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# Geographical distribution of hepatitis A, B and C infection in Al-Muthanna province, comparative study

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#### **Abstract:**

Background:

Research Article

This study was conducted in Al-Muthanna district to describe the epidemiological characteristics of hepatitis virus infection using geospatial analysis at the level of the governorate and its regions. We used geospatial analysis to determine the geographic, spatio-temporal trends of viral hepatitis infection in the governorate.

Objective:

This study aims to assess the prevalence of the disease in Al-muthanna province, southern Iraq, and the geographical distribution of hepatitis A, B, and C

Patients and methods: TA descriptive study of (364) patients with hepatitis in the governorate over three years. The information for this research was obtained through a systematic review, published scientific literature, the official websites of the various government agencies and health sectors in the governorate in addition to the Center for Communicable Disease Control between the years 2019-2021.

#### Results:

The highest infection rates in the province were 66% for hepatitis A, while hepatitis B and C were 22% and 12%, respectively. The highest incidence rates by sex were in males for hepatitis A and B. The infection rate of type A viral hepatitis increased significantly in 2021, in contrast to the previous two years, while the infection rate of types B and C decreased in 2021. The highest rates of infection according to age groups were less than 10 years. The geographical distribution showed that the highest infections were in the Al-Khader region, with a rate of 68%, and it increased more and clearly in the year 2021, and most of the infections were with viral hepatitis type A.

## Conclusions:

This study confirmed that HAV, HBV and HCV infection are endemic in Iraq, and constitute a serious problem in Muthanna Governorate, during the period between 2019-2021. The results show a clear variation in the prevalence of hepatitis virus infection during the period 2019-2021. This suggests that intervention strategies for hepatitis virus prevention should consider both individual traits and differences and geographic area variation.

**Keywords:** viral, geographical, Al-muthanna province, hepatitis A, B, C

### Introduction

Hepatitis A is a viral infection of the liver that can cause mild illness to become severe. Hepatitis A virus (HAV) is transmitted through ingestion of contaminated food and water or through direct contact with infected people. Almost everyone who fully recovers from hepatitis A gets lifelong immunity. However, a very small percentage of people with hepatitis A can die from hepatitis. The risk of hepatitis A infection is associated with a lack of safe drinking water and poor sanitation and hygiene (such as dirty hands). A safe and effective vaccine is available to prevent hepatitis A [1]. Symptoms of hepatitis A can last up to two months and include fatigue, nausea, stomach pain, and jaundice. Most people with hepatitis A do not usually have a long-term illness. The best way to prevent hepatitis A is to get vaccinated [2].

Hepatitis B type is a viral infection that attacks the body, especially the liver, and can cause serious and chronic diseases. The virus is most commonly transmitted from mother to child during childbirth, as well as through contact with blood or other body fluids during sex with an infected person. partner, as well as unsafe injections or exposure to sharp objects. The World Health Organization estimates that about 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year. In 2019, hepatitis B resulted in an estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma [1]. Approximately about one-third of the world's population is infected with the hepatitis B virus. About 5% of these are chronic carriers and a quarter of these carriers develop serious and potentially fatal liver diseases such as chronic hepatitis, liver cancer, and cirrhosis. Every year, approximately 780,000 deaths related to hepatitis B virus are documented worldwide [3].

Hepatitis C is a liver infection caused by the hepatitis C virus (HCV). Hepatitis C is spread through contact with blood from an infected person. Today, most people become infected with the hepatitis C virus by sharing needles or other equipment used to prepare and inject drugs. Chronic hepatitis C can result in serious, even life-threatening health problems like cirrhosis and liver cancer. People with chronic hepatitis C can often have no symptoms and don't feel sick. When symptoms appear, they often are a sign of advanced liver disease. There is no vaccine for hepatitis C. The best way to prevent hepatitis C is by avoiding behaviors that can spread the disease, especially injecting drugs. Getting tested for hepatitis C is important, because treatments can cure most people with hepatitis C in 8 to 12 weeks [4]. Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 70% (55–85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years [5].

