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Worldwide prevalence, genotype distribution and management of hepatitis C

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Abstract

Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma, resulting in major global public health concerns. The HCV infection is unevenly distributed worldwide, with variations in prevalence across and within countries. The studies on molecular epidemiology conducted in several countries provide an essential supplement for a comprehensive knowledge of HCV epidemiology, genotypes, and subtypes, along with providing information on the impact of current and earlier migratory flows. HCV is phylogenetically classified into 8 major genotypes and 57 subtypes. HCV genotype and subtype distribution differ according to geographic origin and transmission risk category. Unless people with HCV infection are detected and treated appropriately, the number of deaths due to the disease will continue to increase. In 2015, 1.75 million new viral infections were mostly due to unsafe healthcare procedures and drug use injections. In the same year, access to direct-acting antivirals was challenging and varied in developing and developed countries, affecting HCV cure rates based on their availability. The World Health Assembly, in 2016, approved a global strategy to achieve the elimination of the HCV public health threat by 2030 (by reducing new infections by 90% and deaths by 65%). Globally, countries are implementing policies and measures to eliminate HCV risk based on their distribution of genotypes and prevalence. (Acta gastroenterol. belg., **2021,** 84**, 637-656**).

Keywords: Hepatitis C virus, epidemiology, genotype, molecular biology, prevention.

This review article focuses on the epidemiology and molecular biology of HCV, as well as strategies for preventing infection. It is organized by countries, with economies categorized as developed, developing, or in transition. The included regions are stratified according to the United Nations (U.N.) definitive report titled, "World Economic Situation and Prospects 2020" (6). The previous review articles focused on epidemiology and prevalence data on hepatitis C only about specific regions and countries, but they were not stratified based on U.N. definitive reports globally. Through this review article, we would like to emphasize the global prevalence and genotypic variations of HCV that were not particularly concentrated in a single research study.

Limitations

Our review has certain limitations such as the search was confined to only major countries of the continents based on the available data. Treatment and preventive measures were emphasized in these specific countries. We did not classify the HCV population according to any particular age group or pregnant women distinctly.

DEVELOPED ECONOMIES

North America, United States (U.S.)

As a leading cause for morbidity and mortality from liver disease, HCV holds a hefty disease burden in the U.S (7,8). The total cost for HCV and its sequelae costs the country's health care system billions of dollars per year (9,10). It has been estimated that HCV causes approximately 399,000 deaths each year, primarily due to progressive complications of HCC and cirrhosis (1). In the U.S, it is the most commonly reported bloodborne infection (10), and surveys conducted during the years 2013 to 2016 showed that an estimated 2.4 million people (1.0%) in the nation were living with HCV (11,12). Chronic Hepatitis C infection is the leading cause of HCC in the U.S. Complications related to HCV infection usually arise 3-4 decades after the initial infection, and the country is currently experiencing a peak in HCV-related problems due to the high incidence of HCV infection from the 1970s and 1980s (7,8).

Epidemiology

Statistics report a century-low number of acute HCV cases in 2005; however in 2017, the rate increased approximately fourfold (10). The viremic prevalence of the United States is shown in Figure 1 and Table 1.

While the incidence was higher for males than females in 2017 (1.2 and 0.9, respectively, per 100,000 population) (12,13), the risk of new HCV infections has significantly increased among women with live births. Data illuminated the increasingly vulnerable position

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Submission date : 13/07/2021
Acceptance date : 22/08/2021

