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The epidemiology of Hepatitis A in Portugal and in the World A comparative study

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Abstract

Introduction: Hepatitis A is caused by a virus of the family Picornaviridae, of the genus Hepatovirus. It is a fecal-oral disease that can cause jaundice, nausea, abdominal pain, fever, dark urine, among other symptoms. In Portugal the vaccine is not part of the National Vaccination System, however it is advised to all individuals who travel to endemic areas. Currently the endemicity of a region is classified when 50% of a population, of a specific age group, has immunity against HAV. **Objectives**: To understand the epidemiological situation of Hepatitis A in Portugal and to compare it with the rest of the world. **Methods:** Two selection moments were created with the aid of four inclusion criteria. A total of 16 studies were selected for this systematic review. **Discussion/Conclusion:** Africa and Latin America present intermediate to very high endemicities, North America low endemicity, Asia low to very high endemicities, Australia low to high endemicities, Europe low to intermediate endemicities and Portugal low endemicity. As expected, richer regions have lower endemicities. There is an improvement in the living conditions of the general population, leading to the poorer regions presenting some countries with intermediate endemicities, thus pointing to a positive evolution against the Hepatitis A virus. The best strategy to improve this evolution is through vaccination.

Introduction

The first signs of diseases identified as hepatitis, both in isolated cases and in outbreaks, were reported in China 5000 years ago [1]. More accurate descriptions of Hepatitis A emerged in the 17th century, associated with military campaigns. It was a very common disease in Civil War troops in the United States of America, the first outbreak being reported in 1812 in Norfolk, where more than 40,000 cases were documented. Hepatitis A remained associated with war until the 19th century, giving rise to terms such as "kriegsikterus" (war jaundice) or "jaunisse des camps" (field jaundice). During the First and Second World War, more than 16 million cases of hepatitis A were estimated among combatants and the civilian population [2].

In other reports, Virchow designated the disease as catarrhal jaundice, due to the verified biliary obstruction, which the author defined as the cause of the disease. Later, in 1908-1912, McDonalds and Cockayne began to use the term "virulent agent" as the cause of disease, but only in its general sense, as a harmful agent. In the early 1930s, Findlay and Cols admitted that the cause of the disease is an ultramicroscopic virus [3].

Between 1942 and 1945, studies were carried out in Germany, the Middle East and the USA on volunteer subjects who showed the transmission of the disease from Man to Man. At Yale University, it was found that inoculation of serum was capable of causing jaundice with a much longer incubation time than catarrhal jaundice [1,3]. The same study also found the existence of two forms of the disease, infectious hepatitis, defined as Hepatitis A, and serum jaundice, defined as Hepatitis B [4]. An outbreak in New York made it possible to obtain two standard sera, MS-1 and MS-2, which transmitted hepatitis A and B, respectively. MS-1 was later inoculated into Sanguis, a primate species, which led to the first experimental model. The first viral particles in the feces of patients in the early stages of Hepatitis A were demonstrated through infected primates [3].

Hepatitis A

Hepatitis A virus (HAV) is part of the Picornaviridae family and the Hepatovirus genus, non- enveloped and single-stranded RNA [5]. This virus can survive at low pH and resist moderately high temperatures, allowing it to survive in the environment and pass through stomach acid, surviving until it reaches the liver [6]. The HAV RNA genome is positive-sense and is ready for translation.

HAV is mostly transmitted via the fecal-oral route, through consumption of contaminated water or food, but also through direct contact with infected individuals, use of infected syringes and in homosexuals through sexual intercourse [5].

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After the virus enters the body, it has the ability to survive the digestive process, reaching the hepatocytes, in the liver, through the bloodstream. Once in the hepatocytes, virus particles will be replicated and will aggregate, being, later, secreted by the apical membrane of the hepatocytes into the bile canaliculi. From there, they travel through the bile duct and large intestine to be eliminated in the feces [7]. This enterohepatic cycle of HAV does not stop until its interruption is caused by antibodies or other mechanisms of the immune system [3,5].