In 2015, the number of people living with chronic infection with hepatitis B virus was approximately (257 million), and (887,000) people died, mainly due to hepatocellular carcinoma. Therefore, at the 69th session of the World Health Assembly in 2016, 194 Member States committed themselves to eliminating viral hepatitis by 2030 [6]. Viral hepatitis results from inflammation of the liver caused by a viral infection. Although "epidemic jaundice" has existed since ancient times, only in the past few years has the viral etiology of hepatitis been identified. Almost all of these infections are caused by five viruses, namely hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus

(HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV) [7]. Strategies to prevent and control viral hepatitis can be implemented, such as raising awareness through public education, vaccination, blood transfusion safety strategies, early diagnosis and effective medical support [8].

**Phase 1** (viral replication phase): Patients are asymptomatic through this phase. Laboratory studies demonstrate serological and enzyme markers of hepatitis. **Phase 2**: (prodromal phase): Patients experience anorexia, vomiting, nausea, alterations in taste, arthralgia, fatigue, malaise, urticarial, and pruritus, and some develop an aversion to cigarette smoke. When seen by a health care provider throughout this phase, patients are often diagnosed as having gastroenteritis or a viral syndrome. **Phase 3:** (icteric phase): Patients note dark urine, followed by pale-colored stools, in addition to the predominant gastrointestinal symptoms and malaise. Patients become icteric and may develop right upper quadrant pain with hepatomegaly. **Phase 4**: (convalescent phase): Symptoms and icterus resolve and liver enzymes return to normal [5].

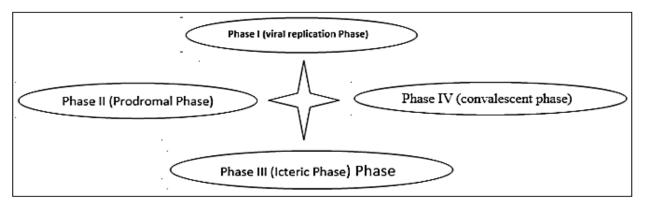


Figure 1. Infectious hepatitis involves four phases [5].

Aim of study.

Hepatitis A, B and C infection remains a major public health problem in Al-Muthanna Province. The aim of the study was to assess the epidemiological situation of hepatitis in the province in 2019-2021, based on the data collected as part of the epidemiological surveillance in three years, and to compare it with data from previous years, and to show the role of geography in analyzing a pathological phenomenon on a geographical basis and alerting to the seriousness of this disease and the spread of its types in the province.

# Research methodology

#### **Research Limits**

The spatial and temporal boundaries of the study area were represented by (Al-Muthanna Province). This study was conducted in Al-Muthanna Province from the period 2019-2021, and included some villages and towns affected by viral hepatitis. These villages and towns are located in the Muthanna Governorate in southern Iraq. The area of Al-Muthanna Governorate is 51,740 km2 (11.9% of Iraq). The desert occupies 47 thousand square kilometers, or 91% of the total area of the province. The population

of the province is (788.262) people. The main cities are Samawah, Rumaitha, Al Khader, Salman and Al Warka.

#### Research Problem

Viral hepatitis of all types is a serious disease that causes a large number of infections and deaths that increase every year, as most people are unaware of their health condition. Although many infection control programs are in use, eradication or significant reduction of the disease remains difficult. The global burden of disease remains high. This paper presents the local prevalence status and the difference between the different types of the disease. The research problem came to identify one of the most important and dangerous pathological phenomena that was and still is of global and local interest, which is a geographical and analytical study of viral hepatitis infection in the province.

