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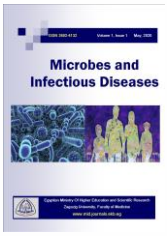

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Review article

Hepatitis C virus infection: Innate and adaptive immunity, risk factors, genotypes and prevalence in Nigeria – A systematic review

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ABSTRACT

Background: HCV burdens Nigeria with chronic infections, influenced by genotypes (1, 2, 3) and evasive immune responses. Tailored strategies are crucial. **Aims and Objective:** This review examined HCV in Nigeria, emphasizing immunity, risk factors, genotypes, and prevalence. **Methodology:** A comprehensive search was conducted across electronic databases, including PubMed, Scopus, Web of Science, Springer Nature/Nature and online African Journals. The following keywords were used: "Hepatitis C Virus," "HCV," "innate immunity," "adaptive immunity," "genotypes," "prevalence," "Nigeria," and related term. Inclusion criteria encompassed Nigerian studies on immunity, genotypes, and prevalence. Extracted data included study specifics, demographics, methods, and prevalence were assessed using quality tools. Findings were synthesized to uncover immune responses, genotypes, and prevalence patterns. **Findings:** Transmission risk factors in Nigeria encompass blood transfusion, injection drug use, healthcare exposure, tattooing, sexual contact, HIV, and HBV co-infections. HCV prevalence ranges from 2.2% to 24.2%. Genotype 1 dominates, particularly subtypes 1a and 1b, with genotypes 2, 3, 4, 5, and 6 also present. HCV's evasion tactics hinder innate and adaptive immunity responses. In Nigeria, HCV infection is a significant health burden. The prevalence of Hepatitis C Virus (HCV) genotypes in Nigeria varies, with genotype 1 being the most prevalent at 64.7%, followed by genotypes 3, 2, 4, and 6 at 7.4%, 5.9%, 4.4%, and 2.9% respectively. Genotype 5 was found to be absent in the studied cohorts. Nigeria has identified genotypes 1, 3, 2, 4, and 6, with genotype 1 being the most prevalent at 64.7% Research gaps include limited immune profiling, genotype-host dynamics understanding, immune interventions scarcity, and data integration absence. Co-infection impacts and regional prevalence variations necessitate further exploration. Addressing these gaps is crucial for a holistic comprehension of HCV in Nigeria, guiding effective strategies. Globally, HCV prevalence varies from 1.7% to 13.8% with around 62 million affected by chronic HCV in 2019. Innate and adaptive immune responses are pivotal for controlling HCV. **Conclusion**: This review offers a comprehensive understanding, bridging knowledge gaps, and influencing evidence-based interventions to combat HCV in Nigeria.

Introduction

Hepatitis C virus (HCV) infection represents a substantial global health burden, with approximately 71 million individuals affected worldwide [1] . It is a significant cause of chronic liver diseases, including cirrhosis and hepatocellular carcinoma, leading to considerable morbidity and

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mortality. Nigeria, a West African nation with a population exceeding 200 million, is not immune to this public health challenge. The epidemiological landscape of HCV infection in Nigeria is complex, with diverse genotypic distribution, varying prevalence rates, and a unique interplay between the virus and the host's immune responses[2] . This systematic review aims to comprehensively analyze the available data on HCV infection in Nigeria, with a particular focus on innate and adaptive immunity, HCV genotypes, and prevalence rates. By synthesizing and examining the existing literature, this review seeks to contribute to a deeper understanding of the immunological dynamics, genotypic diversity, and prevalence patterns of HCV infection within the Nigerian context.

Nigeria, the most populous country in Africa, faces numerous health challenges, including a significant burden of infectious diseases. Hepatitis C is a formidable contributor to this burden, and its prevalence in Nigeria is of particular concern. While the exact prevalence remains elusive due to limited systematic data collection, various studies suggest that Nigeria is home to a considerable number of individuals living with chronic HCV infection. Prevalence estimates have exhibited geographical variations, with higher rates reported in certain regions, underscoring the need for a comprehensive evaluation of the nation's HCV epidemiology[3] .

The genetic diversity of HCV is well documented, and its classification into distinct genotypes and subtypes has significant clinical implications. HCV genotypes exhibit distinct geographical distributions, and understanding the prevalent genotypes within a specific region is crucial for informed public health interventions[4]. In Nigeria, studies have revealed the presence of multiple HCV genotypes, with genotypes 1, 2, and 3 being the most prevalent. This diversity might impact disease progression, treatment response, and potential vaccine development efforts. A systematic assessment of the genotypic distribution within Nigeria can provide insights into the genetic makeup of circulating HCV strains and their potential implications[5] .

The host's immune response plays a pivotal role in determining the outcome of HCV infection. Innate immunity represents the initial defense mechanism, activating cellular responses and initiating inflammation upon viral encounter. Subsequently, adaptive immunity, orchestrated by T and B cells, becomes crucial for viral clearance. However, HCV's ability to evade these immune responses often results in chronic infection. In Nigeria, the interplay between HCV and the host's immune responses remains a topic of investigation. Studies exploring the dynamics of innate and adaptive immune responses in the Nigerian population contribute to a broader understanding of the immune evasion strategies employed by HCV [6] .

The complex epidemiology of HCV infection in Nigeria underscores the importance of tailored public health strategies. Understanding the prevalence rates, genotypic distribution, and immunological interactions is fundamental for designing effective prevention and control measures. Additionally, access to accurate epidemiological data enables healthcare policymakers to allocate resources efficiently and develop strategies to mitigate the burden of HCV-related liver diseases[7] . This systematic review aims to provide a comprehensive synthesis of data that can inform evidence-based interventions and guide policymakers in addressing the challenges posed by HCV infection in Nigeria.

While individual studies have contributed valuable insights into various aspects of HCV infection in Nigeria, a comprehensive synthesis of these findings is lacking. Existing literature is often scattered across different journals and databases, making it challenging to draw meaningful conclusions. This systematic review addresses this gap by collecting, analyzing, and synthesizing the available data on HCV infection in Nigeria. By employing a systematic approach, this review seeks to provide a comprehensive overview of innate and adaptive immune responses, genotypic diversity, and prevalence rates. Such a synthesis can offer a clearer understanding of the multifaceted aspects of HCV infection in Nigeria and guide future research endeavors and public health interventions[1,2,3,4] .

Hepatitis C virus infection remains a significant public health concern in Nigeria, affecting the lives of countless individuals and exerting pressure on the healthcare system. This systematic review aims to consolidate the existing knowledge on HCV infection in Nigeria, with a specific emphasis on innate and adaptive immunity, HCV genotypes, and prevalence rates. By providing a comprehensive synthesis of data, this review aspires to contribute to a more profound

understanding of the epidemiological and immunological dynamics of HCV infection in Nigeria, ultimately aiding in the development of targeted interventions and policies to combat this persistent health challenge[1,2,3,4,8].

Study objectives

1. Data compilation and assessment: To systematically gather and evaluate existing research data concerning hepatitis C virus (HCV) infection within the Nigerian population.
2. Innate and adaptive immunity analysis: To analyze and synthesize the literature concerning the innate and adaptive immune responses triggered by HCV infection in the context of Nigeria.
3. Genotypic diversity examination: To investigate the distribution of HCV genotypes prevalent in Nigeria by reviewing and summarizing relevant studies.
4. Prevalence rate assessment: To assess the prevalence rates of HCV infection in different regions of Nigeria through a comprehensive analysis of available prevalence data.
5. Comprehensive overview creation: To develop a comprehensive overview of HCV infection in Nigeria, incorporating insights from innate and adaptive immunity, genotypic diversity, and prevalence rates, thereby contributing to a better understanding of the epidemiology and immunology of HCV in the Nigerian population.

Methodology

In this systematic review, a comprehensive analysis of existing literature was conducted to investigate the various aspects of hepatitis C virus (HCV) infection in Nigeria, focusing on innate and adaptive immunity, genotypes, and prevalence. The aim was to synthesize and summarize the available data to enhance our understanding of the epidemiological and immunological landscape of HCV infection in the Nigerian population [9,10].

Search strategy

A comprehensive search was conducted across electronic databases, including PubMed, Scopus, Web of Science, Springer Nature/Nature and online African journals. The following keywords and their combinations were used: "Hepatitis C Virus", "HCV", "innate immunity" ,"adaptive immunity", "genotypes", "prevalence", "Nigeria", and related terms [9, 10].

Inclusion and exclusion criteria

Studies were included if they met the following criteria:

1. Original research articles, cross-sectional studies, case-control studies, and cohort studies.
2. Studies conducted in Nigeria.
3. Studies focusing on innate and/or adaptive immune responses to HCV infection, HCV genotypes, or prevalence data.
4. Studies with available full-text articles.