Clinical manifestations

There are six different types of hepatitis caused by viruses: A, B, C, D, E and G. The symptoms caused by any type of hepatitis are similar and their extrahepatic manifestations can differ quantitatively as well as qualitatively. Thus, hepatitis A can occur as a sporadic, endemic or epidemic infection, since the unique characteristics of this type of hepatitis are observed in different populations, independent of geographic and racial conditions [8]. Hepatitis A infection has four clinical phases. The first consists of an incubation period of about 30 days [6]. This phase is asymptomatic; however, the virus is transmissible. The second phase is the pre-icteric period, where the infected individual may experience non- specific and gastrointestinal symptoms for days or weeks. In the third stage, jaundice is the main feature and the remaining symptoms begin to decrease and/or disappear. The fourth and final phase is the period of convalescence, in which, as the name implies, the individual recovers from the infection [9].

In any case of HAV infection, the clinical spectrum varies from asymptomatic infection to fulminant hepatitis [5]. Clinical manifestations depend on the age of the infected individual, with 70% of infected children under the age of 6 being asymptomatic and, in contrast, about 70% of infected adults presenting jaundice, gastrointestinal symptoms (nausea, malaise, , vomiting, abdominal pain), fever, dark urine, among others [6].

Fulminant hepatitis, although rare (less than 1% of cases), is the main complication of HAV infection and consists of acute liver failure. This type of hepatitis is more common in adults, however it can affect all age groups. The way to combat it is liver transplantation, although there are spontaneous recoveries in about 35% of cases [8,10].

Humoral Immune Response

Once an individual is infected, the Hepatitis A virus will induce a humoral immune response, causing antibodies of the IgM, IgG and IgA class to be directed against the virus capsid [3,11].

IgM is produced only during the initial phase of infection, as IgA is produced for a short time, however its immune function is uncertain. IgG, on the other hand, has a later, but much longer-lasting, response and plays a role in resistance against possible reinfection [8].

IgM tend to disappear, approximately, up to 4 months after infection, while IgG may remain for years or even a lifetime [11].

Vaccination

The Hepatitis A virus is practically restricted to humans, which leads to many discussions about the possibility of total elimination of the disease with the help of the vaccine. Some authors indicate that it would be possible if there were no political and economic conflicts [12].

There are currently four vaccines available that are quite safe and effective. All of them are divided into two doses, with the first intended for short-term protection and the second long- term dose. [5,13]. Hepatitis A vaccine is recommended for travelers to endemic areas, male homosexuals, intravenous drug users and patients with liver diseases [4].

Vaccines against HAV are available to everyone from 12 months of age and WHO recommends that this vaccine be part of the national immunization schedule for children over 1 year of age. [13,14].

In Portugal, the vaccine is not part of the National Vaccination System, however it is recommended for all individuals traveling to countries with intermediate, high or very high endemicity, who have chronic liver diseases or belong to a community that has suffered an outbreak [15].

Several studies prove that mass worldwide vaccination can and should be carried out in order to combat the Hepatitis A virus, especially in non-endemic countries, in order to protect the population [12,15].

Epidemiology

The incidence of Hepatitis A virus in developed countries has decreased over the last few years, due to the improvement of hygiene, sanitation and socioeconomic conditions. The introduction of an effective vaccine in less developed regions has also been an asset to this decrease in incidence.

However, HAV continues to infect many people, causing temporary impairment and rarely liver failure [16].

The Global Burden of Morbidity study indicates that approximately 1.46 million people die each year from viral hepatitis, most of which are due to hepatocellular carcinoma. It is estimated that in 14,900 of these deaths, the viral hepatitis involved is Hepatitis A [17].

The Global Burden of Morbidity study seeks to offer a unique perspective on health. It simultaneously covers all age- and sex-specific causes of death, illness or disability. It allows countries to channel efforts, prioritizing situations with greater health gains [18].

It is currently estimated that over 100 million HAV infections occur, leading to an average of 22,500 deaths per year worldwide. However, according to the World Health Organization (WHO), only one and a half million cases are registered per year, due to the high number of asymptomatic cases that exist in the younger population [19]. Recently, the endemicity of the Hepatitis A virus has received new classification proposals, based on the "susceptibility of the average age of the population" That is, it is the average age at which at least 50% of the population of an age group has IgG anti-HAV antibodies, thus indicating that there has been contact with the virus [20]. There are four categories: very high (50% <5 years), high (50% 5-14 years), intermediate (15-34 years) and low (50% >35 years) [21].

Objectives

Understand the epidemiological situation of Hepatitis A in Portugal.

Comparing the epidemiological situation of Hepatitis A in Portugal with the rest of the world.