#### **Data and information sources**

There are many sources of data and information that the researcher relied on, depending on the nature of the study axes and the justifications for accessing them, and they are as follows:

- Sources of data and information: The study relied on the data provided by the records of patients with diseases in the Communicable Diseases Control Center and patients' files in the governorate's hospitals and health centers that collected them. The data and information are in the form of separate monthly statistics in the Health Planning Department, and the Statistics Department in the Governorate Health Department.
- Theses and theses: Theoretical dependence on theses, theses, recent books and refereed scientific periodicals.
- Field sources: The procedures included many personal interviews conducted with doctors, specialists and officials in most health institutions and units in the governorate, in addition to the dialysis center in the governorate, and taking notes regarding.

#### **Results**

# Viral Hepatitis in province

The results showed that hepatitis A virus in years 2019-2021 is the predominant type in Muthanna province—with a percentage of 66 % compared to hepatitis B (22%) and hepatitis C (12%) Figure 2. These results were consistent and similar with the findings of researchers in the same province in 2012, in which they stated that the study showed that the incidence of hepatitis A (71%), followed by hepatitis B (19%) and hepatitis C (10%) [9].

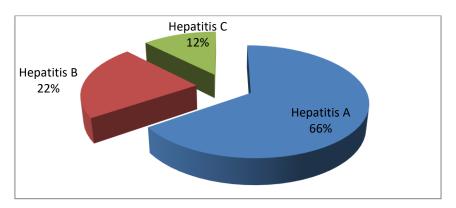


Figure 2. Shows the incidence of viral hepatitis in Muthanna Province.

The distribution of hepatitis A according to years of study, showed a significant and noticeable increase in hepatitis A virus in Muthanna province in 2021 compared to the previous two years Figure 3. Millions of people have been infected with hepatitis A virus by eating contaminated food and drinking water. The incidence rate is closely related to access to safe drinking water as is the socioeconomic indicator. In general, all high-income global regions have very low levels of HCV endemicity, while low-income regions have high levels of endemicity. Middle-income areas of society have both medium and low levels of endemism [10]. Hepatitis cases have increased during the last decade among Iraqi people. An escalation, as three times more, had been recognized in cases of HAV from 2009 to 2014 [11]. Hepatitis A is an acute, typically self-limiting liver disease and one of the most common infectious diseases in the world. Poor personal hygiene and health education might be the main reason for the increasing number of HAV cases. Most of migrants' families lived in camps far away from the city center where poor sanitations and limited access to safe drinking water. This may contribute to the incidence of HAV [12].

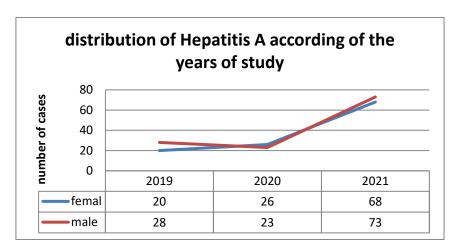


Figure 3. Distribution of hepatitis A according to years of study.

The distribution of hepatitis B infections according to the years of study showed a significant and clear decrease in hepatitis B virus in Al-Muthanna province in 2020, then it began to decline further to reach its lowest level in 2021 Figure 4. The research was consistent with the results that stated that hepatitis B virus and hepatitis C virus

type are less prevalent than type A, Iraq is considered a low-endemic country compared to neighboring countries. The increased incidence of all types of hepatitis in Iraq may be due to the security situation and the overcrowding of refugees and migrants; Hence, the unavailability of vaccination [11]. Also, HAV infections were the predominant one among viral hepatitis infections followed by HBV and HCV respectively in Misan province, Iraq [13].

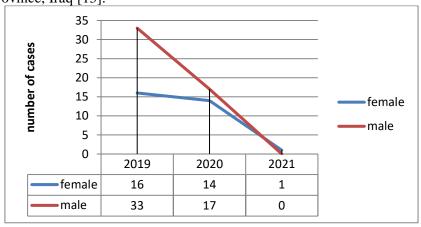


Figure 4. Distribution of hepatitis B according to years of study

The distribution of hepatitis C infections according to the years of study showed a significant and clear difference in hepatitis A virus in Al-Muthanna Governorate in 2020, then male infections began to decline, in contrast to female infections, which were high in 2020, then infections for both sexes began to decline dramatically to reach the lowest His level in a year Figure 5. The research came in agreement with many of the results that stated that the regions of the eastern Mediterranean have a low endemicity with the exception of Somalia, Djibouti and Sudan, which show a higher prevalence. The percentage of the population infected with hepatitis B virus in the following countries is: Pakistan 4.5% [14], Yemen 12.7%-18.5%, Sudan 5%-8.2% [15,16], and Somalia 5.6%-21.3% [17].