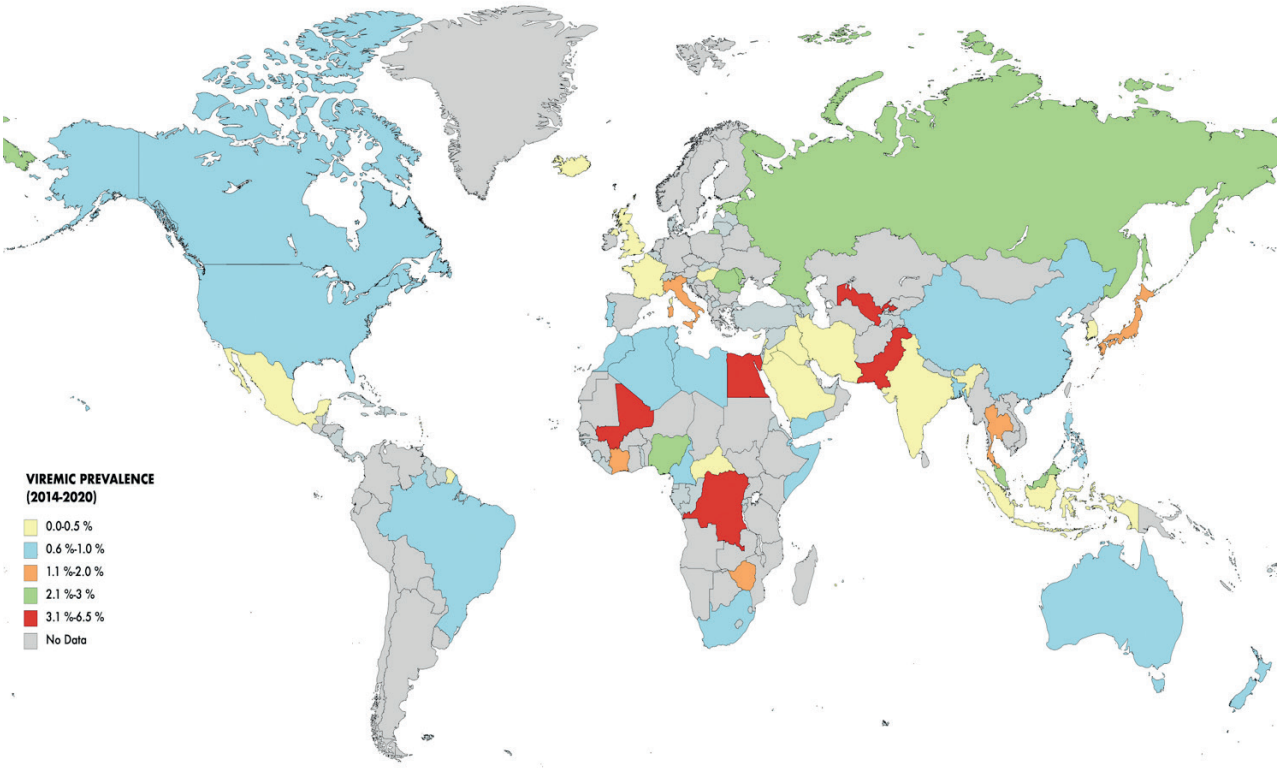

Figure 1. — A map chart showing the worldwide prevalence of hepatitis C virus (HCV) infection.

of reproductive-aged women with nearly a doubling of acute HCV incidence rates during 2009 and 2014 (14). In 2015, 0.4% of live births were delivered by mothers with HCV (11,14). Additionally, peripartum HCV infection rates have risen from 2000 to 2015, from 0.8 to 4.1 per 1,000 live births, respectively (15).

Regarding age, the acute HCV incidence in 2017 was highest for people aged 20-29 years (2.8 per 100,000 population) and 30-39 years (2.3 per 100,000 population), while those aged ≤19 year s were the lowest (0.1 per 100,000 population). Of note, amongst newly reported chronic cases, a bimodal distribution of age was detected. Specifically, data shows a greater occurrence among those aged 20-39 and 50-69 years (10); a deviation seen equally among males and females. Baby Boomers, individuals born from 1945 to 1965, had the highest prevalence of chronic HCV in the U.S. (10). These same individuals comprised 36.3% of newly reported HCV cases in 2018, whilst Generation X (those born between the years 1966 and 1980) and Millennials (those born between 1981 and 1996) accounted for 23.1% and 36.5%, respectively (10).

National Health and Nutrition Examination Survey (NHANES) data from the years 2015 to 2018 report 60.6% of HCV-RNA-positive individuals greater than 20 years old as being confirmed with Hepatitis C (10). The North American region overall has a 1% prevalence of HCV among the adult population (16).

Molecular biology

North America experienced the origin of its subtype GT1a epidemic at the beginning of the 20th century. The affected population size remained low until 1955 but was later met with two phases of rapid growth between the years 1955 and 1975. The effective population size stabilized, and declined slightly after the 1990s. Comparatively, North America's subtype GT3a epidemic, which emerged decades after its subtype GT1a counterpart, encountered an exponential increase between 1955 and 1970, which later reduced after 1995 (17,18). The origins of these genotype distributions in North America, as shown in Table 2, parallel the development of medical technology and treatment practices during the First and Second World War eras, respectively (17).

In the U.S., GT1 is the most prevalent genotype, which accounts for approximately 75% of the cases (16). High rates of HCV RNA genome mutations are expected to play a role in the pathogen's ability to evade the immune system (18).

In regards to acquiring future HCV infections, little to no protection is afforded to those previously infected, whether it be of identical or different genotypes (12).

Prevention

The United States Public Health Service (USPHS) has issued several guidelines recommending HCV testing of all blood and organ donations planned for human use (10).