Methodology

The scientific terms were selected in Portuguese on the platform "Descriptors in Health Sciences" (DeCS) and in English in "Medical Subject Heandings" (MeSH), between June and July 2021: Hepatitis A, Hepatitis A virus, Viral hepatitis and Hepatitis A, Hepatitis A virus, viral hepatitis.

An exhaustive and prolonged search was started, mostly in PubMed. The scientific terms were searched individually and, later, they were crossed with the words "outbreaks", "in Portugal" and "around the world". The research ran from September 2020 to November 2021. Initially, three inclusion criteria were defined:

• Chronology from 2000 to 2021, with more recent articles prevailing (2010-2021)

• Full text (preferably free)

• Languages in English and Portuguese (Pt and Br).

47 studies were collected. However, the second selection phase was necessary, since many of the studies initially selected were without data or incomplete for the proposed objectives. Thus, this second phase sought to improve the method of selection of studies in order to improve data collection.

The second inclusion moment presented the following inclusion criteria:

Present percentages of Hepatitis A seroprevalence or number of Hepatitis A cases in a population

After the second selection phase, 25 studies were collected.

Therefore, the pre-selected literature was analyzed, including some references from the literature itself, which may not follow the aforementioned chronology criterion.

Of the 25 studies analyzed, 9 were not selected because they were repeated, or focused on other types of viral hepatitis.

Therefore, 16 studies were included for this article.

Results

The 16 works cover all continents of the world, with 1 covering all continents, 3 are about Africa (Table 1.), 3 about North America (Table 2.), 2 about Latin America (Table 3.), 1 on Asia (Table 4.), 0 on Oceania (Table 5.) and 6 on Europe (Tables 6. and 7.), 4 of the latter are specifically about Portugal (Table 8.).

The following graphs (Figures 3- 9) compile the data for each continent and region, in order to better understand the epidemiological situation of Hepatitis A in the world and help in its comparison.

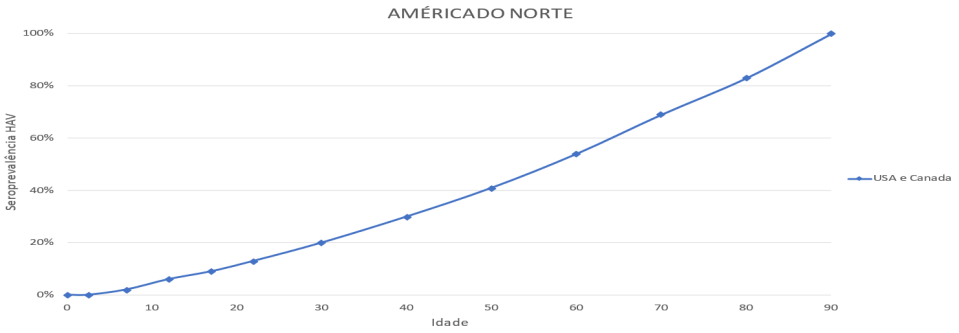

Figure 1. *Graph estimating HAV seroprevalence by age in North America. Adapted from 214 (World Health Organization, 2010).*

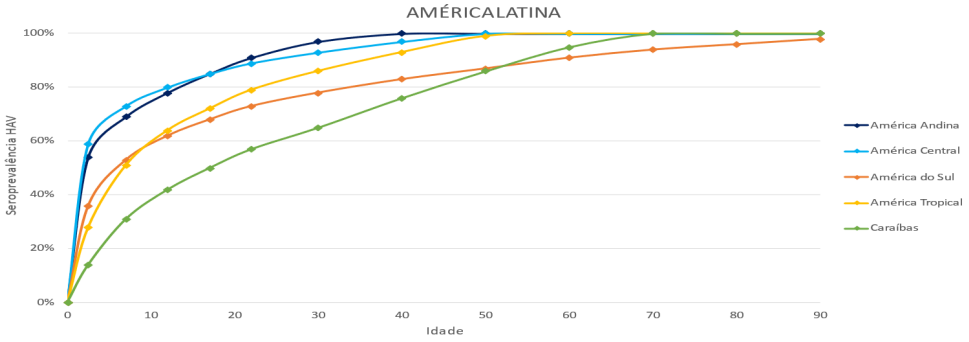

Figure 2. *Graph estimating HAV seroprevalence by age in Latin America. (World Health Organization, 2010).*