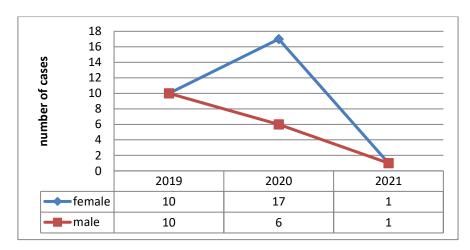


Figure 5. Distribution of hepatitis C according to years of study.

The distribution of viral hepatitis (A, B, C) infections according to years of study showed a slight decrease in 2020 compared to the previous year, then it began to

gradually increase to reach its highest level in 2021 Figure 6. Globally, only 1.5 million clinical cases of HCV are reported annually while the incidence is much higher [18].

Viral hepatitis is an inflammation of the liver caused by a variety of infectious and non-infectious viruses leading to a range of many health problems, some of which can be fatal. There are five main strains of hepatitis virus referred to as types A, B, C, D, and E. All of them cause liver disease, but they differ in important aspects including modes of transmission, virulence, geographic distribution, and prophylaxis. In particular, types B and C lead to chronic diseases in millions of people, and together they are the leading cause of cirrhosis, liver cancer, and viral hepatitis-related deaths. About 354 million people worldwide are living with hepatitis B or C, and for most people, testing and treatment are still out of reach [1].

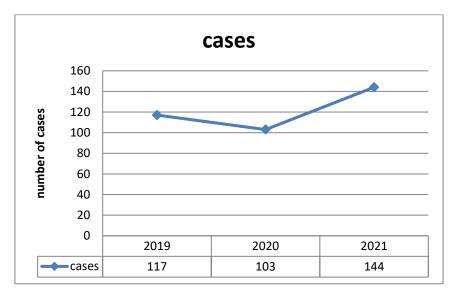


Figure 6. Distribution of viral hepatitis infections (A, B, C) according to years of study.

#### Distribution of viral hepatitis infections according to the gender

The research also revealed that the incidence of infection in males is higher than in female, Figure 7, and it is consistent with previous research that mentioned, the higher infection rates according to the sex was in males in hepatitis A, B and C 61%,75% and 100% respectively.

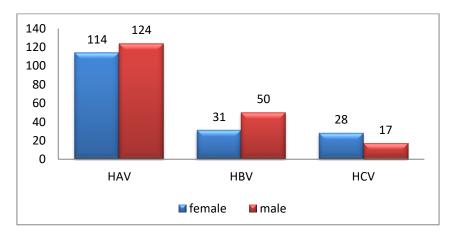


Figure 7. Shows the distribution of infection by gender.

Table 1 shows the distribution of infection by gender, these results were consistent with some research conducted in the province in previous years that stated that higher infection rates of hepatitis (type A, B and C), and higher infection in males in types A, B and C of hepatitis [9]. The results of the study indicated that the gender of the infected person plays an important role in preparing for infection, and these results were consistent with the research that stated that the ratio of males to females was more infected with A virus in the study that took place on the dental staff [19]. In Iran, it was found that the infection rate was higher in males than in females in patients infected with the B virus [20].