The Centers for Disease Control and Prevention (CDC) has also played a preventative role in the U.S. since the year 1998, CDC has expanded the HCV inter-agency testing guidelines, which recommend testing individuals at high risk. The at-risk population referred to

Table 1. — **Worldwide prevalence of hepatitis C virus (HCV) infection**

VARIABLES	PREVALENCE (%)	YEAR OF ESTIMATE
DEVELOPED COUNTRIES		
NORTH AMERICA		
UNITED STATES	1.0	2020
CANADA	0.60	2015
ASIA AND PACIFIC		
JAPAN	1.10	2014
AUSTRALIA	1.0	2015
NEW ZEALAND	1.0	2015
EUROPE		
BELGIUM	0.12	2017
NETHERLANDS	0.20	2015
HUNGARY	0.50	2015
PORTUGAL	0.80	2015
FRANCE	0.30	2015
ESTONIA	2.05	2019
ICELAND	0.30	2015
ROMANIA	2.50	2015
ITALY	2.0	2015
UNITED KINGDOM	0.30	2015
SCOTLAND	0.92	2019
CYPRUS	0.60	2014
ECONOMIES IN TRANSITION		
RUSSIAN FEDERATION	2.20	2019
UZBEKISTAN	4.10	2019
REPUBLIC OF MOLDOVA	2.74	2019
DEVELOPING COUNTRIES		
AFRICA		
NORTH AFRICA		
EGYPT	6.30	2015
MOROCCO	0.80	2015
ALGERIA	1.0	2015
LIBIA	0.70	2015
TUNISIA	0.90	2015
EASTERN AFRICA		
DJIBOUTI	1.0	2016
SOMALIA	1.0	2016
YEMEN	0.80	2015
KENYA	0.20	2015
ETHIOPIA	0.60	2015
SOUTHERN AFRICA		
ZIMBABWE	1.63	2019
MAURITIUS	1.30	2019
WEST AFRICA		
MALI	3.10	2019
NIGERIA	2.10	2019
IVORY COAST	1.70	2019
CAMEROON	0.70	2019
CENTRAL AFRICA		
DEMOCRATIC REPUBLIC OF THE CONGO	4.30	2014
CENTRAL AFRICAN REPUBLIC	0.30	2015
ASIA		
SOUTH-EASTERN ASIA		
CHINA	0.70	2015
KOREA	0.50	2015
PHILIPPINES	1.0	2016
THAILAND	1.70	2015
INDONESIA	0.50	2016
MALAYSIA	2.50	2016
INDIA	0.50	2015
PAKISTAN	3.80	2015
BANGLADESH	1.0	2014
WESTERN ASIA		
SAUDI ARABIA	0.30	2015
LEBANON	0.20	2015
IRAN	0.20	2015
IRAQ	0.20	2015
JORDAN	0.30	2015
LATIN AMERICA AND CARRIBEAN		
MEXICO	0.40	2015
SOUTH AMERICA		
BRAZIL	0.90	2015

people who had: ever injected drugs or shared syringes, needles, or other equipment used for drug preparation; received clotting factor concentrates produced before 1987 or ever been on maintenance hemodialysis; had persistently abnormal aspartate transaminase (ALT)/ aspartate aminotransferase (AST) levels; received blood transfusions or organ transplants before July 1992; had a recognized exposure, or were born to a mother infected with HCV (19). In 1999, the CDC added all individuals with HIV to the groups recommended for testing (20). Moreover, the CDC suggests HCV screening for people 18 years of age once in their lifetime, and for all pregnant women during each pregnancy with an exception for settings where the prevalence of HCV infection is <0.1 (12). In 2012, due to concern regarding the limited effectiveness of risk-based HCV testing and a high prevalence of HCV among people born during the years 1945-1965, the CDC also recommended one-time testing, even in the absence of a known risk factor, for all Baby Boomers (10,14). Currently, the CDC recommends that healthcare providers should take initiatives in promoting universal HCV screening until the prevalence of HCV RNA-positivity in their population is established to be less than 0.1%; only then will universal screening no longer be explicitly recommended.

The U.S. health policy initiatives reflect the WHO's ambition to decrease HCV incidence by 2030. Should there be a met growth in treatment uptake and implementation of universal screening, there is hope for improvement in the HCV care cascade. A national strategy will be needed to support the creation and development of systems aimed at increasing diagnosis. A comprehensive plan should also include outlining effective and timely retreatment of patients who have failed on direct-acting antiviral drugs (DAAs) to achieve HCV elimination (21).