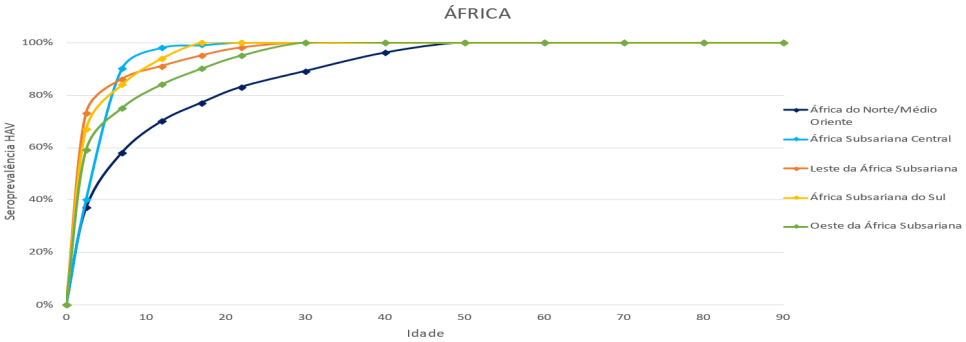

Figure 3. *HAV seroprevalence estimation chart by age in Asia. Adapted from (World Health Organization, 2010).*

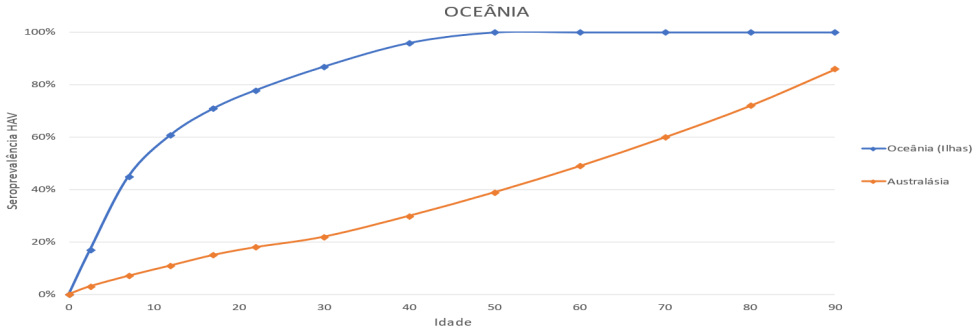

Figure 4. *Graph estimating HAV seroprevalence by age in Oceania. Adapted from (World Health Organization, 2010).*

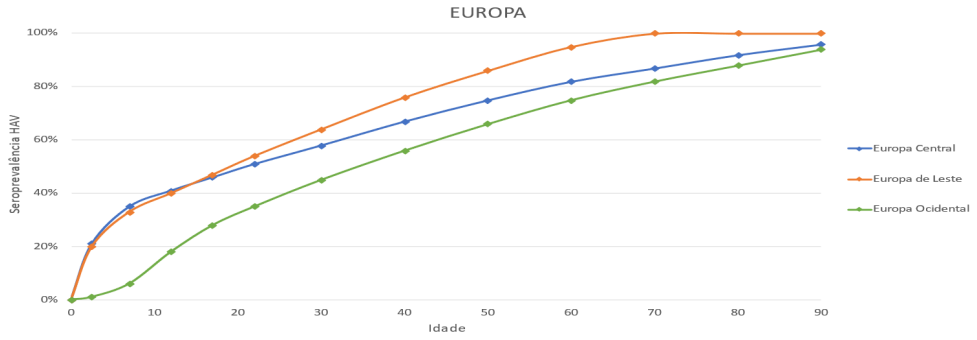

Figure 5. *Graph estimating HAV seroprevalence by age in Europe. Adapted from (World Health Organization, 2010).*