Studies were excluded if they:

1. Were review articles, case reports, or conference abstracts.
2. Were conducted outside Nigeria.
3. Were not directly related to the innate and adaptive immune responses, genotypes, nor prevalence of HCV infection.

Data extraction

Data from the selected studies were extracted using a standardized data extraction form. The extracted information included study characteristics (authors, publication year, study design), participants' demographics, sample size, methods for assessing innate and adaptive immune responses, HCV genotyping methods, and reported prevalence rates [9, 10].

Quality assessment

The quality of included studies was assessed using appropriate tools such as the Newcastle-Ottawa Scale for observational studies. This assessment aimed to evaluate the methodological rigor and bias potential of each study [9, 10].

Data synthesis and analysis

A narrative synthesis approach was employed to summarize the findings from the selected studies. Themes related to innate and adaptive immune responses, HCV genotypes, and prevalence were identified and discussed. Due to the expected heterogeneity of the studies, a meta-analysis was planned if feasible, considering similar study designs and outcomes [9, 10].

Ethical considerations

This systematic review solely utilized publicly available data and did not involve human subjects, thus ethical approval was not required [9, 10].

Filters and limits used in search strategy

Search databases

1. PubMed.
2. Scopus.
3. Web of Science.
4. Springer Nature/Nature.
5. African Journals Online.

Keywords and their combinations

1. "Hepatitis C Virus".
2. "HCV".
3. "innate immunity".
4. "adaptive immunity".
5. "genotypes".
6. "prevalence"..
7. "Nigeria"

Inclusion criteria for studies

1. Original research articles.
2. Cross-sectional studies.
3. Case-control studies.
4. Cohort studies.
5. Studies conducted in Nigeria.
6. Studies focusing on innate and/or adaptive immune responses to HCV infection, HCV genotypes, and prevalence data.
7. Studies with available full-text articles.

Exclusion criteria for studies

1. Review articles.
2. Case reports.
3. Conference abstracts.
4. Studies conducted outside Nigeria.
5. Studies not directly related to the innate and adaptive immune responses, genotypes or prevalence of HCV infection.

Data extraction

Standardized data extraction form was used. Extracted information included study characteristics (authors, publication year, study design), participant demographics, sample size, methods for assessing innate and adaptive immune responses, HCV genotyping methods, and reported prevalence rates.

Quality assessment

The quality of included studies was assessed using appropriate tools such as the Newcastle-Ottawa Scale for observational studies. Assessment aimed to evaluate the methodological rigor and bias potential of each study.

Data synthesis and analysis

Narrative synthesis approach was employed to summarize findings. Themes related to innate and adaptive immune responses, HCV genotypes, and prevalence were identified and discussed. Meta-analysis was planned if feasible, considering similar study designs and outcomes, due to expected heterogeneity of the studies.

Prospero registration

The systematic review was not registered in Prospero.

Methods used to decide whether the study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process

Number of reviewers: The systematic review involved two reviewers independently screening each record.

Independence of reviewers: The 2 reviewers worked independently to screen records and reports to reduce bias. Each reviewer assesses whether a study meets the inclusion criteria based on predefined criteria.

Automation tools: The systematic reviews used reference management software and specialized tools to streamline the screening process. These tools helped to manage citations and facilitate collaboration among reviewers.

Screening process: Reviewers screened records in multiple stages. In the first stage, they reviewed titles and abstracts to exclude obviously irrelevant studies. In the second stage, full-text articles of potentially relevant studies were assessed to determine final inclusion.

Resolution of discrepancies: Discrepancies between reviewers regarding inclusion or exclusion were resolved through discussion and consensus.

Documentation of screening process: Best practices involve documenting the screening process, including details on how many records were screened, reasons for exclusion, and any disagreements between reviewers.

Data extraction and quality assessment: Data extraction and quality assessment followed the inclusion of studies. Again, the number of

reviewers involved in these processes worked independently and used automation tools.

Methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, processes for obtaining or confirming data from study investigators, and details of automation tools used in the process

Data extraction: Two reviewers were involved in the data extraction process. They worked independently to extract information from the selected studies using a standardized data extraction form. The extracted data included study characteristics (authors, publication year, study design), participant demographics, sample size, methods for assessing innate and adaptive immune responses, HCV genotyping methods, and reported prevalence rates.

Independence of reviewers: Both reviewers worked independently during the data extraction process to minimize bias. Each reviewer was responsible for extracting data from the selected studies based on the predefined criteria outlined in the data extraction form.

Automation tools: The systematic review utilized reference management software and specialized tools to facilitate the data extraction process. These tools helped organize and manage the extracted information, ensuring consistency and accuracy in the data collection process.

Quality assessment: The quality assessment of included studies was conducted by the two reviewers independently. Appropriate tools, such as the Newcastle-Ottawa Scale for observational studies, were employed to assess the methodological rigor and potential bias of each study.

Independence of reviewers in quality assessment: Similar to the data extraction process, both reviewers worked independently during the quality assessment phase. Each reviewer assessed the quality of the included studies based on predetermined criteria, and any discrepancies were resolved through discussion and consensus.

Automation tools in quality assessment: This systematic review used reference management software and other specialized tools to streamline the quality assessment process. These tools assisted in organizing assessment criteria, recording judgments, and facilitating collaboration between reviewers.

Documentation: Best practices in systematic reviews involve thorough documentation of the data extraction and quality assessment processes which was used in this review . This documentation includes details on the number of reviewers involved, whether they worked independently, any discrepancies between reviewers, and the tools used to enhance efficiency and accuracy. This documentation contributes to the transparency and reproducibility of the review.

Methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and details of automation tools used

In this systematic review, the risk of bias assessment was considered to evaluate the internal validity of included studies using Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies, as mentioned in the text for quality assessment.

Processes used to decide which studies were eligible

Inclusion and exclusion criteria: The text mentions specific inclusion and exclusion criteria for studies, such as study design, location (Nigeria), and relevance to innate and adaptive immune responses, HCV genotypes, and prevalence. These criteria likely guided the decision-making process for including or excluding studies.

Screening process: Two independent reviewers conducted the screening process, which involved multiple stages. Initially, they reviewed titles and abstracts to exclude irrelevant studies, followed by the assessment of full-text articles for potentially relevant studies. The screening process aimed to ensure that each included study met the predefined inclusion criteria.

Decision-making and resolution of discrepancies: The two reviewers worked independently to assess whether a study met the inclusion criteria. Any discrepancies between the reviewers regarding inclusion or exclusion were resolved through discussion and consensus. This process likely involved careful consideration of the predefined criteria.

Automation Tools in Screening: Reference management software and specialized tools were used to streamline the screening process. These tools facilitated the management of citations and

collaboration among reviewers, possibly improving efficiency in the study selection process.

Documentation: Best practices in systematic reviews involve thorough documentation of the screening process. The text mentions the importance of documenting details such as the number of records screened, reasons for exclusion, and any disagreements between reviewers. Documentation contributes to transparency and reproducibility.

Literature review

Introduction

HCV infection remains a global health challenge with diverse clinical outcomes and transmission routes. Genotypic diversity and host immune responses are crucial factors influencing disease progression and treatment response. In the Nigerian context, addressing the specific challenges and understanding the local immunogenetic landscape are essential steps towards mitigating the impact of HCV and improving public health interventions[2,3,4,5,6,7,8, 11, 12, 13, 14, 15,16] .

Innate immunity and HCV infection

Innate immunity plays a pivotal role in the host's initial defense against hepatitis C virus(HCV) infection. It involves a range of responses orchestrated by pattern recognition receptors (PRRs), interferons (IFNs), and cytokines. These responses are instrumental in shaping the outcome of HCV infection by influencing its replication, spread, and eventual clearance [11,12,13,14,15,16]

PRRs are specialized sensors that identify molecular patterns associated with pathogens, including HCV. Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) are key PRRs in the context of HCV infection. Upon recognizing HCV RNA, these receptors trigger signaling cascades that result in the production of interferons and pro-inflammatory cytokines. Interferons, specifically type I interferons (IFN-α and IFN-β), are crucial antiviral cytokines that activate an array of cellular responses designed to inhibit viral replication and spread [11,12,13,14,15,16] .

During the early stages of HCV infection, the innate immune system acts as the first line of defense. PRRs detect HCV components, alerting the immune system and stimulating the production of interferons and cytokines. This prompts an antiviral state within infected and neighboring cells, inhibiting viral replication and spread. Additionally, the innate immune response contributes to the activation of adaptive immunity, further enhancing the overall defense against HCV [11,12,13,14,15,16].