Table 2. — **Global hepatitis C virus (HCV) genotype variations in developed countries**

VARIABLES	GENOTYPE
DEVELOPED COUNTRIES	
NORTHERN AMERICA	
UNITED STATES	1a, 3a
CANADA	1, 3, 2, 4, 6, 5, 7
ASIA AND PACIFIC	
JAPAN	1b, 2
AUSTRALIA	3a, 1a, 1b, 2, 4, 6
NEW ZEALAND	1a, 3, 1b, 2, 6
EUROPE	
BELGIUM	1a, 1b, 2, 3, 4, 5, 6
NETHERLANDS	1a, 1b, 2a/b, 3a, 4a/d
HUNGARY	1b, 1a, 3, 4, 2
PORTUGAL	4a, 4d, 4b, 4f
FRANCE	4a, 4d,4f, 4k, 4h, 4i, 4o, 4p, 4r, 4t, & 4u
ESTONIA	1, 3, 2
ICELAND	3, 1, 4, 2
ROMANIA	1b
ITALY	1a, 1b, 3a, 2, 4
UNITED KINGDOM	1a, 1b, 2, 3, 4
SCOTLAND	1a, 3a
CYPRUS	1b, 3a, 1a; 2k/1b

Canada

Epidemiology

The viremic prevalence in Canada was estimated to be 0.6% (0.4-0.7) in 2015 (22), as shown in Figure 1 and Table 1. From 2012 to 2018, there was a decline from 1% to 0.6% in viral prevalence due to the introduction of public health insurance and treatment initiation with DAAs in Canada (22, 23, 24).

Molecular biology

From the year 2001 to 2017, GT1 was the most prevalent HCV genotype (59.7%), followed by GT3 (25.7%), GT2 (8.6%), GT4 (3.8%), GT6 (1.6%), GT5 (0.6%) and GT7 (0.01%), summarized in Table 2. Notably, a specific cluster of HCV GT4 was identified in HIV-positive male patients via molecular phylogenetic-based surveillance in Quebec (23).

Prevention

British Columbia (BC) in Canada has reached progress towards attaining the first WHO elimination goal of diagnosing 90% of people living with HCV (24). In 2014, the first DAAs were approved in Canada but they were not prescribed widely in British Columbia until they were funded in the health insurance scheme in early 2015. The introduction of public health insurance advanced the treatment initiation and achievement of the hepatitis C cure rate with DAA in Canada (24).

Asia and Pacific

The Asia and Pacific region includes Japan, Australia, and New Zealand (6). The HCV prevalence is shown in Figure 1 and Table 1, whereas the different genotype distribution of these countries is listed in Table 2.

Japan

Epidemiology

A global epidemiology and genotype distribution study in 2014 estimated the viremic prevalence of Japan to be 1.1% (25). According to the Japanese liver transplantation society, 0% to 54% of the annual liver transplants between 1989 to 2011 were attributed to HCV (26). Japan has one of the oldest and most diverse histories of hepatitis C in the world. HCV and its complications are the leading causes of hepatic cancer in Japan (27).

Molecular biology

Japan predominantly has the GT1b HCV subtype with a 64.7% prevalence rate, and GT2 at 34.2% (25).

Prevention

The Basic Act on Hepatitis Measures was established in 2009 to focus on viral hepatitis prevention. The Ministry of Health and Labour along with Welfare and The Council for Promotion of Hepatitis Measures designated workers and epidemiologists to prevent hepatitis (28).

Australia and New Zealand

Epidemiology

In Australia, surveillance data suggests that IVDU and HCV infection incidence have declined since the early 2000s (17). Native Australians, non-employed people, people with IVDU, and prisoners are at the greatest risk of HCV infection (29). The viremic prevalence was 1% (0.7-1.0) in 2015 (22) with approximately 230,000 HCV cases, 75% of which had already been diagnosed (30, 31). The prevalence in New Zealand was 1% (0.6-1.3) in 2015 (22).

Molecular biology

Phylogenetic analysis has shown the GT1a epidemic for Australia began around 1915. The country experienced a period of rapid growth between 1955 and 1975. On the other hand, the GT3a epidemic had more recent origins, seemingly originating around 1953 (17). The other genotypes found in Australia include GT1b, GT2, GT4, and GT6 (22).

In New Zealand, the most predominant form of HCV is GT1a (44.0%), followed by GT3 (35.0%), GT1b (11.0%), GT2 (7.0%), and GT6 (1.0%) (22).

Prevention

The National Hepatitis C Strategy (2014 - 2017) of Australia aims to bring about a 50% reduction in the incidence of HCV infections over four years by strengthening needle syringe programs (NSP) activities and peer education (32). The National Hepatitis C Strategy Action Plan (2018-2022) of Australia focuses on encouraging connections between existing programs and policies based on previously successful approaches, to minimize duplication of effort (32). However, to achieve the objective of viral hepatitis elimination, additional interventions and strategies are required (33).

Australia and New Zealand are both high-income countries, with universal healthcare, policies that allow for heavily subsidized medications, and with surveillance systems for viral hepatitis (34). In regards to New Zealand, survival from HCC is poor and has been attributed to the fact that the cancer is incurable in a great number of individuals at the time of detection (35). Accordingly, the country has invested in strategies to increase access to testing and treatment for HCV; examples of which include community advocacy programs, promotion of health research, and health service and political leadership.