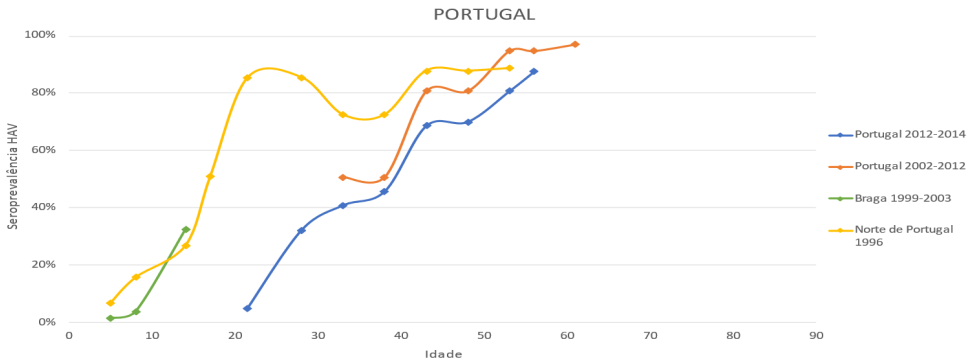

Figure 6. *HAV seroprevalence estimation chart by age, in Portugal.*

Discussion

Areas with fewer resources and poorer sanitation systems tend to be at higher risk of HAV transmission, such as some areas of Africa, Latin America, Asia and Eastern Europe. In some countries in these regions, most of the population is infected in childhood, which, in general, is not necessarily a negative situation, since Hepatitis A infection is chronic, making it a universal protection for life. [21,22]. On the other hand, in wealthier areas with better hygiene and sanitation conditions, such as Western Europe, Australia, North America and some countries in Asia, the reverse of the coin is shown. If, on the one hand, most children do not have any contact with the Hepatitis A virus, on the other hand, young adults (20-40 years old) are vulnerable. In these situations, any contact with the virus, even on rare occasions (for example: import of food), can start several outbreaks of transmission. If there is no immunity created in these populations, there is a high probability of contracting the disease and with symptoms [21,22].

Whether a rich country or a poorer country, there are always people more susceptible to virus infections. For HAV, there are 10 types of populations at risk for Hepatitis A virus infection: 1) Travelers to endemic areas, the main cause of cases in non-endemic countries; 2) Men who have sex with men [23], many of the most recent outbreaks in Europe report male homosexuals [24]; 3) individuals who use illegal drugs, mainly in needle sharing; 4) Individuals in charge of food, mostly shellfish and seafood, which lead to outbreaks; 5) workers in the health area are constantly in

contact with numerous diseases; 6) sewage workers, since the virus leaves the human body through faeces; 7) Military, war missions where hygiene conditions are low or even null; 8) Prisoners often

share the same private facilities with dozens of other inmates; 9) Recipients of blood transfusions, which is rarer considering the short period of time the virus is present in the blood; 10) Hemophiliacs, also related to blood transfusions [23].

According to the proposed classification of HAV endemicity based on the "susceptibility of the average age of the population" [20], the African continent and the Middle East area show regions that differ between very high, high and intermediate endemicity. . North America has low endemicity, while Latin America and the Caribbean range from very high to intermediate. Asia and Oceania are where the greatest difference in endemicity occurs, with countries with low endemicity and others with very high endemicity. The European continent varies from low to intermediate [9].

The African continent is divided into two major zones, north of the Sahara desert (North Africa and the Middle East) and south of the Sahara desert (Sub-Saharan Africa).

Sub-Saharan Africa can be divided into four regions, Central, East, South and West. All these regions have very high levels of endemicity. In general, these areas are poor and with poor sanitation and hygiene conditions. The four regions present values greater than 50% in the population aged less than 5 years [9,25,26].

On the other hand, North Africa and the Middle East have different values for different countries. In general, this region has a high endemicity, with more than half of children and adolescents already having contact with the virus. However, there are countries, mostly in the Middle East, that show intermediate endemicity values [9,25].

Egypt, Iraq and Morocco present values > 50% at ages below 5 years, making them very high endemic countries. On the other hand, neighboring countries such as Saudi Arabia, Iran and Tunisia have values < 50% in the population under 15 years of age [27]. To the north of the American continent are two countries, the United States of America and Canada, known for their great development and high socioeconomic level. Both have a low endemicity. Canada, in 2004, had values below 50% up to the age of 50, and a decade and a half later, these data are expected to be lower. The United States of America, in 2010, had values below 50% in the population aged over 60 years [25,28,29].

It should be noted that, in 2009-2010, in the USA, the population between 6 and 19 years old had seroprevalence values above 40%. This may be related to the high immigration that occurs in the country or even to the 2008 crisis.

Latin America is made up of five regions: the Caribbean, Andean America, Central America, South America and Tropical America. Most of Latin America has high endemicity, however, in the last 20 years there has been a decrease in endemicity [25]. The Caribbean is a region composed mainly of paradisiacal islands present in the Caribbean Sea, which makes this area live and depend a lot on tourism. It is an underdeveloped region, and adding this characteristic to its dependence on international tourism, it becomes an area of inconstant endemicity, although, in general, its endemicity is intermediate, where 50% of the population, aged between 15 and 34 years, has already been infected [9].

Andean America is the set of countries crossed by the Andes. This region is one of the areas with the highest endemicity of Hepatitis A. Although there are not many recent studies on the subject, it is estimated that this area has a very high endemicity. However, an improvement in sanitation and hygiene conditions is expected in the countries involved in order to reduce the impact of the virus on the population [30,9].

Central America also has a very high level of endemicity, with around 59% of the population under 5 years of age with some previous contact with HAV [9]. However, more recent studies indicate that countries in this area have shown socioeconomic growth, exposing a decrease in this percentage value and, consequently, the average age of infection increases (Andani et al., 2020; van Effelterre et al., 2017) .

Finally, we have the regions of South America and Tropical America. Both have values of 50% for ages between 5 and 14 years, making them areas of high endemicity. Although the countries in these regions are growing and developing and recent studies indicate an increase in the average age of infection, the biggest problem is the great territorial diversity [9,30,31].

For example, in Brazil and Mexico, a major problem that occurs is population distribution. The population in rural areas has poor sanitation and access to potable water, but there are small communities, limiting the spread of the virus. In urban areas, although there are better living conditions, there are more people per square meter, making the risk of transmission easier [31,32].

Asia is the largest and most populous continent in the world and is divided into 5 areas: Asia- Pacific, Central Asia, East Asia, South Asia and Southeast Asia.

Asia-Pacific is generally the richest and most developed area on the continent. In the last 30 years, countries in this region have gone from very high to low endemicity, thus showing an enormous sanitary evolution [33]. Almost no child up to the age of 14 has any previous contact with the virus and it is only from the age of 35 that 50% of the population has a possible previous infection [9].

Central Asia and South Asia both have a very high endemicity, where 50% of the population under 5 years old has an episode of infection. Most countries in these regions are poor and with many failures in sanitation systems and access to safe water [9,33], such as India.

East Asia and Southeast Asia, in general, are areas of high to moderate endemicity, where about 50% of the population aged 15 years and over has some previous sign of HAV infection. However, there are countries with lower endemicities, such as Thailand, which in 2016 had a 17% seroprevalence in young adults (21-30 years) [9,33]

Oceania is the most recent continent and can be divided into Australasia (Australia and New Zealand) and Islands.

Both countries belonging to the Australasian zone are developed countries that have good sanitation and hygiene conditions. For these reasons, its endemicity is low, with approximately 50% of the population being naturally immunized only at age 65 [9].

In relation to the surrounding islands of Oceania, its endemicity is estimated to be high, in which half of the population over 10 years of age is considered to be naturally immunized. However, there are no recent studies that corroborate these estimates [9].

Europe is divided into centre, east and west.

Central and Eastern Europe are very similar in all age groups, having an intermediate endemicity, where 50% of the population, between 15 and 34 years old, is naturally immunized [9]. Both regions are mostly made up of underdeveloped countries that have grown rapidly and exhibit more and better conditions of protection against future infections, which may predict some countries with low endemicities in the coming years [25,34].

Poland is an excellent case of this growth, showing that since

2009 the number of cases has also kept low. This growth is due not only to the creation of routines in order to verify and control the seroprevalence of the Polish population, but also to pay attention to possible outbreaks that occur in neighboring countries. For example, it took place in 2016 in Hungary, Romania and Bulgaria [24].

Western Europe is mostly made up of developed countries. They are one of the richest countries and considered to be the greatest powers in the world. Mainly for these reasons, its endemicity for Hepatitis A is low, with about 50% of the population having natural immunity only after the age of 35 [9,25]. However, as Europe is a highly developed continent and has low endemicities, it also makes its population more susceptible to severe HAV infection. Recent studies indicate that cases of Hepatitis A have increased in these richer countries [34]. These increases may be related to international travel, which is the highest risk of contracting Hepatitis A in Europe. The population aged between 5 and 44 years is the one that travels the most, which includes the ages with the highest risk of serious infections (20-35 years). Although most travel takes place within Europe, the largest number of cases come from travel to Asia and Africa, both regions of high endemicity [35]. Portugal has been the target of several studies concerning the seroprevalence of HAV in the last decades. These studies have shown a positive evolution against the transmission of Hepatitis A, over time, showing a socio-economic evolution of the country, but also an improvement in hygiene and sanitation conditions [36,37]. Thus, today, it is a country with low endemicity, with seroprevalence values below 50% up to 40 years of age [37,38].