Diseases	2019		2020	2020		2021	
	male	female	male	female	male	female	
HAV	28	20	23	26	73	68	238
HBV	33	16	17	14	0	1	81
HCV	10	10	6	17	1	1	45
Total	71	46	46	57	74	70	364

Table 1. Shows the distribution of infection by gender

# Distribution of viral hepatitis infections according to the age group

The distribution of viral hepatitis infection by age in 2019 showed an increase in children and youth at a rate higher than the rest of the ages in patients infected with hepatitis A virus, and the results also showed that there was a difference and a slight increase in the ages of the elderly compared to the rest of the ages infected with hepatitis B virus, as well as showed Distribution of infection The incidence is equal at all ages among people infected with hepatitis C virus. Figure 8.

Distribution of infections according to age groups, it was clear that the prevalence of viral hepatitis infection was significantly higher among people with age group (children and youth) followed by age group (21-40 years), and these results were consistent with [21], who reported that the 20-24-year age group had the highest prevalence with a large majority of the affected population being <50 years of age. In some countries in the western Pacific, the pattern of seroprevalence through age in Australia shows a rapid increase in prevalence peaking at age 20-24 years. In addition, an early peak at ages 1-4 years was observed in Europe and especially in Central Europe [22]. The prevalence of hepatitis C virus (HCV) infection showed a decrease with older ages after the age of 60, which may be due to lack of physical movement and poverty, which leads to a decrease in the number of examinations of the elderly.

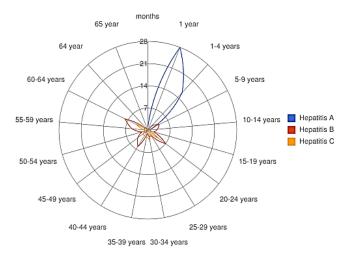


Figure 8. Distribution of infections according to age groups in 2019.

The distribution of viral hepatitis infection by age in 2020, it was almost equal to the results that appeared in the previous year, an increase in children and youth was observed at a higher rate than the rest of the ages in patients infected with hepatitis A virus, and a slight increase in the ages of the elderly compared to the rest of the ages Infected with hepatitis B virus, the distribution of infection also showed that the incidence is equal at all ages among those infected with hepatitis C virus. Figure 9.

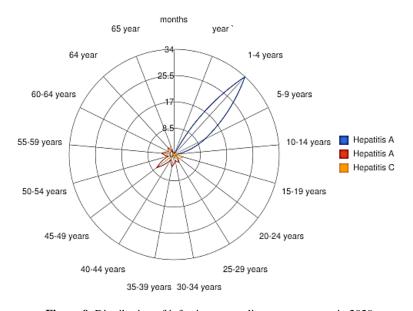
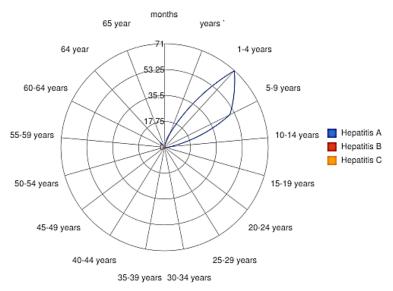


Figure 9. Distribution of infections according to age groups in 2020.

The distribution of viral hepatitis infection according to age in 2021 is completely different from the results that appeared in the past two years. The hepatitis A virus was very high and made up almost the vast majority of infections for both types. The distribution of infection showed that the infection is low and almost non-existent in the other two types, B and C. The research also showed that the results are equal at all ages among those infected with hepatitis B and C viruses, Figure 10.



**Figure 10.** Distribution of infections according to age groups in 2021.

Geographical distribution areas can be characterized as having high, intermediate or low levels of hepatitis A virus infection. However, infection does not always mean disease because infected young children do not experience any noticeable symptoms. Infection is common in low- and middle-income countries with poor sanitary conditions and hygienic practices, and most children (90%) have been infected with the hepatitis A virus before the age of 10 years, most often without symptoms. Infection rates are low in high-income countries with good sanitary and hygienic conditions. Disease may occur among adolescents and adults in high-risk groups, such as persons who inject drugs (PWID), men who have sex with men (MSM), people travelling to areas of high endemicity and in isolated populations, such as closed religious groups. In the United States of America, large outbreaks have been reported among persons experiencing homelessness. In middle-income countries and regions where sanitary conditions are variable, children often escape infection in early childhood and reach adulthood without immunity [23].