Numerous studies underscore the intricate relationship between innate immunity and HCV. While a robust innate response is associated with effective control and clearance of the virus, HCV has evolved mechanisms to counteract these defenses, enabling persistent infection. Certain viral proteins can inhibit the activation of innate immune pathways or directly interfere with interferon signaling, allowing the virus to replicate and establish chronic infection [11,12,13,14,15,16].

Efforts to harness innate immunity for HCV clearance have gained attention. Therapeutic strategies targeting PRRs or enhancing interferon signaling have been explored. Toll-like receptor agonists and RLR agonists have been investigated as potential adjuvants to boost innate responses. However, the challenge lies in balancing these strategies to achieve an effective antiviral state without triggering excessive inflammation, which could lead to tissue damage [11,12,13,14,15,16].

Innate immune responses orchestrated by PRRs, interferons, and cytokines are central to the initial defense against HCV infection. The delicate balance between viral evasion and host defense determines the outcome of infection. Understanding these intricate interactions opens avenues for innovative therapeutic approaches that enhance innate immunity, paving the way for improved strategies to control and potentially clear HCV infection [11,12,13,14,15,16].

Adaptive immunity and HCV infection

Adaptive immunity constitutes a sophisticated defense mechanism against hepatitis C virus (HCV) infection, orchestrated by T cells (CD4+ and CD8+) and B cells. These components engage in a complex interplay to recognize and neutralize the virus, leading to the generation of long-lasting immunity[15]. The dynamics of adaptive immune responses evolve significantly over the course of HCV infection, shaping disease progression and outcomes. During the acute phase of HCV infection, CD4+ T cells assist in orchestrating the immune response by providing help to B cells and CD8+ T cells. CD8+ T cells, on the other hand, play a pivotal role in directly targeting and eliminating infected cells. B cells produce antibodies that neutralize the virus and

contribute to viral clearance. However, HCV's high genetic variability poses a challenge for neutralizing antibody responses, allowing the virus to escape immune detection and persist[16].

As HCV infection transitions to the chronic phase, adaptive immune responses undergo changes. CD4+ and CD8+ T cells can become dysfunctional due to continuous antigen exposure, leading to exhaustion. This exhaustion is characterized by reduced effector functions, impaired proliferation, and altered cytokine production. T cell exhaustion is a key contributor to viral persistence, as it hampers the immune system's ability to control viral replication effectively[17].

Studies have demonstrated that T cell exhaustion plays a central role in HCV chronicity. Persistent antigen exposure drives the upregulation of inhibitory receptors such as PD-1, CTLA-4, and TIM-3 on T cells, rendering them less responsive to stimulation. This phenomenon is further exacerbated by the presence of regulatory T cells that dampen immune responses. As a result, HCV-specific T cells lose their capacity to clear the infection effectively [18].

Immunotherapeutic approaches aimed at restoring adaptive immune responses offer promise in combating HCV infection. Checkpoint inhibitors targeting inhibitory receptors on exhausted T cells have shown potential in reinvigorating T cell functions and promoting viral control. Strategies to alleviate T cell exhaustion, such as blocking inhibitory pathways or enhancing co-stimulation, are being explored to enhance the effectiveness of HCV-specific T cell responses [19].

Adaptive immune responses involving T cells (CD4+ and CD8+) and B cells are pivotal in determining the outcome of HCV infection. The evolution of these responses from acute to chronic phases significantly influences disease progression. T cell dysfunction and exhaustion contribute to viral persistence, highlighting the importance of immunotherapeutic strategies aimed at restoring adaptive immune functions. A comprehensive understanding of these dynamics is essential for devising effective interventions to combat HCV infection and mitigate its impact [20,21].

Genotypes and variability of HCV in Nigeria

Hepatitis C virus (HCV) is a major public health concern worldwide due to its high prevalence and potential for chronic liver disease. HCV is characterized by its genetic diversity, which is primarily attributed to the existence of distinct genotypes and subtypes. These genotypes show geographical variations and have implications for disease progression, treatment responses, and vaccine development. This article focuses on the genotypes of HCV, their distribution in Nigeria, and their potential impact on immune responses and treatment outcomes [22, 23, 24, 25].

Global distribution of HCV genotypes

HCV exhibits a diverse array of genotypes and subtypes, with at least 7 major genotypes (1-7) identified. These genotypes have distinct geographic distributions, with some being more prevalent in certain regions than others. For instance, genotype 1 is widespread globally and associated with higher resistance to treatment, while genotypes 2 and 3 are more prevalent in specific regions such as Asia. Understanding the distribution of these genotypes is crucial for tailoring effective prevention and treatment strategies [22, 23, 24, 25].

Prevalence of HCV Genotypes in Nigeria

In Nigeria, HCV infection is a significant health burden. The prevalence of Hepatitis C Virus (HCV) genotypes in Nigeria varies, with genotype 1 being the most prevalent at 64.7%, followed by genotypes 3, 2, 4, and 6 at 7.4%, 5.9%, 4.4%, and 2.9% respectively. Genotype 5 was found to be absent in the studied cohorts. Nigeria has identified genotypes 1, 3, 2, 4, and 6, with genotype 1 being the most prevalent at 64.7% However, due to the scarcity of comprehensive studies, the true prevalence of HCV genotypes in Nigeria remains unclear. Improved surveillance and broader studies are necessary to obtain a more accurate picture of genotype distribution, which would aid in designing targeted interventions [22, 23, 24, 25, 26, 27].

Comparison with global genotype distribution

Comparing HCV genotype distribution in Nigeria with other regions reveals unique patterns. While genotype 3 seems to dominate in Nigeria, genotype 1 is more prevalent in many Western countries. This divergence could influence the effectiveness of treatment regimens imported from other regions, highlighting the importance of region-specific approaches. Additionally, migration and globalization may contribute to shifts in genotype distribution, further emphasizing the need for continuous monitoring [22, 23, 24, 25].

Implications for immune responses and treatment outcomes

The genotypic diversity of HCV can impact immune responses and treatment outcomes. Certain genotypes might exhibit varying degrees of resistance to antiviral therapies, complicating treatment success. Furthermore, genotypic variability can influence the development of vaccines, as immune responses triggered by one genotype may not be protective against others. In Nigeria, understanding these implications is vital for optimizing treatment strategies and developing region-specific vaccines [22, 23, 24, 25].

HCV genotypes exhibit a diverse global distribution, with genotype prevalence varying across regions. As research progresses, efforts to improve genotypic surveillance and promote international collaboration will enhance our understanding of HCV's complex dynamics [22, 23, 24, 25].

Prevalence of HCV infection in Nigeria

Hepatitis C virus (HCV) infection remains a global health concern, with its prevalence varying across regions and populations. In Nigeria, HCV has garnered attention due to its impact on public health. This article provides an overview of HCV prevalence studies in Nigeria, analyzes trends over time and geographical regions, identifies high-risk populations and transmission modes, and discusses contributing factors to its [22, 28, 29, 30, 31, 32].

HCV prevalence studies in Nigeria

Several studies have been conducted in Nigeria to assess the prevalence of HCV infection. These studies have employed various methodologies, such as serological assays and molecular techniques to estimate the prevalence accurately. The diversity of methods used has led to variations in reported prevalence rates, but collectively they highlight HCV as a significant health concern in Nigeria [22, 28, 29, 30, 31, 32].

Trends in HCV prevalence over time and regions

Analysis of these studies revealed varying trends in HCV prevalence over time and across different regions of Nigeria. While data from earlier studies are limited, recent reports suggest a concerning upward trend in some areas. Northern regions have shown higher prevalence rates compared to the Southern regions, with factors like cultural practices and healthcare disparities possibly influencing this discrepancy [22, 28, 29, 30, 31, 32].

High-risk populations and transmission modes

Certain populations in Nigeria are identified as being at a higher risk of HCV infection. These include people who inject drugs (PWID), individuals undergoing blood transfusions, healthcare workers, and those engaging in risky sexual behavior. Inadequate infection control measures, including unregulated healthcare practices and non-sterile equipment use, contribute to the spread of HCV [22, 28, 29, 30, 31, 32]..

Contributing factors to HCV prevalence

Multiple factors contribute to the prevalence of HCV in Nigeria. The healthcare infrastructure in some areas lacks proper infection control measures, leading to contaminated blood products and unsafe medical practices. Socioeconomic factors, such as poverty and limited access to healthcare, also play a role. In regions with poor sanitation and limited awareness, transmission through unsafe injections and improper disposal of medical waste remains a concern [22, 28, 29, 30, 31, 32]. The prevalence of Hepatitis C Virus (HCV) in Nigeria is a significant health concern, with various factors influencing its spread. To address this challenge effectively, a comprehensive approach is necessary. Strengthening healthcare infrastructure, promoting safe medical practices, and raising awareness about HCV transmission are crucial steps. Targeting high-risk populations for early detection, treatment, and prevention is also essential. This multi-pronged strategy aims to improve diagnosis rates, provide timely treatment, and ultimately reduce the burden of HCV in Nigeria [22, 23, 24, 25, 26, 27].

Challenges and opportunities in HCV research in Nigeria

Hepatitis C virus (HCV) research in Nigeria is vital for understanding the epidemiology, immunity, and genotypes of the infection. This article focuses on the existing gaps in knowledge, challenges faced in diagnosis and treatment, potential opportunities for future research, and the transformative impact that improved HCV research could have on prevention, management, and public health policies [33, 324 35, 36].

Gaps in knowledge about HCV infection, immunity, and genotypes

Despite progress in HCV research globally, gaps persist in understanding the specific dynamics

of the virus in the Nigerian context. Limited data on the prevalence of different HCV genotypes hinder a comprehensive understanding of transmission patterns and treatment responses. Moreover, insights into the host immune response against HCV in the Nigerian population remain largely unexplored, necessitating further investigation [33, 34, 335 36].

Challenges in diagnosing and treating HCV in resource-limited settings

Resources limitations pose substantial challenges in diagnosing and treating HCV in Nigeria. Access to accurate diagnostic tests and antiviral medications is constrained, especially in remote and underserved regions. Additionally, inadequate awareness and screening programs hinder early detection leading to delayed interventions. These challenges underscore the urgency of developing cost-effective strategies tailored to resource-limited settings [33, 34,35,36].

Opportunities for future research in Nigeria

Nigeria presents a unique opportunity for HCV research due to its diverse population and healthcare landscape. Large-scale epidemiological studies can provide insights into the prevalence of specific genotypes and risk factors across different regions. Immune profiling studies could uncover the nuances of host responses, guiding the development of personalized treatment strategies. Furthermore, conducting clinical trials in Nigeria could evaluate the efficacy of novel antiviral treatments in real-world conditions [31, 32, 33, 34].

Potential impact on HCV prevention, management, and public health policies

Enhanced HCV research in Nigeria could yield transformative outcomes. A comprehensive understanding of genotype distribution and transmission dynamics would aid in tailoring prevention strategies. Insights into host immunity could inform the development of vaccines and more effective treatment regimens. Robust research data could also drive evidence-based policies, leading to improved screening programs, increased access to treatment, and better healthcare resource allocation [33, 34, 35, 36].

HCV research in Nigeria stands at a critical juncture, marked by gaps in knowledge and challenges in resource-limited settings. However, the country's diverse population and healthcare landscape offer opportunities for meaningful research that could revolutionize HCV prevention, management, and public health policies. Bridging these gaps and addressing challenges would contribute significantly to reducing the burden of HCV, improving patient outcomes, and advancing global efforts to combat this formidable infection [31, 32, 33, 34].

Findings and discussion

The risk factors for HCV transmission in Nigeria

The risk factors for HCV transmission in Nigeria are not fully understood, but some factors have been identified based on available studies. These risk factors include:

1. Blood transfusion: HCV is parenterally transmitted, and blood transfusion is a known risk factor for HCV transmission in Nigeria [38, 39].
2. Injection drug use: Injection drug use is a known risk factor for HCV transmission globally, and it is also a risk factor in Nigeria [37, 38].
3. Healthcare exposure: Healthcare exposure, including medical procedures, injections, and surgeries, has been identified as a risk factor for HCV transmission in Nigeria [37 40].
4. Tattooing and body piercing: Tattooing and body piercing have been identified as risk factors for HCV transmission in Nigeria[37].
5. Sexual contact: Sexual contact is a less common mode of HCV transmission, but it can occur, especially among people with multiple sexual partners or those with sexually transmitted infections[37].
6. HIV co-infection: HIV co-infection is a risk factor for HCV transmission in Nigeria, as people with HIV are more likely to acquire HCV [37, 41].
7. Hepatitis B virus (HBV) co-infection: HCV coinfection with HBV is common in Nigeria and is a risk factor for HCV transmission[37].

Prevalence of HCV in Nigeria

The prevalence of HCV in Nigeria is reported to be between 2.2% and 24.2% [22,51]. A retrospective review of data found a prevalence of 2.2% [22].Another study reported a prevalence range of 2.8% to 24.2% [22,51]. HCV antibody prevalence was higher among males (7.1%) compared to females (6.5%) [42].

However, it is important to note that the available data on HCV prevalence in Nigeria is limited and may not be fully representative of

the entire population. It is also worth noting that HCV prevalence can vary widely depending on the region and population group being studied. For example, a study on prisoners in a Nigerian prison found a higher prevalence of HCV among males (31.0%) than females (15.4%) [40,42]. There are several studies on the prevalence of hepatitis C virus (HCV) and serology in Nigeria. Here are some key findings:

1. A study conducted in 2020 found that genotypes 1 and 4 have the highest prevalence of HCV in Nigeria, with 58.4% of subjects with anti-HCV antibodies having HCV viremia[43].
2. Another study conducted in Port Harcourt, Nigeria, found a moderate prevalence of HCV infection (5%) among apparently healthy blood donors. The prevalence was higher among commercial donors and those with blood group O[44].
3. A 2019 study on HIV/HCV co-infected patients in Nigeria found that HCV genotype 5 (subtype 5a) is the predominant strain circulating in the study population[45].
4. A 2013 study on pregnant women attending the first antenatal clinic of a tertiary hospital in Nigeria found a seroprevalence of HCV antibodies of 1.3%[46].
5. Trasmission in the hospitals to clients like pregnant women attending the first antenatal clinic according to the World Health Organization (WHO), HCV is a bloodborne virus and is most commonly transmitted through the reuse or inadequate sterilization of medical equipment, transfusion of unscreened blood and blood products, and injecting drug use through the sharing of injection equipment[47]
6. A study conducted in Nigeria in 2019 found a seroprevalence of 7.2% for HCV among HIV-infected patients[45].
7. Another study found that the prevalence of HCV was highest among migrants from East Africa (66.1%) and West Africa (53.7%)[48].

These studies suggest that HCV is present in Nigeria, with varying prevalence rates depending on the population studied. It is important to continue monitoring the prevalence of HCV in Nigeria and to implement measures to prevent its transmission.

Globally, the prevalence of HCV in the general population is estimated to be 6.0%, ranging between 1.7% and 13.8%, depending on the country[49].Globally, approximately 62 million individuals were affected by HCV infection on a chronic basis in 2019. Although the quality of epidemiological data and prevalence assessments varies significantly across nations and regions. The most recent global estimations from 2019 demonstrate that the viremic prevalence of HCV infection indicated by the presence of HCV RNA, stands at less than 1.0% in the majority of developed countries. Notably, the United States exhibits a similar prevalence.HCV prevalence exhibits notable variations, with considerably higher rates observed in certain regions. For instance, countries in Eastern Europe show elevated prevalence rates such as Ukraine (3.1%), Russia (2.9%), Moldova (2.9%), Romania (2.5%), and Latvia (2.1%). Likewise, specific countries in Africa (e.g., Gabon with 5.9%, Burundi with 3.6%, Egypt with 2.1%), the Middle East (Syria with 1.6%), and the South Caucasus and Central Asia (Georgia with 3.1%, Uzbekistan with 3.0%, Tajikistan with 2.7%, Turkmenistan with 2.7%) also experience higher HCV prevalence rates [49,50].

HCV genotypes in Nigeria

The most common HCV genotype in Nigeria is genotype 1, specifically subtypes 1a and 1b. This information is supported by multiple search results:

1. A study found that genotype 1 was the most frequent HCV genotype observed in Nigeria, with genotype 1b present in 55.3% of samples and genotype 1a in 9.5% [52].
2. Another study mentioned that HCV genotypes 1 and 3 are the most prevalent globally, with Nigeria showing a prevalent circulation of genotype 1 (85%) [49].
3. A retrospective review of data also confirmed the presence of genotype 1 as the most common genotype in Nigeria[22].
4. Additionally, a phylogenetic analysis of HIV/HCV co-infected patients in Nigeria revealed that the predominant HCV

genotype was genotype 5, followed by genotype 1 (subtype 1a) [45].

It's important to note that other genotypes, such as genotypes 2, 3, 4, and 5 have also been identified in Nigeria[51,53]. However, genotype 1 appears to be the most prevalent.

Other HCV genotypes found in Nigeria

According to the search results, the other HCV genotypes found in Nigeria, besides genotype 1, are:

1. Genotype 2: A study found that genotype 2 was present in 23.67% of samples[52].
2. Genotype 3: The prevalence of genotype 3 was reported to be 7.4%[52].
3. Genotype 4: A study reported the presence of genotype 4 in Nigeria[54].
4. A study on HIV/HCV co-infected patients in Nigeria found HCV genotype 5 (subtype 5a) to be the predominant strain[45].
5. Genotype 6: Another study found that genotype 6 was present in 2.9% of samples[52].

It's worth noting that some of the search results mention the presence of novel or unclassified HCV sequences in Nigeria, which may represent new genotypes or subtypes[54]. However, further research is needed to confirm their classification. Additionally, a review article mentions that some non-epidemic HCV genotypes have been identified in low- and middle-income countries, including Nigeria, which may pose a risk of resistance to current direct-acting antiviral regimens[55]

6. HCV is a small, positive single-stranded, RNA-enveloped virus with seven major genotypes[22].
7. The global distribution and prevalence of HCV genotypes show regional variations[56] .

The immune response to HCV

The immune response to HCV involves both the innate and adaptive immune systems[49].The adaptive immune system plays a significant role in the immune response to HCV[51]. Hepatitis C virus(HCV) infection can lead to chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma[58]. Only a minority of patients can clear the virus spontaneously during acute infection. The elimination of HCV during acute infection correlates with a rapid induction of innate immune responses, especially interferon (IFN)-induced genes, and a delayed induction of adaptive immune responses[58]. However, HCV's genetic agility, resulting from its high rate of replication and its error-prone replication mechanism, enables it to evade immune recognition[15]. The inefficient innate and adaptive immune responses have been shown to play a major pathogenetic role in the development and persistence of HCV infection[59]. Effective innate and adaptive immune responses are essential for the control of HCV infection[60].

The mechanisms that protect HCV from IFN-mediated innate immune reactions are not entirely understood, but they might involve blockade of ISG protein translation at the ribosome, localization of viral replication to cell compartments that are not accessible to anti-viral IFN-stimulated effector systems, or direct antagonism of effector systems by viral proteins[58].

A functional adaptive immune response is the major determinant for clearance of HCV infection. However, in the majority of patients, HCV establishes chronic infection by evading and suppressing the adaptive immune response[61].

In summary, both innate and adaptive immune responses play a crucial role in determining the outcome of HCV infection. The rapid induction of innate immune responses, especially IFN-induced genes, is associated with the elimination of HCV during acute infection. However, HCV's genetic agility enables it to evade immune recognition, leading to inefficient innate and adaptive immune responses and the establishment of chronic infection. Effective innate and adaptive immune responses are essential for the control of HCV infection.

Research gaps

A systematic review of existing data on hepatitis C virus infection in Nigeria reveals several research gaps concerning innate and adaptive immunity, genotypes, and prevalence. Addressing these gaps is essential for a comprehensive understanding of HCV infection in the Nigerian context and the development of tailored strategies for prevention, treatment, and public health policy.

1. Limited immune profiling in Nigerian population: Comprehensive studies investigating the innate and adaptive immune responses to HCV infection in the Nigerian population are lacking. Understanding how the immune system

interacts with HCV, particularly within the context of Nigeria's diverse genetic landscape remains an underexplored area.

2. Host-pathogen interaction dynamics: The intricate interplay between HCV genotypes and the host's innate and adaptive immune responses is not well-characterized in Nigeria. Unraveling these dynamics could reveal insights into why certain genotypes are more prevalent and how the immune system's effectiveness varies.
3. Diversity of HCV genotypes and subtypes: Despite Nigeria's high disease burden, there's a scarcity of comprehensive genotype and subtype data for HCV. Investigating the distribution and prevalence of different genotypes across regions would shed light on transmission patterns and potential variations in treatment responses.
4. Subtype-specific immune responses: Research into subtype-specific immune responses is lacking. As different genotypes and subtypes might interact differently with the host immune system, understanding these nuances could inform targeted therapeutic strategies.
5. Longitudinal studies: Few longitudinal studies have been conducted in Nigeria to track the natural progression of HCV infection and its interaction with the immune system over time. Such studies are crucial for identifying factors that contribute to disease progression or resolution.
6. Paucity of immune-based interventions: There's a dearth of studies exploring the potential of immune-based interventions like therapeutic vaccines or immunomodulatory drugs tailored to the Nigerian population's immune characteristics.
7. High-risk groups and immune variation: Investigating how innate and adaptive immunity might differ in high-risk groups, such as people who inject drugs (PWID) or healthcare workers, could provide insights into their susceptibility to infection and potential targets for prevention.
8. Limited data integration: Often, studies on HCV immunity, genotypes, and prevalence are conducted in isolation. Integrating data from different disciplines (e.g.; epidemiology, immunology, virology) could provide a more holistic understanding of HCV in Nigeria.
9. Impact of co-infections: Nigeria also has a substantial burden of other infectious diseases like HIV and malaria. The impact of these co-infections on HCV infection dynamics, immune responses, and treatment outcomes remains an area of research with limited exploration.
10. Geographical variation in prevalence: The prevalence of HCV is known to vary across different regions of Nigeria. However, there's a lack of detailed spatial mapping of HCV prevalence and genotype distribution, which could aid in targeting interventions and healthcare resource allocation.

Outcomes for which data were sought, specific results that were compatible with each outcome domain in each study

Innate immunity and HCV infection outcomes: Understanding the role of pattern recognition receptors (PRRs), interferons, and cytokines in the initial defense against HCV infection. Definition: Investigating how innate immune responses, triggered by PRRs and interferons, influence HCV replication, spread, and clearance.

Adaptive immunity and HCV infection outcomes: Evaluating the dynamics of adaptive immune responses (T cells, B cells) during acute and chronic phases of HCV infection. Definition: Studying how CD4+ and CD8+ T cells, along with B cells, contribute to recognizing and neutralizing the virus, and how T cell exhaustion affects viral persistence.

Genotypes and variability outcomes: Understanding the distribution and prevalence of HCV genotypes in Nigeria and their implications for immune responses and treatment outcomes. Definition: Investigating how different genotypes impact disease progression, treatment responses, and the potential development of region-specific vaccines.

Prevalence of HCV infection outcomes: Assessing the prevalence of HCV in Nigeria, trends over time, and identifying high-risk populations and transmission modes. Definition: Examining the

extent of HCV infection, variations in prevalence across regions, and identifying factors contributing to the spread of HCV in Nigeria.

Challenges and opportunities in HCV research outcomes: Identifying gaps in knowledge, challenges in diagnosis and treatment, and potential opportunities for future HCV research in Nigeria. Definition: Highlighting areas where research is lacking, understanding limitations in diagnosis and treatment, and proposing avenues for future research to address these challenges.

Findings and discussion outcomes: Presenting key findings related to risk factors for HCV transmission, prevalence rates, genotypic distribution, and the immune response in Nigeria. Definition: Summarizing the results of various studies and discussions on the multifaceted aspects of HCV infection in the Nigerian context.

Research gaps outcomes: Identifying gaps in knowledge related to innate and adaptive immunity, genotypes, and prevalence of HCV in Nigeria. Definition: Recognizing areas where further research is needed to enhance understanding and develop targeted strategies for prevention, treatment, and public health policy.

Table 1. Results of individual studies and syntheses.

Results of individual studies and syntheses
Adaptive Immunity and HCV Infection [20,21]
Role of Adaptive Immunity [15,20,21] CD4+ and CD8+ T Cells [15, 17] T Cell Exhaustion [18] Immunotherapeutic Approaches [19]
Impact on Disease Progression [20, 21].
Genotypes and Variability of HCV in Nigeria [22, 23,24,25]
Global Distribution of HCV Genotypes [22, 23,24,25] Prevalence in Nigeria [22, 23,24,25] Comparison with Global Distribution [22, 23,24,25] Implications for Immune Responses [22, 23,24,25]
Prevalence of HCV Infection in Nigeria [22,28, ,29, 30, ,31, ,32]
Prevalence Studies [22,28, ,29, 30, ,31, ,32] Trends Over Time and Regions [22,26,27,28,29,30] High-Risk Populations and Transmission Modes [22,28, ,29, 30, ,31, ,32] Contributing Factors [22,28, ,29, 30, ,31, ,32]
Challenges and Opportunities in HCV Research in Nigeria [33,34,35,36]
Gaps in Knowledge [33,34,35,36]

Conclusion

In conclusion, hepatitis C virus (HCV) infection remains a significant global health concern, affecting millions of individuals worldwide, including Nigeria. This systematic review has provided a comprehensive analysis of HCV infection in Nigeria, focusing on innate and adaptive immunity, genotypes, and prevalence rates. Despite challenges in obtaining accurate data, it is evident that Nigeria bears a substantial burden of chronic HCV infection, with varying prevalence rates across regions. The presence of multiple genotypes, particularly genotypes 1, 2, and 3 highlights the complexity of the disease's epidemiology in the country. The immune responses of the host, both innate and adaptive, play critical roles in determining the outcome of HCV infection.

However, the virus's ability to evade these immune responses often leads to chronic infection. This review underscores the importance of understanding the intricate interactions between HCV and the host's immune system, as well as the impact of diverse genotypes on disease progression and treatment outcomes. Addressing the gaps identified in this review is essential for advancing our knowledge of HCV infection in Nigeria and

developing effective strategies for prevention, management, and public health policies.

Recommendations

The following recommendations are crucial for guiding future research and interventions:

1. In-depth immune profiling: Conduct comprehensive studies to investigate innate and adaptive immune responses to HCV infection in the Nigerian population. Understanding the immune system's interactions with the virus is crucial for developing targeted therapeutic approaches.
2. Genotype-host interaction dynamics: Investigate the complex interactions between HCV genotypes and the host's immune responses in Nigeria. This knowledge can provide insights into the virus's evolution, prevalence patterns, and treatment outcomes.
3. Longitudinal studies: Conduct longitudinal studies to track the natural progression of HCV infection over time. This will help identify factors that contribute to disease resolution or progression and guide clinical management.
4. Tailored immune-based interventions: Explore the potential of immune-based interventions, such as therapeutic vaccines or immunomodulatory drugs tailored to the Nigerian population's immune characteristics.
5. High-risk group analysis: Study innate and adaptive immune responses in high-risk groups, such as people who inject drugs and healthcare workers, to understand their susceptibility to infection and develop preventive strategies.
6. Integration of data: Integrate data from various disciplines including epidemiology, immunology, and virology, to gain a comprehensive understanding of HCV infection dynamics in Nigeria.
7. Impact of co-infections: Investigate the impact of co-infections, such as HIV and malaria, on HCV infection dynamics, immune responses, and treatment outcomes.
8. Geographical mapping: Develop detailed geographical maps of HCV prevalence and genotype distribution to inform targeted interventions and resource allocation.
9. Collaborative research: Foster collaboration between researchers, healthcare professionals, and policymakers to ensure that research findings are translated into evidence-based interventions and policies.
10. Education and awareness: Increase public awareness about HCV infection, its modes of transmission, and preventive measures through educational campaigns and community outreach programs.

By addressing these recommendations, Nigeria can take significant strides towards mitigating the burden of HCV infection, improving healthcare outcomes, and enhancing the overall well-being of its population. This systematic review offers valuable insights into the complexities of HCV infection in Nigeria and serves as a foundation for evidence-based interventions and policies to combat this persistent health challenge.

Contributions to knowledge

This systematic review on hepatitis C virus (HCV) infection in Nigeria contributes significantly to the understanding of HCV epidemiology and immunology in the country. By comprehensively analyzing available data, the study provides valuable insights into several key aspects:

1. Comprehensive overview: The review offers a comprehensive overview of HCV infection in Nigeria, covering innate and adaptive immunity, genotypes, and prevalence rates. This consolidation of information aids in building a holistic understanding of the disease landscape in the country.
2. Immune responses: The study sheds light on the roles of innate and adaptive immunity in HCV infection outcomes. By highlighting the virus's ability to evade immune defenses, the review underscores the challenges in developing effective immune-based interventions.
3. Genotypic diversity: The identification of multiple prevalent genotypes (1, 2, 3) and their impact on disease progression and treatment response enriches the knowledge of HCV genotypic diversity within Nigeria. This insight is crucial for tailoring treatment strategies.
4. Prevalence patterns: By presenting a range of prevalence rates (2.2% to 24.2%) and outlining the dominance of genotype 1, the study offers a clearer picture of HCV prevalence patterns across regions in Nigeria.

5. Research gaps identification: The review identifies several research gaps, such as limited immune profiling, unclear genotype-host dynamics, and paucity of immune interventions. These gaps provide a roadmap for future research efforts in the field.
6. Importance of integration: The study underscores the significance of integrating data from diverse disciplines to gain a more holistic understanding of HCV infection dynamics. This approach promotes a multidimensional view of the disease's impact.
7. Public health implications: By emphasizing the need for tailored public health strategies to manage Nigeria's complex HCV epidemiology, the review offers practical insights for policymakers and healthcare professionals.

Limitations

While this systematic review contributes valuable insights, it is important to acknowledge certain limitations:

1. Data availability: The review highlights challenges in obtaining accurate and comprehensive data on HCV infection in Nigeria. The scarcity of systematic data collection might have introduced bias and impacted the completeness of the analysis.
2. Heterogeneity of studies: Due to the heterogeneity of the studies included in the review, conducting a meta-analysis to quantitatively synthesize the findings might have been challenging.
3. Incomplete immune profiling: The review identifies limited immune profiling in the Nigerian population. The lack of comprehensive immune response data might hinder a thorough understanding of the immune dynamics in HCV infection.
4. Geographical variation: The review mentions varying prevalence rates across regions in Nigeria. However, the lack of detailed geographical mapping might limit the precision of recommendations for resource allocation and interventions.
5. Limited intervention insights: While research gaps related to immune interventions are highlighted, the review might not provide in-depth insights into potential strategies for addressing these gaps.
6. Temporal limitation: The review's findings are based on data available up to a certain point in time. New developments in HCV research after that point might not be fully represented.
7. Publication bias: The review's reliance on published studies might introduce publication bias, as negative or inconclusive results might be underrepresented.

Finally, this systematic review significantly contributes to the knowledge of HCV infection in Nigeria by providing a comprehensive overview of immune responses, genotypes, and prevalence. While limitations exist, the review's findings offer a foundation for further research, tailored interventions, and evidence-based policies to combat HCV's health challenge in Nigeria.

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Conflict of Interest

The authors declare no conflicts of interest related to this study.

References

1- **Manns MP, Buti M, Gane E, Pawlotsky JM, Razavi H, Terrault N, et al**. Hepatitis C virus infection. Nat Rev Dis Primers 2017. 2;3:17006. doi: 10.1038/nrdp.2017.6. PMID: 28252637.
2- **Spearman CW, Dusheiko GM, Hellard M, Sonderup M.** Hepatitis C. Lancet 2019. 19;394(10207):1451-1466. doi: 10.1016/ S0140-6736(19)32320-7. PMID: 31631857.
3- **Roudot-Thoraval F**. Epidemiology of hepatitis C virus infection. Clin Res Hepatol Gastroenterol 2021;45(3):101596. doi: 10.1016/j.clinre.2020.101596. Epub 2021 Feb 17. PMID: 33610022.
4- **Rabaan AA, Al-Ahmed SH, Bazzi AM, Alfouzan WA, Alsuliman SA, Aldrazi FA**, **et**

al. Overview of hepatitis C infection, molecular biology, and new treatment. J Infect Public Health 2020; 13(5):773-783. doi: 10.1016/j.jiph.2019.11.015. Epub 2019 Dec 20. PMID: 31870632.

5- **Morozov VA, Lagaye S**. Hepatitis C virus: Morphogenesis, infection and therapy. World J Hepatol 2018. 27;10(2):186-212. doi: 10.4254/wjh.v10.i2.186. PMID: 29527256; PMCID: PMC5838439.

6- **Li HC, Lo SY.** Hepatitis C virus: Virology, diagnosis and treatment. World J Hepatol 2015 8;7(10):1377-89. doi: 10.4254/ wjh.v7 .i10.1377. PMID: 26052383; PMCID: PMC4450201.

7- **Millman AJ, Nelson NP, Vellozzi C.** Hepatitis C: Review of the Epidemiology, Clinical Care, and Continued Challenges in the Direct Acting Antiviral Era. Curr Epidemiol Rep 2017 ;4(2):174-185. doi: 10.1007/s40471-017-0108-x. Epub 2017 Apr 20. PMID: 28785531; PMCID: PMC5544136.

8- **Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C**, **et al.** Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol Hepatol 2019 ;4(6):477-487. doi: 10.1016/S2468-1253(19)30046-9. Epub 2019 Apr 11. Erratum in: Lancet Gastroenterol Hepatol. 2020 May;5(5):e4. PMID: 30982721.

9- **Ahn E, Kang H.** Introduction to systematic review and meta-analysis. Korean J Anesthesiol 2018 ;71(2):103-112. doi: 10.4097/kjae.2018.71.2.103. Epub 2018 Apr 2. PMID: 29619782; PMCID: PMC5903119.

10- **Gopalakrishnan S, Ganeshkumar P.** Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. J Family Med Prim Care 2013 ;2(1):9-14. doi: 10.4103/2249-4863.109934. PMID: 24479036; PMCID: PMC3894019.

11- **Schwerk J, Negash A, Savan R, Gale M Jr.** Innate Immunity in Hepatitis C virusInfection. Cold Spring Harb Perspect Med 2021. 1;11(2):a036988. doi: 10.1101/ cshperspect.a036988. PMID: 32341066; PMCID: PMC7849348.

12- **Heim MH.** Innate immunity and HCV. J Hepatol. 2013 ;58(3):564-74. doi: 10.1016/j.jhep.2012.10.005. Epub 2012 Oct 11. PMID: 23063572.

13- **Li K, Lemon SM.** Innate immune responses in hepatitis C virus infection. Semin Immunopathol 2013 ;35(1):53-72. doi: 10.1007/s00281-012-0332-x. Epub 2012 Aug 7. PMID: 22868377; PMCID: PMC3732459.

14- **Ebihara T, Matsumoto M, Seya T.** HCV and innate immunity. Uirusu 2008; 58(1):19-26. doi: 10.2222/jsv.58.19. PMID: 19122385.

15- **Dustin LB.** Innate and Adaptive Immune Responses in Chronic HCV Infection. Curr Drug Targets 2017;18(7):826-843. doi: 10.2174/1389450116666150825110532. PMID: 26302811; PMCID: PMC5625838.

16- **Heim MH, Thimme R.** Innate and adaptive immune responses in HCV infections. J Hepatol 2014 ;61(1 Suppl):S14-25. doi: 10.1016/j.jhep.2014.06.035. Epub 2014 Nov 3. PMID: 25443342.

17- **Kemming J, Thimme R, Neumann-Haefelin C.** Adaptive Immune Response against Hepatitis C Virus. Int J Mol Sci 2020 ;21(16):5644. doi: 10.3390/ijms21165644. PMID: 32781731; PMCID: PMC7460648.

18- **Neumann-Haefelin C, Thimme R.** Adaptive immune responses in hepatitis C virusinfection. Curr Top Microbiol Immunol. 2013;369:243-62. doi: 10.1007/978-3-642-27340-7_10. PMID: 23463204.

19- **Larrubia JR, Moreno-Cubero E, Lokhande MU, García-Garzón S, Lázaro A, Miquel J, et al.** Adaptive immune response during hepatitis C virus infection. World J Gastroenterol 2014 ;20(13):3418-30. doi: 10.3748/wjg.v20.i13.3418. PMID: 24707125; PMCID: PMC3974509.

20- **He XS.** Regulation of Adaptive Immunity by HCV. In: Tan SL, editor. Hepatitis C Viruses: Genomes and Molecular Biology. Norfolk (UK): Horizon Bioscience; 2006. Chapter 14. PMID:21250383.https://pubmed.ncbi.nlm.nih.gov/21250383/

21- **Bowen DG, Walker CM.** Adaptive immune responses in acute and chronic hepatitis C virusinfection. Nature 2005;436(7053):946-52. doi: 10.1038/nature04079. PMID: 16107834.

22- **Audu RA, Okwuraiwe AP, Ige FA, Adeleye OO, Onyekwere CA, Lesi OA**. Hepatitis C viral load and genotypes among Nigerian subjects with chronic infection and implication for patient management: a retrospective review of data. Pan Afr Med J 2020;37:335. doi: 10.11604/pamj.2020.37.335.20299. PMID: 33738023; PMCID: PMC7934184.

23- **Guntipalli P, Pakala R, Kumari Gara S, Ahmed F, Bhatnagar A, Endaya Coronel MK**, **et al.** Worldwide prevalence, genotype distribution and management of hepatitis C. Acta Gastroenterol Belg 2021;84(4):637-656. doi: 10.51821/84.4.015. PMID: 34965046.

24- **Irekeola AA, Malek NA, Wada Y, Mustaffa N, Muhamad NI, Shueb RH.** Prevalence of HCV genotypes and subtypes in Southeast Asia: A systematic review and meta-analysis. PLoS One 2021;16(5):e0251673. doi: 10.1371/journal.pone.0251673. PMID: 34014997; PMCID: PMC8136688.

25- **Chayama K, Hayes CN.** Hepatitis C virus: How genetic variability affects pathobiology of disease. J Gastroenterol Hepatol 2011 ;26 Suppl 1:83-95. doi: 10.1111/j.1440-1746.2010.06550.x. PMID: 21199518.

26- Simon M. Agwale, Lorine Tanimoto, Chad Womack, Lillian Odama, Kimmy Leung, Dolores Duey, Ruth Negedu-Momoh, Israel Audu, Shehu B. Mohammed, Uford Inyang, Barney Graham, Rainer Ziermann, Prevalence of HCV coinfection in HIV-infected individuals in Nigeria and characterization of HCV genotypes, Journal of Clinical Virology, Volume 31 Supplement 1, 2004, Pages 3-6, ISSN 1386-6532, https://doi.org/10.1016/j.jcv.2004.09.001.

27- AP Okwuraiwe, OB Salu, E Anomneze, RA Audu, AO Ujah Hepatitis C virus genotypes and viral ribonucleic acid titers in Nigeria. Vol. 4 No. 2 (2012) 67-72

28- **Okonkwo UC, Okpara H, Otu A, Ameh S, Ogarekpe Y, Osim H**, **et al.** Prevalence of hepatitis B, hepatitis C, and human immunodeficiency viruses, and evaluation of risk factors for transmission: Report of a population screening in Nigeria. S Afr Med J 2017;107(4):346-351. doi: 10.7196/ SAMJ.2017.v107i4.12198. PMID: [PMID].

29- **Roudot-Thoraval F.** Epidemiology of hepatitis C virus infection. Clin Res Hepatol Gastroenterol 2021;45(3):101596. doi: 10.1016/j.clinre.2020.101596. Epub 2021 : 17. PMID: 33610022.

30- **Audu RA, Okwuraiwe AP, Ige FA, Adeleye OO, Onyekwere CA, Lesi OA.** Hepatitis C viral load and genotypes among Nigerian subjects with chronic infection and implication for patient management: a retrospective review of

data. Pan Afr Med J. 2020 Dec 10;37:335. doi: 10.11604/pamj.2020.37.335.20299. eCollection2020.doi:10.11604/pamj.2020. 37.335.20299. PMID: 33738023; PMCID: PMC7934184.

31- **Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al.** Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis 2016;16(7):797-808. doi: 10.1016/S1473-3099(15)00485-5. Epub 2016 : 25. PMID: 26922272. Date last accessed: 04/12/2023.

32- **Azevedo TC, Zwahlen M, Rauch A, Egger M, Wandeler G.** Hepatitis C in HIV-infected individuals: a systematic review and meta-analysis of estimated prevalence in Africa. J Int AIDS Soc 2016;19(1):20711. doi: 10.7448/IAS.19.1.20711. PMID: 27293220; PMCID: PMC4904089. Date last accessed: 02/12/2023.

33- **Duncan JD, Urbanowicz RA, Tarr AW, Ball JK.** Hepatitis C virusVaccine: Challenges and Prospects. Vaccines (Basel) 2020;8(1):90. doi: 10.3390/vaccines8010090. PMID: 32079254; PMCID: PMC7157504.

34- **Bartenschlager R, Baumert TF, Bukh J, Houghton M, Lemon SM, Lindenbach BD**, **et al.** Critical challenges and emerging opportunities in hepatitis C virusresearch in an era of potent antiviral therapy: Considerations for scientists and funding agencies. Virus Res 2018;248:53-62. doi: 10.1016/j.virusres. 2018.02.016. Epub 2018 Mar 2. PMID: 29477639.

35- **Bailey JR, Barnes E, Cox AL.** Approaches, Progress, and Challenges to Hepatitis C Vaccine Development. Gastroenterology 2019;156(2):418-430. doi: 10.1053/j.gastro .2018.08.060. Epub 2018 Sep 27. PMID: 30268785; PMCID: PMC6340767.

36- **Andreoni M, Babudieri S, Bruno S, Colombo M, Zignego AL, Di Marco V, et al.** Current and future challenges in HCV: insights from an Italian experts panel. Infection 2018 ;46(2):147-163. doi: 10.1007/s15010-017-1093-1. Epub 2017 Nov 2. PMID: 29098647.

37- **Obienu O, Nwokediuko S, Malu A, Lesi OA.** Risk factors for hepatitis C virus transmission obscure in Nigerian patients. Gastroenterol Res Pract 2011;939673. doi: 10.1155/2011/939673. Epub 2011 Jul 13. PMID: 21785583; PMCID: PMC3139196.

38- **Onyekwere CA, O Ogbera A, Olusola Dada A, O Adeleye O, O Dosunmu A, Akinbami AA, et al.** Hepatitis C virus(HCV) Prevalence in Special Populations and Associated Risk Factors: A Report From a Tertiary Hospital. Hepat Mon 2016;16(5):e35532. doi: 10.5812/hepatmon.35532. PMID: 27313634; PMCID: PMC4908612.

39- **Edwin N. Okafor, Innocent N. Okonkwo, Martin C. Ugonabo, Ekene E. Chukwukelu, Obiageli U. Odurukwe, Sussan N. Osiri.** Emerging risk factors associated with the prevalence of hepatitis C virus infection among Nigerians: Findings from blood donors in an academic hospital, Enugu South-Eastern Nigeria. The International Journal of Clinical Practice. 2020 : 74,(3) e13460 First published: 10 December 2019 https://doi.org/10.1111/ijcp.13460.

40- **Okafor, I.M., Ugwu, S.O. & Okoroiwu, H.U.** Hepatitis C virus infection and its associated factors among prisoners in a Nigerian prison. BMC Gastroenterol 2020; 20: 360. https://doi.org/10.1186/s12876-020-01504-8.

41- **Lawal MA, Adeniyi OF, Akintan PE, Salako AO, Omotosho OS, Temiye EO**. Prevalence of and risk factors for hepatitis B and C viral co-infections in HIV infected children in Lagos, Nigeria. PLoS ONE 2020; 15(12): e0243656. https://doi.org/10.137.

42- **Isaac Warnow Elon, Ajani Ayomikun, JaloIliya1, Alkali Yaya, Oyeniyi Christianah, Okolie Henry, Saidu Abubakar, Jibrin Bara, Aremu John, Kudi Ayuba, Danlami Halilu and Charanchi Musa** . Hepatitis C in Adults and Children: A Cross-Sectional Review from a Tertiary Hospital, Northeast Nigeria during the Period 2008-2015. J Infect Dis Epidemiol 2019;5:096. doi: 10.23937/2474-3658/1510096.

43- **Audu RA, Okwuraiwe AP, Ige FA, Adeleye OO, Onyekwere CA, Lesi OA.** Hepatitis C viral load and genotypes among Nigerian subjects with chronic infection and implication for patient management: a retrospective review of data. Pan Afr Med J 2020;37:335. doi: 10.11604/pamj.2020.37.335.20299. PMCID: PMC7934184, PMID: 33738023.

44- **Jeremiah ZA, Koate B, Buseri F, Emelike F.** Prevalence of antibodies to hepatitis C virusin apparently healthy Port Harcourt blood donors and association with blood groups and other risk indicators. Blood Transfus 2008;6(3):150-5. doi: 10.2450/2008.0053-07. PMID: 18705239; PMCID: PMC2626867.

45- **Shenge JA, Odaibo GN, Olaleye DO.** Phylogenetic analysis of hepatitis C virusamong HIV/HCV co-infected patients in Nigeria. PLoS ONE 2019;14(2): e0210724. doi: 10.1371/journal.pone.0210724.

46- **Okusanya BO, Aigere EO, Eigbefoh JO, Ikheloa J.** Seroprevalence and clinico-epidemiological correlates of hepatitis C viral antibodies at an antenatal booking clinic of a tertiary hospital in Nigeria. Arch Gynecol Obstet 2013;288(3):495-500. doi: 10.1007/s00404-013-2773-4. Epub 2013 Mar 1. PMID: 23455542.

47- **World Health Organization (WHO).** Hepatitis C. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Published 18 July 2023. Date last accessed: 02/12/2023.

48- **Saaed FMA, Ongerth JE.** Prevalence of Hepatitis B and Hepatitis C in Migrants from Sub-Saharan Africa Before Onward Dispersal Toward Europe. J Immigr Minor Health 2023;25(4):882-888. doi: 10.1007/s10903-022-01448-z. Epub 2023 Jan 14. PMID: 36640255; PMCID: PMC10310585.

49- **Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C.** Global epidemiology of hepatitis C virus infection: An update of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol 2016;22(34):7824-7840. URL: https://www.wjgnet.com/1007-9327/full/ v22 /i34/7824.htm. DOI: https://dx.doi.org/ 10.3748/wjg.v22.i34.7824.

50- **Nemhauser, Jeffrey**, 'Preparing International Travelers', in Jeffrey B. Nemhauser (ed.), CDC Yellow Book 2024: Health Information for International Travel (New York, 2023; online edn, Oxford Academic, 23 Mar. 2023),https://doi.org/10.1093/oso/9780197570944.003.0002, accessed 30 Mar. 2024..

51- **Baeka GB, Oloke JK, Opaleye OO.** Detection of hepatitis C virus among HIV patients in Port Harcourt, Rivers State. Afr Health Sci 2021;21(3):1010-1015. doi: 10.4314/ahs.v21i3.8. PMID: 35222562; PMCID: PMC8843266.

52- **Okwuraiwe AP, Salu OB, Anomneze E, Audu RA, Ujah IA.** Hepatitis C virus genotypes and viral ribonucleic acid titers in

Nigeria. Nigerian Journal of Gastroenterology and Hepatology 2012;4(2):67-72.

53- **Anejo-Okopi, J., O.J. Okojokwu and O. Audu.**. Hepatitis C virus: Molecular epidemiology, treatment and diagnosis challengesin Sub-Saharan Africa (SSA). Hosts and Viruses, 2020: 7(3): 43-49 **(**18) (PDF) Hepatitis C Virus: Molecular Epidemiology, Treatment and Diagnosis Challenges in Sub-Saharan Africa (SSA). Available from: https://www.researchgate.net/publication/342940657_Hepatitis_C_Virus_Molecular_Epidemiology_Treatment_and_Diagnosis_Challenges_in_Sub-Saharan_Africa_SSA#fullTextFileContent [accessed Mar 30 2024]Oni AO, Harrison TJ. Genotypes of hepatitis C virus in Nigeria. J Med Virol 1996;49(3):178-86. doi: 10.1002/(SICI)1096-9071(199607)49:3<178::AID-JMV4>3.0.CO ;2-1. PMID: 8818962.

54- **Shah R, Ahovegbe L, Niebel M, Shepherd J, Thomson EC.** Non-epidemic HCV genotypes in low- and middle-income countries and the risk of resistance to current direct-acting antiviral regimens. J Hepatol 2021;75(2):462-473.https://doi.org/10.1016/j.jhep.2021.04.045.

55- **Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al.** \Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61(1):77-87. https://doi.org/10.1002/hep.27259.

56- **Kouyoumjian SP, Chemaitelly H, Abu-Raddad LJ.** Characterizing hepatitis C virus epidemiology in Egypt: systematic reviews, meta-analyses, and meta-regressions. Sci Rep 2018;8:1661. https://doi.org/10.1038/s41598-017-17936-4.

57- **Heim MH, Thimme R.** Innate and adaptive immune responses in HCV infections. J Hepatol 2014;61(1Suppl):S14-25. doi: 10.1016/j.jhep.2014.06.035. Epub 2014 Nov 3. PMID: 25443342.

58- **Buonaguro L, Petrizzo A, Tornesello ML, Buonaguro FM.** Innate immunity and hepatitis C virus infection: a microarray's view. Infect Agent Cancer 2012;7(1):7. doi: 10.1186/1750-9378-7-7. PMID: 22448617; PMCID: PMC3511806.

59- **Thimme R, Binder M, Bartenschlager R.** Failure of innate and adaptive immune responses in controlling hepatitis C virus infection. FEMS Microbiol Rev 2012;36(3):663-83. doi: 10.1111/j.1574-6976.2011.00319.x. Epub 2012 Jan 4. PMID: 22142141.

60- **Kemming J, Thimme R, Neumann-Haefelin C.** Adaptive Immune Response against Hepatitis C Virus. Int J Mol Sci 2020;21(16):5644.https://doi.org/10.3390/ijms21165644.