At the end of the century XX and beginning of the century. XXI, Portugal had an intermediate endemicity, with 50% of the population infected with HAV between 15 and 20 years of age [36,39]. Over time, this endemicity has decreased, reflected in studies carried out between 2002 and 2014, showing a great evolution of the country. Almost all adolescents and young adults have never had contact with the virus, 379 showing a seroprevalence of 5% in the population under 20 years of age and less than 50% in the population under 40 years of age [37,38].

The endemicity of Hepatitis A varies throughout the world.

Portugal has a low endemicity [38], and therefore it is better than the entire African continent, all of Latin America, all of Eastern and Central Europe, the area of the islands of Oceania and all of Asia, in except for the pacific zone. It is on an equal footing with the Pacific zone in Asia and with the rest of Western Europe (50% > 40 years) and is worse than Australasia and North America, where 50% of the immune population is naturally reached. only at age 60 [9].

The reason why rich countries tend to have lower endemicities is directly related to "Westernism".

Occidentalism currently refers to the influence of Western society on non-Western societies, whether technological, industrial, political, economic, religious, etc. [40]. The very definition of the West is not exact. Initially it was based in Europe, but nowadays it encompasses all regions that present European routines and customs, such as the cases of America, Australia and Japan [41,42]. Europe, North America, Australia and Japan are not only the areas with the lowest endemicity in the world for Hepatitis A, but they are also the richest areas.

However, the poorest areas present some parts with lower endemicities than the generality of the region, thus proving a socio-economic growth, an improvement of sanitation networks and access to drinking water and a westernization of the world [25]. For example Brazil, South Africa and Turkey. These three countries have varied endemicities within their own borders. Brazil has a great population diversity from the indigenous tribes of the Amazon to the Caucasians of high society and the way of thinking, living and the culture itself will affect the endemicity of the region [43]. South Africa also has a great population diversity, with several ethnic groups coexisting in the same space. As can be seen from Table 1, this country has different endemicities depending on the type of ethnicity, which is closely related to the lifestyle of each society, as well as its culture [9,25]. Turkey has three different endemicities that would represent three different countries. The western area, closer to Europe and where the capital is located, has a lower endemicity than the central area, closer to Africa, and the eastern area, closer to Asia [44]. Each of these regions is inhabited by different cultures, with different religions and ideals, which directly and indirectly affect the endemicity of Hepatitis A.

Of course, westernization is not the only reason why Hepatitis A seroprevalence levels have been decreasing. The vaccine plays a very important role in the fight against the Hepatitis A virus. In countries with high endemicity, the vaccine may not help much, as most of the population is already immunized, but in countries with intermediate endemicity it is the ideal weapon to transform the region into a non-endemic area, eliminating viruses as much as possible. In countries that already have low endemicities, the vaccine will serve as a protection for the young adult population to avoid infections and further worsening [13,25].

Turkey shows results that support this premise. In 2012, the vaccine became mandatory in the country, and in the following years a decrease in endemicity has been reported [45]. In many other countries, socio-economic growth is, by itself, the biggest help in the fight against Hepatitis A. The countries called EAGLE (emerging and growth-leading economy) are countries classified as an emerging economy and leader in growth and are the greatest example of this solution. These countries are Russia, Turkey, Philippines, Malaysia, Iran, among others [46].

Conclusion

Richer regions have lower endemicities, as the quality of life in these countries is higher. The poorest areas have very high endemicities, as in many cases not the entire population has access to drinking water.

Thus, the best strategy to combat the Hepatitis A virus in the poorest and most endemic countries is to improve hygiene and sanitation conditions and access to safe drinking water. In richer countries with low endemicity, since sanitation and hygiene conditions are good and access to drinking water is practically national, the best way to eradicate this virus is through vaccination.

In countries with intermediate endemicities, socio-economic growth is the first step towards improving living conditions. This systematic review aimed to understand the epidemiological situation of Hepatitis A in Portugal and compare it with the rest of the world. Both objectives were met, showing that Portugal has improved a lot in recent decades, decreasing its endemicity from high to low.

Our country shows one of the lowest endemicities, along with Japan, North America, Australia and Western Europe.

There were two major limitations in this article. The first is the scarcity of more specific studies. There are countries in regions considered endemic that have low endemicities, for example areas of China, Kuwait or Thailand. The second is a large temporal difference in the data obtained, which may impair the comparative clarity for which the article was intended.

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