Children and infants under 1 year of age who develop hepatitis B infection in the perinatal period have a risk of chronic infection almost 90%, and it is assumed that newborns have an immature immune system [24]. Sexual transmission is a major source of infection for hepatitis B in all regions of the world, especially in economically developed and low endemicity regions. Hepatitis B is a sexually transmitted disease. For a long time, homosexual men were viewed as having a higher risk of infection due to sexual intercourse (almost 70% of gay men became infected after 5 years of continuous sexual activity) [25].

Although epidemic jaundice was clearly known to physicians in ancient times, it is only in recent years that medical science has begun to uncover the origins of hepatitis A virus (HAV) as well as the distinct pathobiology underlying acute hepatitis in the general population. Improvements in sanitation and the successful development of highly effective vaccines have significantly reduced the incidence of this transmissible infection worldwide over the past years, yet the virus continues to circulate in vulnerable populations and those without immunity to HBV A. In economically developed societies, declines in the incidence of hepatitis A virus infection have led to increases

in the average age at which infection occurs, often leading to more severe disease in infected persons and a paradoxical increase in disease burden in some developing and poor countries [26].

In the epidemiology of hepatitis B virus, additional research using appropriately sized population samples is required. Several challenges remain to achieving the goal of universal hepatitis B immunization, such as poor infrastructure contributing to vaccination delays, low interest, and lack of sustainability. Finance. Therefore, to continue the success and enhance access to hepatitis B vaccines worldwide, many and broad efforts are needed to support countries to ensure sustainable funding for immunization prevention programs.

# Geographical distribution of viral hepatitis infections

The geographical distribution of viral hepatitis infection in Al-Muthanna Governorate for the three types of the disease showed a significant and noticeable increase in the Al-Khader region with a high rate (68 %), followed by the Samawah region and nearby areas with a medium rate (28 %) followed by Al-Rumaitha with a low rate (4%), and finally the Al-Warka region with a very low and almost non-existent rate Figure 11.

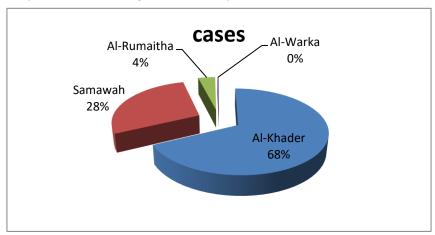


Figure 11. Geographical distribution of viral hepatitis infections in Al-Muthanna province.

The geographical distribution of viral hepatitis infection in Al-Muthanna Governorate for types (A, B, C) during the year 2019 showed an increase in the infection rate in the cities of Al-Khader (45%) and Samawah (44%) with close rates, followed by the Rumaitha region with a low and low rate (11%), and finally the Warka region with a very low rate and almost be nil. The geographical distribution during the year 2020 showed an increase in the infection rate in the cities of Al-Khader (50%) and Al-Samawah (49%) with similar rates as well, followed by the Rumaitha and Al-Warka regions with a very low and almost non-existent rate. The geographical distribution during the year 2021 showed an increase in the infection rate in the cities of Al-Khader (98%) with a very high rate, followed by the Rumaitha (1%) regions and the Warka (1%) region and Samawah with a very low and almost non-existent rate Figure 12.

Viral hepatitis is a major but under-recognized health concern, with approximately 1.4 million people dying each year from cirrhosis related to hepatitis B as well as liver cancer. However, this population faces significant difficulties that must be overcome such as lack of health awareness, vulnerability, increased migration, disease stigma,

discrimination, as well as poor health resources, and differences in health policy development and implementation of disease control programmes. Although infection control measures have been implemented over the past few decades and years, eradication or significant reduction of viral hepatitis remains very difficult [27].