While there is always room for growth, it is important to note the success of both Australia and New Zealand. In 2019, a Lancet Gastroenterology & Hepatology Commission on accelerating the elimination of viral hepatitis reported central policy indicators. Australia and New Zealand scored the highest for HCV policies were Australia and New Zealand, policies in existence a national plan or strategy; reliable national epidemiological data; estimate of economic burden; mandatory screening of donated blood; harm-reduction programs; free birth-dose vaccination; third-dose vaccine coverage; publicly funded screening programs; HBV treatment subsidized by the government or on national emergency medicine list; HCV direct-acting antivirals subsidized by the government or on national emergency medicine list; and free HCV direct-acting antivirals for nationals (34). New Zealand was noted to have 8 policies they are working towards and Australia had 8 policies on track to have an 80% reduction in the incidence of HCV and a 65% reduction in HCV-related mortality by 2030 (36).

Europe

Epidemiology

Europe is subdivided into Eastern, Western, and Central sub areas (6). The viremic prevalence of different countries in Europe is shown in Figure 1 and Table 1.

Eastern European areas include, but are not limited to Belarus, Estonia, Latvia, Moldova, and Russia; the HCV prevalence ranges from 1.3% (Belarus) to 4.5% (Moldova) (37). HCV epidemiology data are sparse in Estonia, but a viremic prevalence of 2.0% was found in 2019 (39). Romania had a viremic prevalence of 1.8% recorded in 2008 (37), which slightly increased to 2.5% in 2015 (22). In Cyprus, the viremic prevalence was estimated at 0.6% in 2014 (25).

Central European areas include Albania, Bosnia, Czech Republic, Hungary, Poland, and Slovenia, which vary in HCV prevalence from 1.4% in Slovakia to 0.7% in the Czech Republic (37) to 0.5% in Hungary (22).

In Western Europe, which includes Austria, Belgium, Cyprus, Denmark, France, Greece, Iceland, Italy, and the Netherlands, HCV prevalence rates range from 0.12-0.2% (Belgium and Netherlands, respectively) (38) to 2.0-2.6% (Italy) in 2009 and 2015 (37,39) In 2015, the viremic prevalence of HCV in the United Kingdom (UK) and France was at 0.3% (22). In Iceland, the overall HCV viremic prevalence is estimated as 0.3% in 2015 (22), whereas 0.9% for the Scottish population in 2019 (40).

Beyond incidence rates, existing geographically wide-spread sequence data also provides researchers with HCV's phylogeographic trends and aids in elucidating the difference in distribution and movement patterns among the subtypes (41) The prevalence of GT2 (most common) is 8.2% in Western Europe, which is almost double that of Eastern Europe (4.3%) and Central Europe (3.2%). GT4 is prevalent in Central (4.9%) and Western Europe

(5.8%) (42). Portugal, in particular, observed a relatively high (16.1%) prevalence of GT4 amongst its population, which is about three times higher than the estimated prevalence for Western Europe as a whole (42, 43, 44), and the overall viremic prevalence was predicted as 0.8% in 2015 (22).

Molecular biology

The first epidemic, caused by GT1b, occurred during the 1930s and the 1960s and was associated with contaminated blood transfusions. The second and third epidemics were caused by GT3a in the 1960s and GT1a in the 1980s, respectively, and were likely associated with the widespread use of IVDU (44,45) The first partial sequences of GT1g were derived in Europe between 1994 and 1995 from chronically infected German patients who immigrated from Egypt and Sudan (44,45).

The Central European areas are predominantly affected by HCV GT1, followed by GT3, GT4, and GT2. The Eastern European regions are affected by HCV GT1, then by GT3, GT2, and GT4. The Western European area has GT1 as the most prominent genotype followed by GT3, GT2, and GT4, as well as small groups of GT5 and GT6 (38).

Concerning subtypes in Eastern and Southern Europe, the most common subtype is GT1b, followed by GT2 and GT3 (46). The Southern Europe region has GT4a and GT4d in high prevalence (46). In Portugal, there is

phylogenetic mixing of genotypes GT1a, GT3a, GT4a, and GT4d amongst IVDU (47,48,49). In HCV-infected Portuguese inmates, GT4 (48), such as GT4a, GT4b, GT4d, GT4f, and GT4k subtypes, were reported (43, 46, 47, 48). The endemic infections for decades have been caused by GT1 and GT3 before generalization but GT4a became an epidemic quickly after being introduced in Portugal, in 1980, and this epidemic is still growing at a faster rate (44). In France, those contaminated through IVDU are destined to be tainted with homogeneous GT4a or GT4d. In France, those infected through IVDU are most likely to be infected with homogeneous GT4a or GT4d. In Scotland, individual clusters formed different transmission zones initially, but these networks subsequently overlapped, resulting in the mixing of genotypes and clusters around regions with the two epidemic subtypes of GT1a, and GT3a. There has been a decrease in HCV prevalence since the 1990s, in that country, due to preventive measures (50). GT1a and GT1b sequences from Greece were dispersed globally (44); among IVDU, the prevalence was higher for GT3a than GT1a (52).

In Italy, HCV GT1b is the most widespread, whereas GT4 is found in the south of the country, exceptionally high in regions such as Calabria (hyper-endemic areas like other countries bordering the Mediterranean) (37,39,42). The GT1b infection was the most prevalent (35.5%), followed by GT1a (22%), GT3a (21.4%) and GT2 (21.3%) (37,39,42). Stratifying them by age groups, GT1a, GT1b, and GT3a had a comparable prevalence (30-35%) in the 0-15 years old, 16-30 years old, and 31-45 years old age groups. In subjects older than 45 years, GT2 prevalence increased, whereas GT1a and GT3a infections decreased markedly; in the same age group, GT1b and GT2 accounted for a prevalence of more than 90% (37,42)

The HCV epidemic in Cyprus suggests a diverse trans-continental pattern for each subtype. GT1a transmissions originated from limited locations in Southeastern Asia, Oceania, and Western Europe.

On the other hand, GT1b transmissions came from the Eastern and Western European areas, from Eastern/Central Asia, and Oceania, whereas GT3a transmissions stemmed from Eastern and Western Europe, Central Asia, and Oceania. Cyprus was a source for HCV transmission to several areas for GT1b and GT3a. GT3a was the most prevalent among IVDU and GT1b among the general population. For IVDU, the GT2k/GT1b recombinant type, previously found in Russia, was also detected (41, 53). The distinct genotype patterns of any European country are shown in Table 2.

Prevention

The "Hepatitis C Strategy for England" with the "Hepatitis C Action Plan" strategies have arisen from growing knowledge of the epidemiology of HCV and recognition of the efficacy of treatment in reducing the burden of disease in infected populations. These strategies include well-defined programs such as drug education in schools, measures to reduce IVDU, preventive programs to reduce infection in current drug users, increasing professional and public awareness of HCV, along with the promotion of more testing (54).

In Belgium, during the interferon era, HCV-positive IVDU and patients untreated presented a higher chance of being missed at surveillance, essentially for distress for side effects linked to antiviral therapy (55). This implies that earnest patients' recall actions by contacting them or the primary physician could boost agreement with HCV treatment (55). Of interest, Belgian people on opioid replacement therapy has been screened more regularly for HCV RNA compared to the other members of the Insurance Fund, and procedures related to disease progression were reimbursed less frequently in the former group (56). However, the global uptake for HCV screening and treatment in both groups persisted suboptimal(56). Besides, in Belgian patients undergoing HCV treatment with DAA regimens, hypertension, HIV coinfection, and type-2 diabetes mellitus resulted in the most usual comorbidities (38).

In Italy, HCV screening and surveillance are minimal at the national level. Sequencing is essential for monitoring epidemiological trends in various geographic areas allowing the identification of HCV GT subtypes and also to search for their resistant mutations following antiviral therapy (46).

In Scotland, individual clusters of infection play a crucial role in HCV transmission. To increase effectiveness, intervention strategies were targeted at Edinburgh (GT1a) and Glasgow (GT3a) regions based on their necessity (50).

From 2016 new French guidelines emphasize a risk factor-based, targeted screening approach including the population-based testing for Hepatitis virus focused on all the adults (57).

The Portugal Ministry of Health announced a National Action Plan for Hepatitis C, a unique risk-sharing model for patient treatment, adequate funding for the patients, and the creation of the registry resulting in a decrease in the time from treatment request to authorization. This effort has been associated with a 73% decrease in the incidence of HCC (57).

HCV elimination can only be continued with a micro elimination strategy leading to improved identification and treatment with DAA's of the people infected with HCV. Micro-elimination can be achieved in the short to medium term in certain populations. In Europe, greater than 50% of new cases of HCV infection are associated with PWID. The harm reduction policies such as needle/syringe service programs, opioid substitution therapy, and supervised injecting centers are important to prevent the transmission of HCV. In contrast to micro-elimination strategies, macro-elimination strategies are not centered on a specific group but are rather directed towards the entire country's population. It should be initiated with a mass-screening program of the entire population (58).

DEVELOPING ECONOMIES

Africa

According to the United Nations definitive report titled, "World Economic Situation and Prospects 2020," Africa is divided into North, West, East, and South Africa (6). The HCV prevalence of a few countries is shown in Figure 1 and Table 1 along with different genotype distribution patterns in Table 4.

North Africa

The countries discussed in this review are Egypt, Morocco, and North African Arab countries (6).

Epidemiology

Egypt is suggested to have the highest HCV prevalence in the world (about 10-20% of the general population is infected). Additionally, according to the historical data in 2015, Egypt had the highest global viremic prevalence at 6.3% (22). Furthermore, HCV is the leading cause of HCC and chronic liver disease in the country (59,60, 61). The spread of the infection stems from parenteral antischistosomal therapy and the use of unsterilized instrumentation during mass treatment (62) The Egypt Demographic and Health Surveys (EDHS) measured antibody prevalence in the adult population aged 15 to 59 years to be 14.7% in 2009 and 10.0% in 2015 (63) respectively substantially greater than the international level (64,65).

The cumulative prevalence of HCV infection in the population in Morocco was 1.58% (66)which was lower than the prevalence rates from adjacent countries such as Algeria (2.5%), Libya (3%), and Egypt (15-20%) (62,66,67,68). The viremic prevalence was 0.8% in Morocco, 1.0% in Algeria, 0.7% in Libya, and 0.9% in Tunisia as estimated in 2015 (22). The identified risk factors for HCV infection are age, dental hygiene, use of glass syringes, and surgical background. Before 1994, the correlation with blood transfusion was attributed to lack of surveillance, however over time, it was more commonly seen in older people, primarily due to iatrogenic transmission from inadequately sterilized instruments and re-use of supplies, which is considered to be the important cause in the general population. This risk of transmission is similar to the one in the general population during the outbreaks in the U.S. and European Union as recorded by the health care (66,69,70).

Table 3. — **Global hepatitis C virus (HCV) genotype variations in countries with economies in transition**

ECONOMIES IN TRANSITION	
RUSSIAN FEDERATION	1b, 3
SIBERIA	1, 3
UZBEKISTAN	1b, 3, 2, 1a

Table 4. — **Global hepatitis C virus (HCV) genotype variations in developing countries**

DEVELOPING COUNTRIES	
AFRICA	
NORTH AFRICA	
EGYPT	4, 1 other types, 1b
MOROCCO	2, 1b, 1a, 3, 4, 5
ALGERIA	1b, 2, 1a, 1 other types, 4, 3, mixed
LIBIA	1, 4
TUNISIA	1b, 4, 1a, 2, 3, mixed
EASTERN AFRICA	
KENYA	2, 1
ETHIOPIA	4, 2, 3, 1a, 1b, 1 other types, mixed
YEMEN	N.A.
SOUTHERN AFRICA	5, 1b, 3, 4, 1, mixed, 1a, 2
ZIMBABWE	N.A.
MAURITIUS	N.A.
TANZANIA	N.A.
PRETORIA	N.A.
WEST AFRICA	
MALI	
NIGERIA	1, 2
IVORY COAST	N.A.
CAMEROON	1, 4, 2
CENTRAL AFRICA	
DEMOCRATIC REPUBLIC OF THE CONGO	4, 2, 7
CENTRAL AFRICAN REPUBLIC	4, 3, 2
ASIA	
SOUTH-EASTERN ASIA	
CHINA	1,2,3,6
SOUTH KOREA	1b, 2a, 1a, 4, 6
PHILIPPINES	1a, 1b, 2, 4, 6
THAILAND	3, 6, 1a, 1b
INDONESIA	1, 2, 3, 4
MALAYSIA	3, 1, 2, 4, 6
INDIA	1, 3, 3a, 3b, 3g
PAKISTAN	2a, 2b, 3a, 3b, 4a, mixed (3a+1b)
BANGLADESH	N.A.
WESTERN ASIA	
SAUDI ARABIA	4,1, 2, 3
LEBANON	1b, 4, 3, 1a, 2, 5, 6
IRAN	1, 3
IRAQ	4,1
JORDAN	4, 1
LATIN AMERICA AND CARIBBEAN	
MEXICO	1, 2 (j, k, r), 3, 4, 5
ARGENTINA	1a, 1b, 2
PUERTO RICO	1a, 1b, 2b
CHILE	1b
SOUTH AMERICA	
BRAZIL	1a, 1b, 3a

N.A.: Not available.

Molecular biology

Genotype 4 alone constitutes about 94% of Egyptian HCV cases (63,71); the most common subtype of which is GT4a (90%) (71). Other common HCV types are

GT1 and GT1b (63). Morocco has predominantly GT2 and GT1b followed by mixed types, GT1a, GT3, GT4, and GT5 (22). According to the Eastern Mediterranean Regional Office (EMRO) of the WHO, North African Arab countries have two kinds of genotypes. Algeria was affected by GT1b, followed by GT2, GT1a, other subtypes of GT1, GT4, GT3, and mixed genotypes. Libya has mostly mixed genotypes. In Libya, GT4 and GT1 account for 32% each. The Nile River region is chiefly affected by GT4, along with Egypt and Sudan. The Maghreb region includes Tunisia and is predominantly subtype 1b. In Tunisia, the prevalence rate of GT1 is 75% and 22% for GT4. In detail, Tunisia's leading subtypes are GT1a, GT2, and GT3, and also mixed genotypes with a percentage of less than 10. GT4 is the major HCV genotype in a Sudan study analyzing patients affected by schistosomiasis (72).

Prevention

According to the standard dynamic model of prevalence decay suggested by Anderson and May in 1991, HCV infection rates in Egypt will rise more than 5% for at least the next 50 years. To meet the present challenge and decrease the long-term burden, Egypt has considered vaccine development (59), developed a national strategy for HCV management, and set up HCV prevention and cure programs (63). Egypt launched a strong National HCV cure program, planning to treat over 250,000 chronically infected people per year to reach a countrywide chronic infection prevalence of less than 2% by 2025 (73). The changes in blood screening and infection management over the next twenty years might decrease HCV propagation. In Morocco, the efforts to prevent HCV transmission have been via health education and nosocomial risk prevention (66). In North African Arab countries that are mainly affected by HCV GT4, notoriously resistant to HCV treatment, prevention strategies need to be implemented (72).

West Africa

The major countries discussed in this review are Mali and Nigeria (6). The prevalence of and genotypes of Ghana, Guinea, Burkina Faso, and Benin are included as well.

Epidemiology

The Malian population is affected by HCV mainly due to contamination of supplies for medical procedures more than through blood transfusions (74). The seropositive rate is higher in older women as compared to younger ones (33.2% vs 13.9%), and the rural population is more susceptible than the urban regions (7% vs 1%) (74). According to Bekondi et al. in 2010 (75) and Nagalo et al. in 2011 (76), the HCV prevalence is approximately 15%, the highest among the countries in West and Central Africa.

Most of the research in Nigeria is related to the serological characterization of selected demographic groups like prisoners, patients with diabetes mellitus, blood donors, HIV-infected individuals, patients with chronic renal disease, or sickle cell anemia. In West Africa, according to Millar & Foege's published paper (1969), medical services facilitated through stationary facilities might have led to the spread of dangerous injection procedures between the 19th and mid-20th centuries. Previous studies have identified a large HCV seroprevalence rate, ranging from 1.9% among pregnant women in Benin City to about 14.5% among apparently healthy individuals with a family history of diabetes in Plateau State or among HIV-positive patients in Lagos (77,78, 79, 80). Nigeria had a viremic prevalence of 1.4% (1.0 - 1.4) in 2015 (22). For the WHO Africa Region, Hepatitis Scorecard 2019 reported HCV prevalence for various countries in West Africa as follows: Mali 3.1%, Nigeria 2.1%, Cameroon 0.7%, and Ivory Coast 1.7% (81).

Molecular biology

Nigeria has about 85% of HCV variants that belong to GT1, although only 15% of HCV variants recovered from other West African countries belong to this GT. The GT1 and GT2 variants found in Ghana, Guinea, Conakry, Burkina Faso, Benin Republic, and Guinea Bissau are different strains endemic in this population (82, 83). In Cameroon, the different variants of GT1 and GT4 are in equal proportions, with GT2 significantly lower in 2015 (22). Based on its geographical location and population density, Nigeria most likely had HCV transmission occur from West to Central Africa. The variation of genotypes is mostly due to the genetic drift and progressive depletion of HCV variants over time. The genetic mechanism and characterization of HCV strains in Nigeria are crucial to designing specific vaccines. This study of genotype distribution in Nigeria is also helpful to predict the molecular epidemiology and the evolving strains in the continent of Africa (77). In Malian medical centers, hygiene is required in rural areas to mitigate nosocomial propagation (74).

East Africa

The countries listed under this review are Yemen, Sudan, Kenya, Ethiopia, Somalia, and Djibouti (6).

Epidemiology

Compared to the national population and other MENA (Middle-East North Africa) countries, the HCV prevalence of Somalia, Sudan, and Djibouti is about 1% (84). Yemen has the third-highest HCV prevalence among MENA (85), but this prevalence is lower than in Egypt (14.7%) (86). The spread is related to procedures like dialysis (87), blood transfusion, and donation

(88). In 2015, the viremic prevalence in Yemen, Kenya and Ethiopia were 0.8% (0.5-0.9), 0.2% and 0.6 %, respectively (22).

Molecular biology

HCV GT4 with subtypes e, c/d were detected from a cohort of patients with schistosomiasis in Khartoum, Sudan (89). No data is available on Yemen. