within the studied population. Among the categories, the largest proportion of HBV cases, comprising 68% are married. Following this, widowed individuals represent 15% of the cases, while divorced individuals account for 7%. In addition, the lowest rate of 10% noted in single patients. This visualization offers insights into how HBV cases are distributed across various marital statuses, indicating a higher prevalence among married individuals compared to other groups.

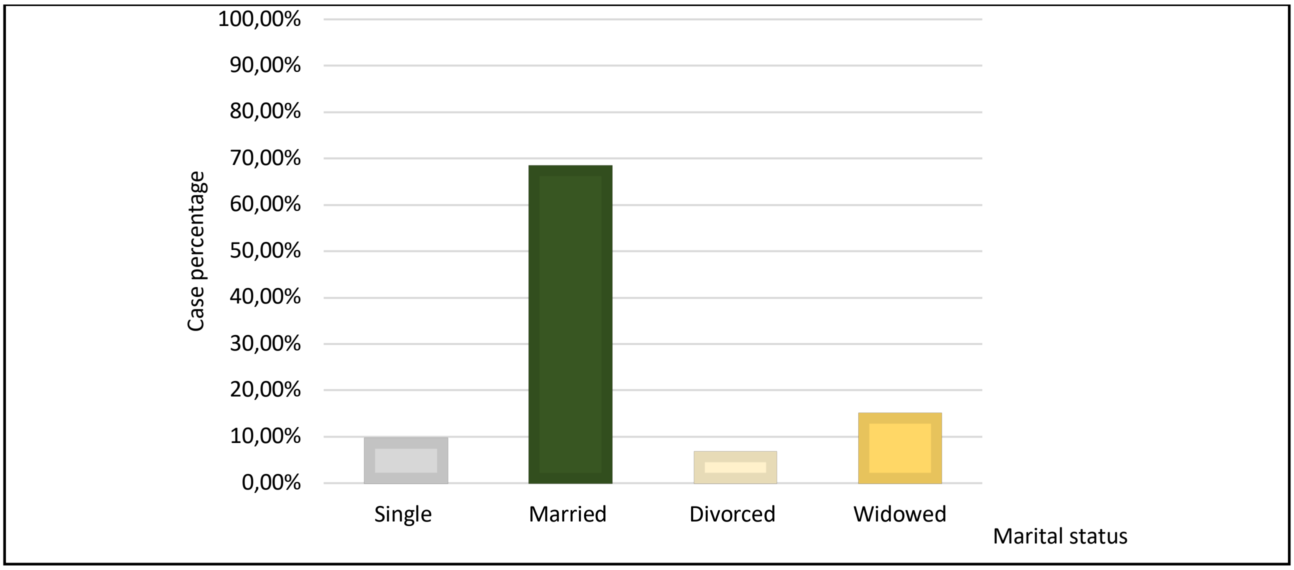

Figure 22: Hepatitis B case distribution according to marital status.

V.1.2.1.4. Case distribution of HBV according to regions:

Via the histogram in figure 24 we can deduce the distribution of Hepatitis B cases across various regions for 2023. Therefore, the M'sila region exhibits the highest prevalence by approximately 35% of the cases. Following this, Ouled Derraj, Chellal, and Hammam Dalaa each show proportions around 10%, while Magra and Bousaada have proportions around 13,7% and 5.5% each respectively. Sidi Ameur has rate less than 2.5%, while Mejedel and Bensour have 0 cases. The regions with the lowest prevalence include Ain Melh, with a proportion just around 1%. These findings highlight variations in the prevalence of Hepatitis B cases across different regions, with M'sila showing the highest incidence.

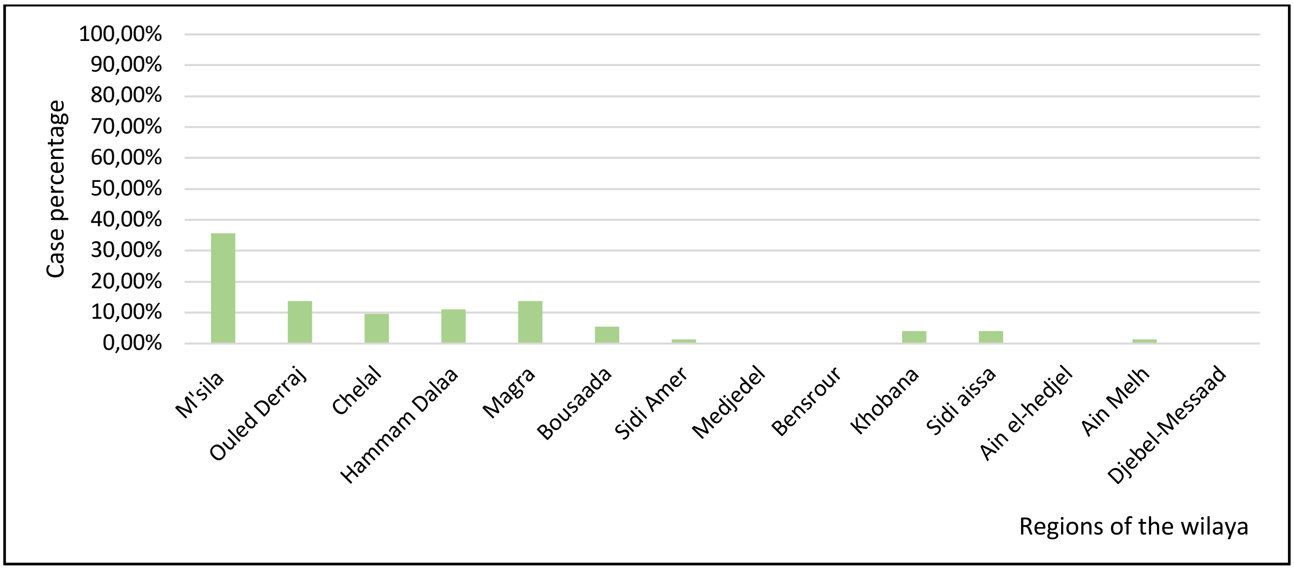

Figure 23: Hepatitis B case distribution according to regions.

V.1.2.1.5. Case distribution of HBV according to treatment options:

The figure 20 displays a pie chart divided into two sections with different colors representing two categories of HBV patients: "without treatment" and "undergoing treatment." The red section, which represents those without treatment, covers 66% of the chart. The blue section covers 34% of the chart, representing those undergoing treatment.

The chart effectively visualizes the proportion of cases receiving treatment versus those not receiving any treatment.

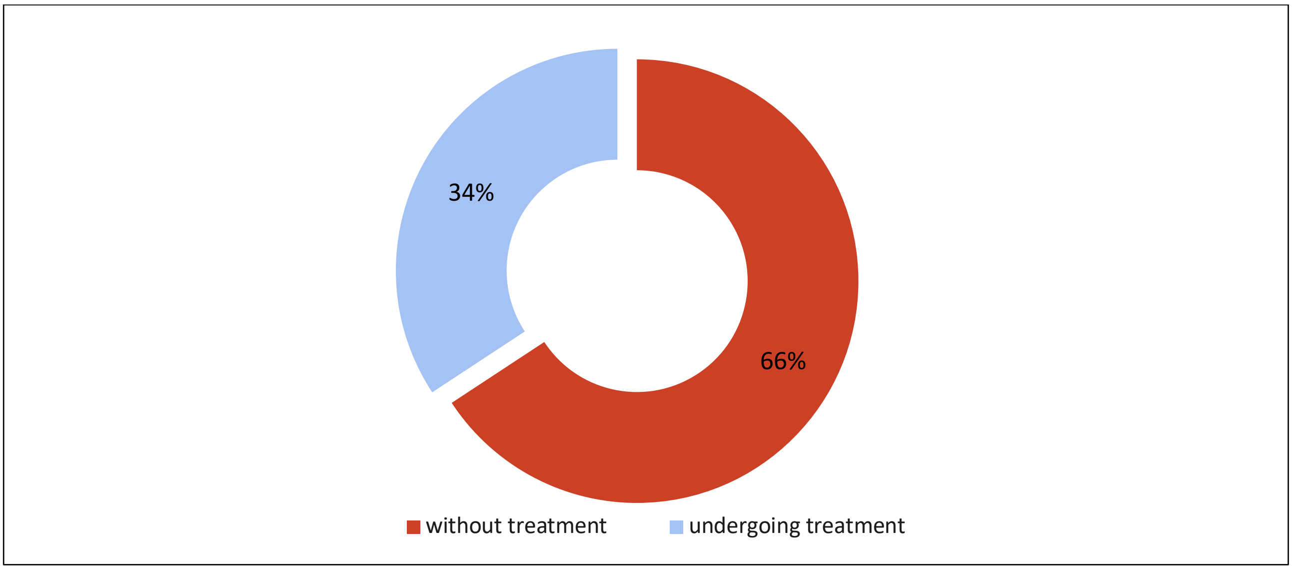

Figure 24: Hepatitis B case distribution according to treatment options.

V.1.2.1.6. Case distribution of HBV according to mode of the infection:

The pie chart visually represents the distribution of Hepatitis B cases according to different modes of infection. It is unfortunate that unknown mode accounts for the highest proportion, with 23% of cases attributed. Dental care and infected family members, contributing 17% and 16% respectively to the overall cases. Additionally, infection from surgery constitutes 11% of the cases, while unprotected sexual intercourse and barber procedures each contribute 8%. Hidjama and dialysis represent 7% and 6% of cases respectively. Lastly, cases categorized as "blood transfusion" make up 4% of the total. This visualization effectively illustrates the various modes through which individuals have reportedly contracted Hepatitis B, providing valuable insights into the risk factors of pathways contamination.

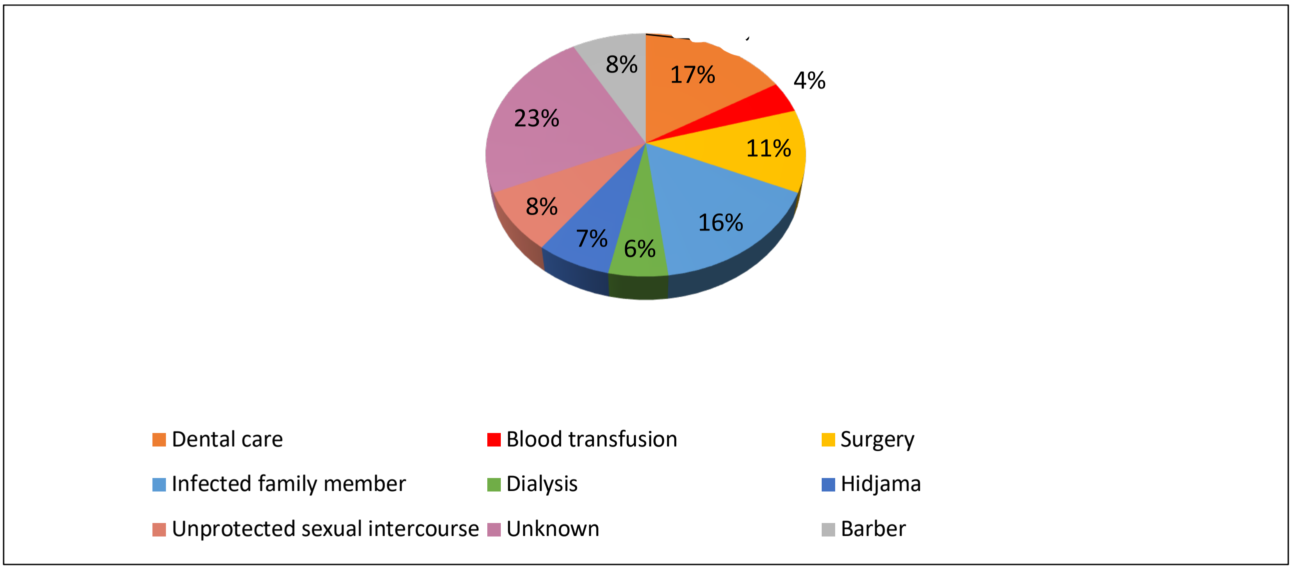

Figure 25: Hepatitis B case distribution according to mode of infection.

V.1.2.1.7. Case distribution of HBV according to stage of the infection:

Figure 26 below represents the distribution of Hepatitis B cases according to the stage of infection, providing insights into the progression of the disease. The largest segment represents the rate of chronic Hepatitis B, accounting for 85% of the total cases, while the cirrhosis cases comprising 10%. In addition to 5% for HBV patients who developed cancer. This visualization effectively illustrates the proportion of Hepatitis B cases that progress to more severe stages such as cirrhosis and cancer, aiding in understanding the severity and impact of the disease.

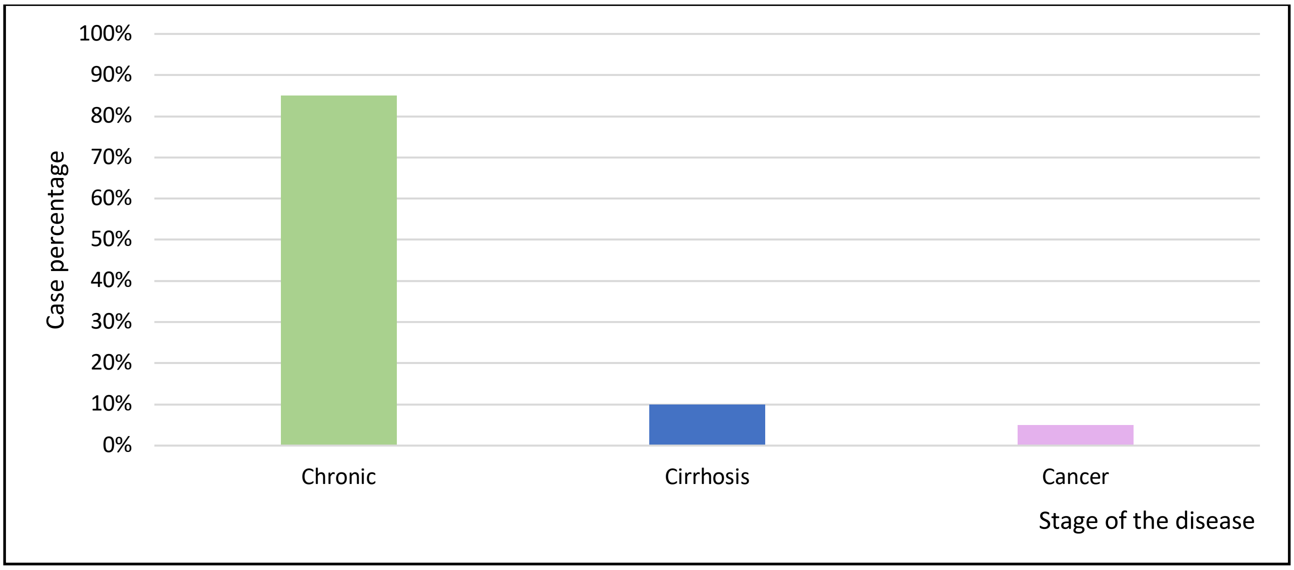

Figure 26: Hepatitis B case distribution according to stage of the infection.

V.1.2.2. Hepatitis C:

V.1.2.2.1. Case distribution of HCV according to sex:

According to the data presented in figure 27, we depict that 67% of cases are female, with the remaining 33% male. This visualization sheds light on the gender distribution of Hepatitis C patients, revealing a greater frequency in females than in males.

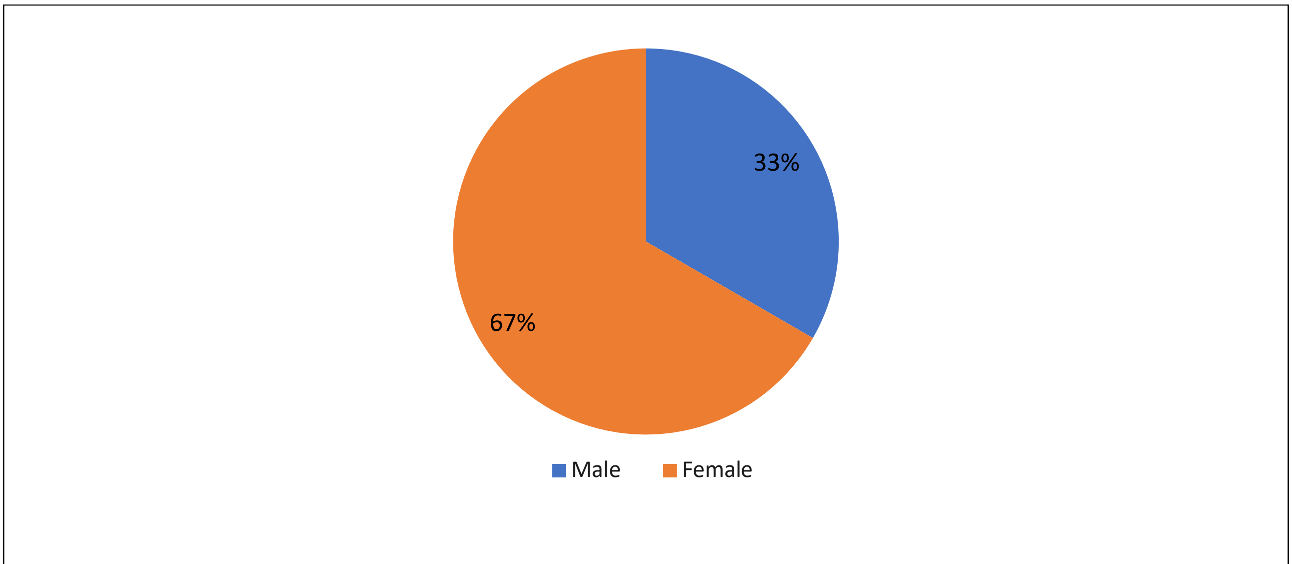

Figure 27: Hepatitis C case distribution according to sex.

V.1.2.2.2. Case distribution of HCV according to age:

The histogram in figure 28 provides a visual representation of the distribution of Hepatitis C cases across different age groups. No case has been reported in the individuals aged 0 to 20. However, the proportion increases to around 9% in individuals aged 20 to 44. In the age group of 45 to 65, the percentage of cases rises further, accounting for approximately 35% of the total. For older people than 65, the prevalence of Hepatitis C is notably higher more than 50% of the cases. This visualization effectively illustrates how the prevalence of Hepatitis C varies across different age brackets, with the highest rates observed among older individuals.

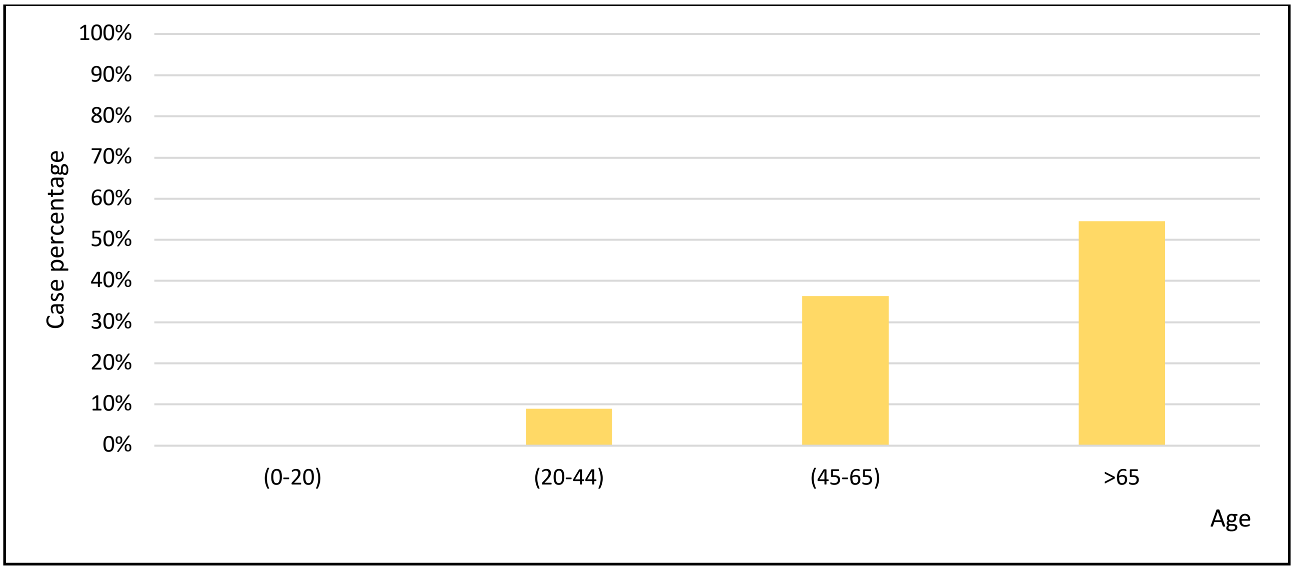

Figure 28: Hepatitis C case distribution according to age.

V.1.2.2.3. Case distribution of HCV according to marital status:

The distribution of HCV cases across various marital statuses is shown in figure 29. Most of cases (70%) are among married individuals. Following this, widowed individuals account for 18% of the cases. Singles patients represent 9% of the cases, while divorced individuals represent 3%. This visualization effectively provides insights into potential factors influencing the spread of the disease.

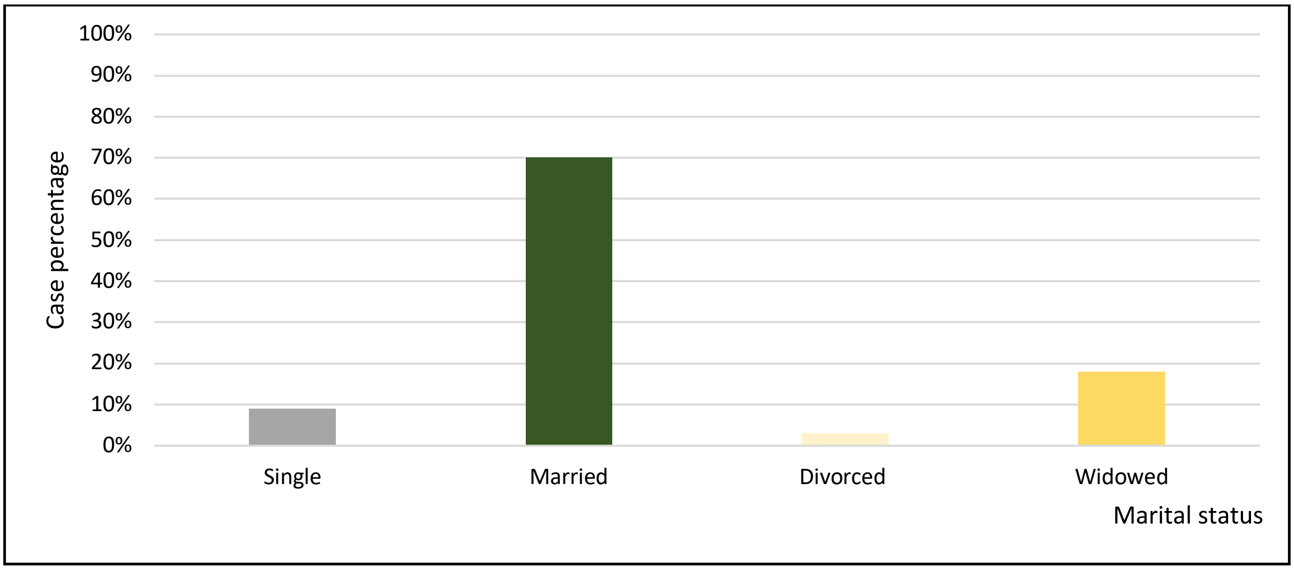

Figure 29: Hepatitis C case distribution according to marital status.

V.1.2.2.4. Case distribution of HCV according to regions:

The figure 30 below shows the prevalence of Hepatitis C cases across various M'sila regions. Where, Magra stands out with a notably higher percentage of cases, approximately 54,54%. This indicates a significant prevalence of HCV within this region compared to others. The remaining regions show lower percentages of cases, ranging from approximately 0% to 20%.

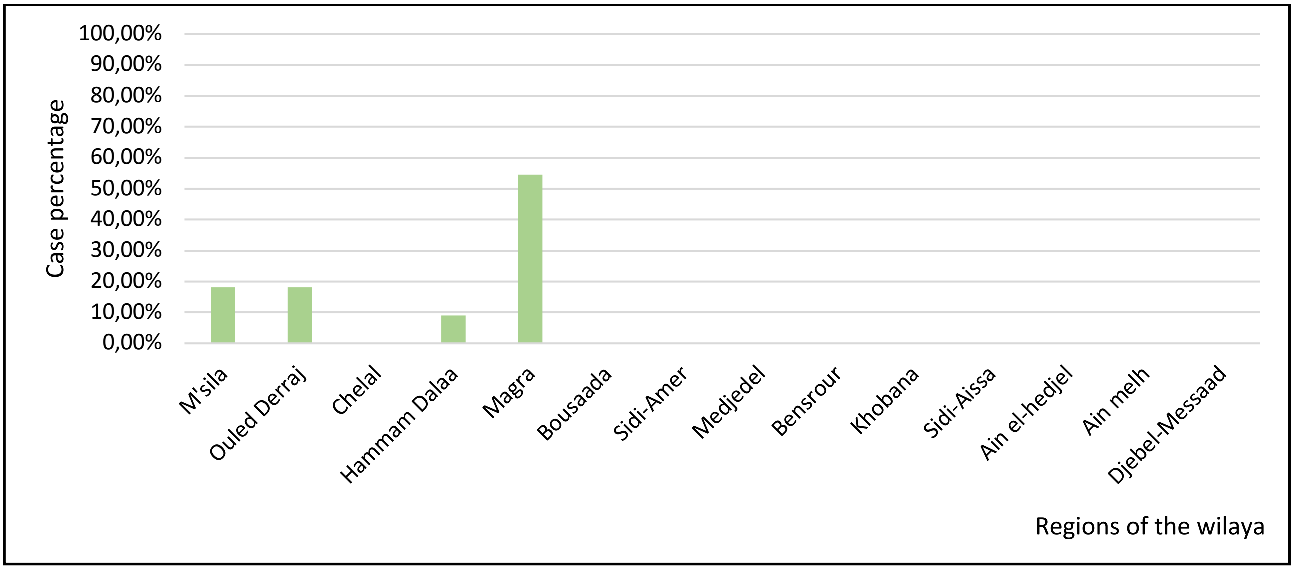

Figure 30: Hepatitis C case distribution according to regions.

V.1.2.2.5. Case distribution of HCV according to mode of the infection:

The different modes of infection are presented in figure 31. The same to HBV, unknown sources stand out as the high rate with 31% of the cases. After that, we noted that the surgery, blood transfusion, and dental care contribute 18%, 12%, and 12% respectively. Contagion from an infected family member and hidjama each account for 9% of the cases. The remaining categories, including dialysis and barber, contribute smaller percentages, with 3% and 6% respectively.

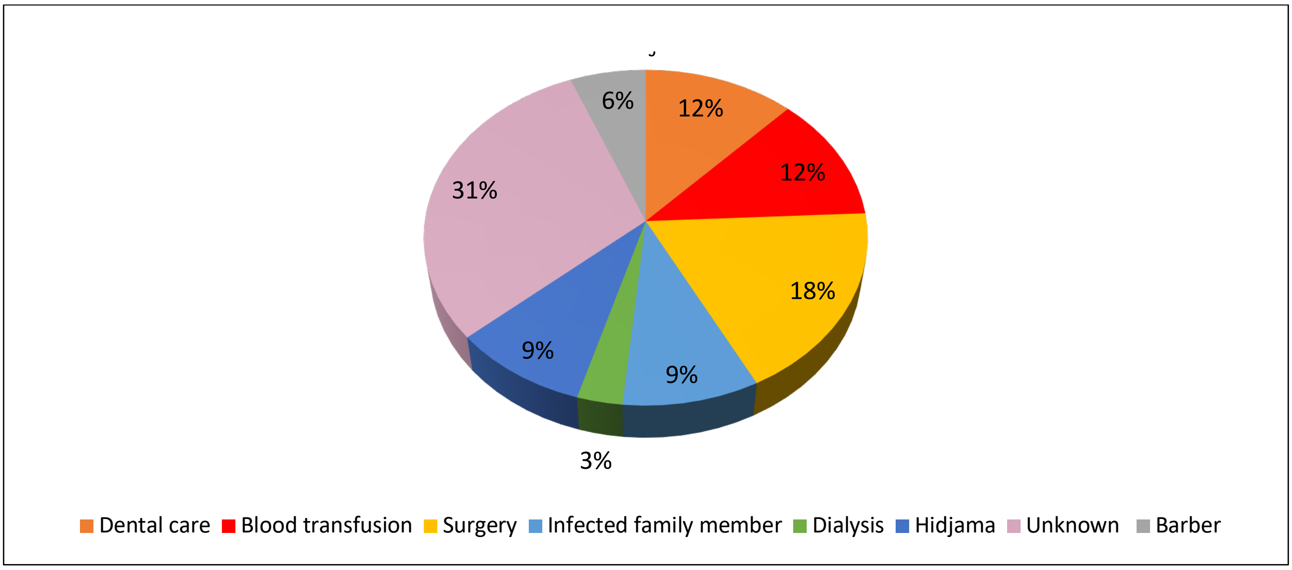

Figure 31: Hepatitis C case distribution according to mode of the infection.

V.1.2.2.6. Case distribution of HCV according to stage of the infection:

In the figure 32 we can see the distribution of HCV cases according to the stage of infection, which can provide valuable insights into the progression of the disease. Chronic hepatitis C cases represent the majority at 64%. Whereas cirrhosis accounts for the remaining 36% of cases.

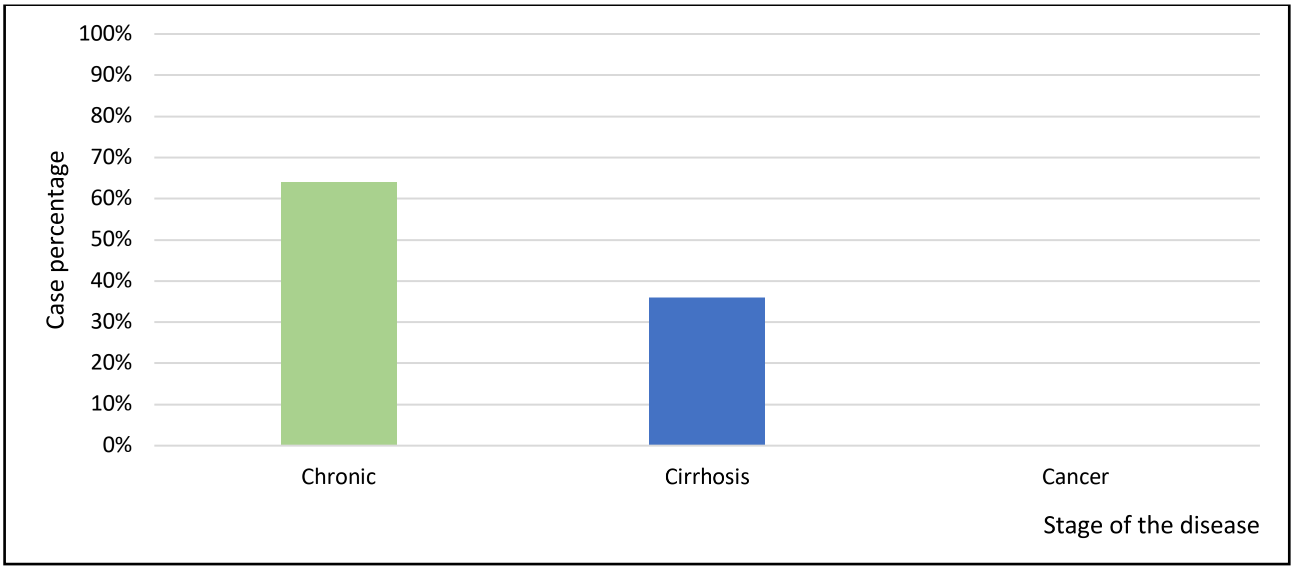

Figure 32: Hepatitis C case distribution according to stage of the infection.

V.2. Discussion:

V.2.1. Data collected from the people and health directorate:

V.2.1.1. Hepatitis B:

The wilaya of M'sila is an administrative region located in the central north of Algeria, it is considered one of the 9 most affected regions by hepatitis B in the country (Bensalem et al., 2017). Geographic and demographic disparities in this wilaya are directly connected to its wide east-west and north-south extensions. The results display that dairas that continuously show the highest incidence of hepatitis B are: M'sila, Ouled Derraj, Chellal, and Magra (Figure 13). The rates may be caused by a relatively high population density. According to statistics provided by the People and Health Directorate in 2022 M'sila alone had a population of 259,270 people, Magra of 172,744 people, and Ouled Derraj 121,251 people. In addition, a decrease in socioeconomic status and poor healthcare coverage in these regions can affect the HBV incidence and prevalence. (Gnyawali et al., 2022)

The region of Magra with its 5 towns unveils an endemic prevalence of hepatitis B, an endemic disease is defined as a disease present within a population in a specific area whose prevalence is maintained at a baseline and that continues to occur at this level for an indefinite period (Center for Disease Control and Prevention). In ten years (2013-2022), the lowest rate in the Magra region was recorded in 2018 (21,4%) while the peak was in 2020 (74,57%) despite the emergence of the COVID-19 world pandemic (Figure 13). The obtained numbers show that different towns in Magra take the lead for the study period (2013-2022) (Figure 14). But it may be in general due to the same socioeconomic factors that define the whole Wilaya as well as the poor healthcare coverage and management of resources and the severe absence of any sensibilization campaigns in the region led by trusted healthcare workers. Additionally, the overall healthcare situation whether it is public or private sector and the unavailability of vaccination for everyone; only high-risk individuals are recommended anti-HBV vaccine later in life. (National Center of Pharmacovigilance and Materiovigilance). Without forgetting that the HBV infection within family members is commonly caused by the ability of HBV to transmit through parenteral, sexual, vertical, and horizontal contacts. (Sofian et al., 2016) (Yang et al., 2016)

Gender represents a risk factor in HBV, for which Gnyawali *et al* declared that male gender is more likely exposed to chronic hepatitis B (Gnyawali et al., 2022). Until now, there is a gap in the understanding of sexual dimorphism in HBV, caused by the lack of studies made to harness this knowledge for translational gains. Differences in outcomes may be explained by differences in immune response, sexual dimorphism of the liver, and androgenic response elements in the HBV genome. Gender effects may also vary with age, with pubertal changes and the effects of menstruation, pregnancy, and menopause in women. Furthermore, gender also has complex effects on education, attitudes, behavior, and access to and use of health services, potentially contributing to inequalities of diagnosis and treatment. These complex factors interact with other host, viral, and environmental characteristics to produce differing outcomes. (Brown et al., 2022)

For people under 20 years old, the low numbers may be due to the implementation of anti-HBV vaccination in Algeria in the early 2000s. While the category between 20- and 44-years old people having a much higher rate is not usual because hepatitis B tends to be diagnosed in median age group (older than 50 years) (Gnyawali et al., 2022), the chart (Figure 15) reveals that there is a decrease in incidence starting from 45 years old. We can link this to both social and sanitary factors; people between 20 and 44 years exist in a riskier environment being more mobile and having more social direct contact, on the contrary those older than 45 years are less likely to be in contact with risk factors considering the transmission mode of hepatitis B is through blood and bodily fluids. (Tosun et al., 2018)

V.2.1.2. Hepatitis C:

The reasons for the widespread of HCV infection in Magra are most likely common with those leading to the region topping the HBV incidence charts as well. Hepatitis C is also a preventable condition that needs very serious sensibilization campaigns along with a fixed healthcare committee, both being absent in the region (Figure 17). The main route of HCV transmission is healthcare-related exposures, including poor sterilization of medical equipment and the re-use of tools, as well as limited screening of blood products. Moreover, barbering, tattooing, piercing, and intravenous drugs play an increasingly important role in HCV-contagious (Mansoor et al., 2023). Unfortunately, it was difficult for us to obtain the above information, as it was not recorded in the patient's files, the admission office or even in the prevention unit. This lack of information inevitably leads to a lack of research into the root causes of the spread of the HCV in the region.

Hepatitis C incidence rates elevating with age may be due to aging-related mechanisms such as the acquired vulnerability to external risk factors and a less active immune system (Reid et al., 2017). In 3 out of the 4 studied age groups, women have shown a higher percentage (Figure 18). In the age group between 45 and 65 years old, men had a rate almost 5 times higher than women. When it comes to hepatitis C, there isn't a specific gender disparity where one gender is more vulnerable or is considered a standing risk factor for infection. Both male and female genders are exposed to HCV at different levels. On the one hand, women are often more at risk of using syringes or blood products due to pregnancy and labor, in addition to other social practices such as ear piercing and Hidjama. Men on the other hand, are more exposed to other socially ruled male experiences such as IV drug consumption, sharing razors, and toothbrushes and circumcision. (Abdel-Gawad et al., 2023)

V.2.2. Data collected from the infectious diseases' hospital department:

This part of the study concerns only cases reported during 2023 who were referred to the infectious disease's hospital department, we noticed a huge lack in the information retailed by healthcare workers at the department that resulted in patients' records missing many epidemiological data. The results reveal that hepatitis B takes the lead in viral hepatitis cases (69%) while hepatitis C comes second (31%) (Figure 19). This is a consequence of their viral nature as HBV is a DNA virus while HCV is an RNA virus. RNA viruses are more fragile in the external environment and can barely survive outside of the host cell. On the contrary, DNA viruses can resist longer outside of the human body which means contracting them more often. (Saeed et al., 2014)

V.2.2.1. Hepatitis B:

Viral load is a necessary test to diagnose and identify the infection stage, an active chronic hepatitis B infection is defined with a viral load > 2000 UI/mL (Diallo et al., 2018). A chronic infection would require anti-viral treatment plan that includes either Tenofovir or Entecavir. The former presents a side effect of nephrotoxicity and is contraindicated in case of kidney failure while the latter is indicated in kidney failure patients to replace Tenofovir (Figure 24). (Wassner et al., 2020) (Robinson et al., 2006)

The majority of patients who contracted HBV infection were married (68%) (Figure 22), this is understandable considering sexual transmission is one of the most common routes of transmission worldwide (Inoue & Tanaka, 2016), and the single most common in the US. (Hepatitis B Foundation). Due to cultural and religious boundaries, the rest of the patients may present an infection through a different mode of contamination. (Adibi et al., 2004)

M'sila, Ouled Derraj, and Magra present the highest rates as usual with 35,6%, 13,7%, and 13,7% respectively (Figure 23). As we discussed it previously, the socioeconomic status in the entirety of the Wilaya is not considered at top levels, the endemic situation of hepatitis B in these regions may refer mostly to the high population density.

Recent studies suggest that in high prevalence areas, the most common transmission route for HBV is the perinatal mother-to-child transmission (Sabeena & Ravishankar, 2022). In our result, 23% of patients did not have a clear idea of the route of first exposure. Thus, it confirms the low level of both socioeconomic and educational status among this population and the absence of true public health programs for the hepatitis disease. 17% named dental surgery and procedures as their contamination mode, this is a horizontal route that is usually uncommon (Sabeena & Ravishankar,

2022) but could lead to great incidence in case of continuous recklessness and lack of control. 16% contracting the infection due to an already infected family member is a reasonable percentage owing to the known transmission ways of the virus. Surgery, dialysis, Barber, and Hidjama are also important routes in this population because they include sharing blood or its products (Figure 25).

A study conducted in Singapore revealed that after a 10-year follow-up 16,2% developed cirrhosis, and 7,8% developed HCC, while 76% continued to harbor a chronic infection (Poh et al., 2015). In our study, during the year 2023, 85% patients presented a chronic infection while 10% were diagnosed with cirrhosis and 5% with HCC (Figure 26). These numbers include patients who were reported to the hospital ID department before 2023 but who only developed any of these two complications during 2023 but they could be easily correlated with results from the first mentioned study. Hepatitis B is the most important risk factor for HCC accounting for about 50%-80% of the overall cases of HCC. (Petruzziello, 2018)

V.2.2.2. Hepatitis C:

According to WHO, Hepatitis C is only transmitted through blood exposure meaning other bodily fluids such as sperm don't contain the virus and couples in monogamous relationships are not in danger of contracting HCV if one of them presents the infection (WHO). Consequently, A study showed that spouses with hepatitis C reported exposure to blood or blood products and tools more often than those who were not infected. (Stroffolini et al., 2001)

According to a study led in the USA, the most common route of transmission of HCV is through intravenous injected drugs and the infection is prevalent among drug users (Soza et al., 2010). As an Algerian society, drug use and sexuality represent a religious, moral, social and financial burden and therefore most patients are reluctant to report any case of drug use or unethical sexual practices. In our case, 31% of the patients reported not knowing how they contracted the infection; the only plausible explanation is if they were to have multiple blood transfusions, surgeries, or Hidjama. Dental care (12%), infected family members (9%), and barber (6%) are all very uncommon transmission routes due to the HCV being fragile and the minimal blood infection possibilities in those situations (Figure 31).

Worldwide, HCV patients with liver cirrhosis can develop HCC, with an annual incidence range between 2% and 8%, but the risk of HCC development in HCV patients without liver cirrhosis has been reported to be much lower (Shin et al., 2021). In France, 21,4% of patients infected with hepatitis C and enrolled in a nationwide study were found to be cirrhotic (Roudot-Thoraval et al., 1997). In our data 36% of patients presented cirrhosis at the time of diagnosis or later, while none were found to have cancer (Figure 32) although about 34% of HCC cases in the US were due to HCV infection. It is estimated that 20% of chronic HCV cases will develop into cirrhosis within

20-30 years and the risk of developing HCC after that 1%-4% higher every year. (Axley et al., 2018)

Conclusion

Conclusion

Despite all the scientific worldwide progress made by international organizations and health partners, documented to us by official statements regarding the global situation of viral hepatitis and specifically type B and C, a huge specialized epidemiological study gap exists in the Algerian health system and data. In a way, our study comes in hopes of filling a part of this gap by launching a descriptive and retrospective approach covering ten years in time and the Wilaya of M'sila as a place. Our main goal is to collect enough data on hepatitis B and C case distribution that might lead to an extensive understanding of associated risk factors such as gender, age, familial status, and route of infection. We found that, for HBV, contracting the virus and developing a chronic infection is more common among male subjects specifically those aged under 44 years old. While for HCV, the gender data revealed little about a certain viral tropism, but the risk of infection increases with age. A good share of study participants had announced not knowing how any of the two viruses contaminated them, these reflect the awareness levels.

In brief, Hepatitis B and C are two similar diseases that might lead to the same outcomes and that are endemic in certain regions of the Wilaya, whether that is due to health and systematic reasons or to socioeconomic ones. Therefore, a serious system switch must be suggested. The general awareness level of M'sila population should not be a barrier, healthcare workers should receive professional training that allows them to lead campaigns to inform the people of prevention ways and offer free diagnosis options to them. A switch in the system also must include supporting the healthcare establishments in the wilaya financially for them to be able to afford more diagnosis kits and control measurements, not to mention, leveling the current hygiene methods in the hospitals up. Taking the current situation of viral hepatitis into account shouldn't stop us from getting ready to face future challenges that might surge up which is even more reason to solidify our knowledge of these diseases in our country, that is only possible with serious and official attempts of collecting epidemiological data and further supporting the scientific research.

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- Governmental/ non-governmental organizations:

World Health Organization (WHO)
Algerian Health ministry
Coalition for Global Hepatitis Elimination
French Association of general medicine (SFMG)
Hepatitis B foundation
Global Gastroenterology Organization (WGO)
The Nobel prize Assembly
Center for Disease Control and Prevention
National Center of Pharmacovigilance and Materiovigilance

Annex

Annex

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Survey Form: Epidemiological profile of hepatitis B and C

redacted by 2nd year Applied Microbiology students in order to carry out master's degree thesis.

Hepatitis type	Hepatitis B ☐		Hepatitis C ☐	
Identification number				
Gender	Female ☐		Male ☐	
Age				
Marital status	Single ☐	Married ☐	Divorced ☐	Widowed ☐
Residence				
Viral load	Positive ☐		Negative ☐	
Mode of infection	☐ Dental care ☐ Blood transfusion ☐ Surgical procedure ☐ Infected family member ☐ Dialysis		☐ Hidjama practice ☐ Unprotected sexual intercourse ☐ Mode not identified. ☐ Other:	
Antiviral treatment	☐ Tenofovir ☐ Sofosdac ☐ Not used			
Stage of the disease	☐ Chronic ☐ Cirrhosis ☐ Cancer			

ملخص

تعد كل من الفيروسات التهاب الكبد B (HBV) وC (HCV) من الأسباب الأكثر شيوعًا لالتهاب الكبد الفيروسي المزمن في جميع أنحاء العالم وفي الجزائر خاصة وذلك لسرعة انتشارها خاصة في الدول النامية. الهدف من هذه الدراسة وصف وبائي دقيق ومفصل للمرضى الذين أصيبوا بالتهاب الكبد B وC في ولاية المسيلة.

من أجل ذلك قمنا باعتماد المنهج الوصفي التحليلي الرجعي سواء للمعطيات على مستوى مديرية الصحة والسكان الفترة 2013- 2022 وعلى مستوى وحدة الأمراض المعدية لمستشفى الزهراوي لعام 2023 ولتحليل المعطيات ورسمها استخدمناExcel 2021.

سجلت الاحصائيات أن بلدية مقرة تملك أكثر انتشار لHBV بأعلى بنسبة 79,54% في عام 2020 تليها بلدية برهوم وعين الخضراء بالنسب التالية على التوالي 47,17% و 35,89%. أما بالنسبة الى انتشار HCV كانت بلدية مقرة الأعلى بنسبة 58,3%، عام 2020. تعتبر الفئة العمرية الأكبر من 65 سنة أكثر إصابة بالنسبة إلى HCV وبين 20 و44 سنة إلى HBV. على الرغم من عدم توفر معلومات كافية بهذا الصدد إلا أن الدراسة أظهرت أن سبب العدوى الرئيسي للالتهاب الكبدي الفيروسي B هو علاج الأسنان بنسبة 17% وسبب العدوى للالتهاب الكبدي الفيروسي C هو العمليات الجراحية بنسبة 18%.

يمكن **استغلال هذه النتائج الأولية من أجل توجيه البحوث المستقبلية وسياسيات الصحة العمومية الهادفة للحد من آثار هذه العدوى في منطقة المسيلة** كما يمكن التقليل من مشكلة عدوى التهاب الكبد الفيروسي المزمنة وذلك بإتباع الإجراءات الوقائية اللازمة ونشر التوعية.

Abstract

Hepatitis B (HBV) and Hepatitis C (HCV) viruses are among the most common causes of chronic viral hepatitis worldwide, particularly in Algeria, due to their rapid spread and especially in developing countries. The aim of this study is to provide a detailed epidemiological description of patients who contracted hepatitis B and C in the Wilaya of M'Sila.

For this purpose, we adopted a descriptive, analytical, and retrospective approach using data from the Health and People's Directorate for the period 2013-2022, and from the Infectious Diseases Departement of Zahrawi Hospital for the year 2023. For data analysis and visualization, we used Excel 2021.

Statistics recorded that the region of Magra had the highest prevalence of HBV with a rate of 79.54% in 2020, followed by the regions of Berhoum and Ain Khadra with rates of 47.17% and 35.89% respectively. As for the prevalence of HCV, Magra had the highest rate at 58.3% in 2020. The age group over 65 years old was the most affected by HCV, while the 20-44 age group was most affected by HBV. Although there is insufficient information in this regard, the study showed that the main cause of HBV infection was dental treatment at 17%, and the main cause of HCV infection was surgical procedures at 18%.

These preliminary results can be used to guide future research and public health policies aimed at reducing the impact of these infections in the M'Sila region. Additionally, the problem of chronic viral hepatitis infections can be mitigated by following necessary preventive measures and raising awareness.

Résumé

Les virus de l'hépatite B (VHB) et de l'hépatite C (VHC) sont parmi les causes les plus courantes de l'hépatite virale chronique dans le monde, en particulier en Algérie, en raison de leur propagation rapide notamment dans les pays en développement. Le but de cette étude est de fournir une description épidémiologique détaillée des patients ayant contracté l'hépatite B et C dans la Wilaya de M'Sila.

Pour cela, nous avons adopté une approche descriptive, analytique et rétrospective en utilisant les données de la Direction de la Santé et de la Population pour la période 2013-2022, et du service des Maladies Infectieuses de l'Hôpital Zahrawi pour l'année 2023. Pour l'analyse et la visualisation des données, nous avons utilisé Excel 2021.

Les statistiques ont enregistré que la commune de Magra avait la plus forte prévalence de VHB avec un taux de 79,54 % en 2020, suivie des communes de Berhoum et Ain Khadra avec des taux respectifs de 47,17 % et 35,89 %. Quant à la prévalence du VHC, la commune de Magra avait le taux le plus élevé à 58,3 % en 2020. Le groupe d'âge de plus de 65 ans était le plus touché par le VHC, tandis que le groupe d'âge de 20 à 44 ans était le plus touché par le VHB. Bien qu'il y ait des informations insuffisantes à cet égard, l'étude a montré que la principale cause d'infection par le VHB était le traitement dentaire à 17 %, et la principale cause d'infection par le VHC était les interventions chirurgicales à 18 %.

Ces résultats préliminaires peuvent être utilisés pour orienter les recherches futures et les politiques de santé publique visant à réduire l'impact de ces infections dans la région de M'Sila. De plus, le problème des infections chroniques par l'hépatite virale peut être atténué en suivant les mesures préventives nécessaires et en sensibilisant la population.