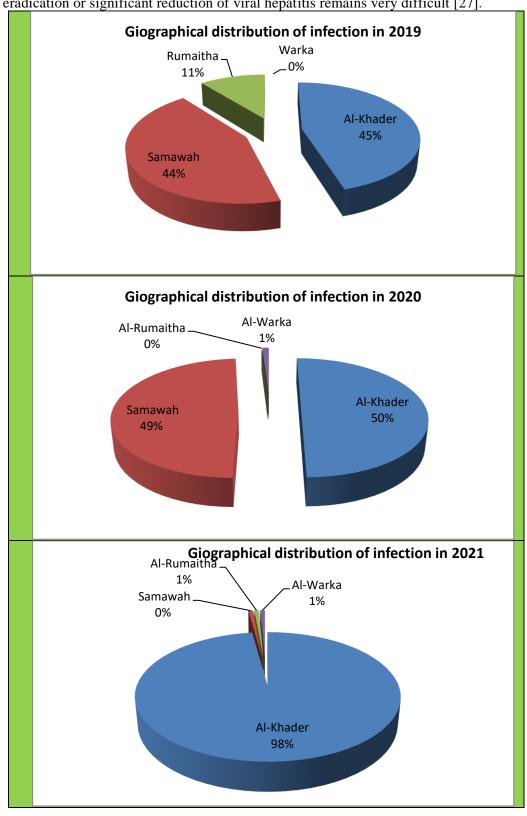


Figure 12. Geographical distribution of viral hepatitis infection during the study years

The distribution of viral hepatitis according to the years of study showed a significant increase in hepatitis A virus in the Al-Khader region in 2021 compared to the previous two years. As for hepatitis B and C viruses, the rates were very low and ineffective compared to type A Figure 13. The research came in line with many of the previous conclusions, especially in the rural areas of the Republic of Egypt, where the use of village water, direct contamination of drinking water sources with sewage water, and the use of dry pits are the main risk factors for infection and transmission of hepatitis A virus infection. Also, in Libya, similar to the Republic of Egypt, most cases of HCV infection have been acquired since childhood. Antibodies to hepatitis A virus were detected in (60-70%) of three-year-olds and in (100%) of seven-year-olds [28]. HAV virus is a widespread virus, especially as it maintains stability in heat as well as cold under normal environmental conditions and is very resistant to external influences. Hepatitis A virus infection is largely and directly acquired through fecal-oral transmission [29]. In another study, hepatitis A infection was slightly higher in men than in women. A possible explanation for this male dominance is that males in Iraqi society are usually more susceptible to outdoor-acquired infections and tolerating risky health behaviors than women [30].

Hepatitis A virus is found in the feces of infected people and is transmitted by ingestion of contaminated food and water. It spreads easily and rapidly in countries and cities with low standards for sewage handling and disposal; However, it can also spread in homes, day care centers, schools, and restaurants when hygienic hand washing is not practiced, especially after changing diapers, using restrooms, and before eating. More importantly, the virus can be transmitted by an infected person a week or two before Onset of disease signs and symptoms.

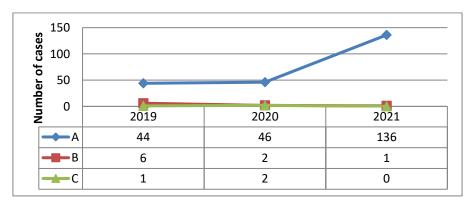


Figure 13. Geographical distribution of viral hepatitis according study years in Al-Khader region.

The distribution of viral hepatitis A according to the years of study in the Samawah region in 2019 was very low and ineffective. As for hepatitis B and C viruses, the rates were high and at medium rates in the years 2019-2020, then they began to decrease to disappear in the year 2021 Figure 14. The results we obtained were similar to previous research reported that millions of people infected with hepatitis A virus by eating contaminated food and drinking water. The incidence rate is closely related to access to healthy and safe drinking water and to the socioeconomic index. In general, all high economic income regions of the world have very low levels of HCV endemicity (<50%

of the population), while low income regions have high levels of endemicity (>90% of the population). Middle-income community areas have medium and low levels of endemism [31]. Hepatitis A virus infection is highly endemic in Iraq with a national estimated IgG seroprevalence rate of 98%. The prevalence rate is almost constant in the second decade of life, reflecting the poor hygiene situation in the country. The results of our study were consistent with previous results, which stated that this increasing percentage is due to many reasons related to social and economic factors and water and sanitation services, such as poverty, education, poor hygiene, and lack of health education. In addition to the damage to the water supply infrastructure and its pollution with sewage [32]. Hepatitis A virus (HAV), is a common cause of hepatitis worldwide. The spread of infection is generally from person to person or through the mouth after fecal contamination of the skin or mucous membranes. Hepatitis A is endemic in developing and poor countries, and most of the population is exposed to it in childhood. In contrast, adult populations in economically developed countries show lower exposure rates with improvements in hygiene and sanitation. The export of food that cannot be sterilized, from endemic countries to areas with low infection rates, is an important potential cause and source of infection [8].

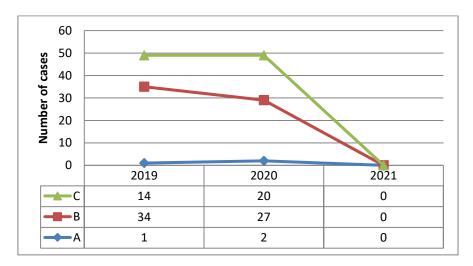


Figure 14. Geographical distribution of viral hepatitis according study years in Al- Samawah center.

The distribution of viral hepatitis of the three types (A, B, C) according to the years of study in the Al-Rumaitha area in 2019 was very low and ineffective, then it began to decline to fade in the year 2020-2021 Figure 15. As for the Al-warka region, there were no infections, except for one case of type C in 2021.



Figure 15. Geographical distribution of viral hepatitis according study years in Al-Rumaitha area.

#### **Conclusions**

This study confirmed that HAV, HBV and HCV infection are endemic in Iraq, and constitute a serious problem in Muthanna Governorate, during the period between 2019-2021. This study was conducted in Al-Muthanna district. The infection rate of type A viral hepatitis increased significantly in 2021, in contrast to the previous two years, while the infection rate of types B and C decreased in 2021. The highest infection rates in the province were 66% for hepatitis A . The highest incidence rates by sex were in males for hepatitis A and B. We recorded higher infection rates according to age groups less than 10 years. A high incidence of hepatitis A, B and C was observed in males. The highest infections were in the Al-Khader region, with a rate of 68 %, and it increased more and clearly in the year 2021, and most of the infections were with viral hepatitis type A. In Al-Khader, the majority of the population lives in rural areas.

## Recommendation

Health education is an essential pillar in disease prevention and control. The use of new media and communication channels helps a lot in raising awareness of the disease and ways to prevent it. We need universal coverage of hepatitis A vaccination of children in our country. Since the occurrence of hepatitis, A is mainly linked to contaminated water and food supplies, controlling it requires the cooperating sectors to work together to provide safe water and safe disposal of wastewater. Avoid dealing with blood and its derivatives only when necessary. Avoid dealing with wrong practices when transfusions of blood and glaucoma.

#### Conflict of interest

The author declared that there are no competing interests.

#### Ethical issues

In this research, ethical considerations have been fully considered.

# Acknowledgement

This research could not have been completed without the participation and help of many people who may not be enumerated here all, we sincerely appreciate their contributions and extend our thanks and gratitude. However, the author would like to express his deep appreciation especially to the communicable disease staff of Muthanna County Health Department and Department of Infectious Disease Control, especially Mr. Rasoul Jieyad Fahd for their assistance in patient data collection and collaboration with the author.

#### Authors contributions

We wrote and conceptualized the review, designed the manuscript, and submitted it to the journal.

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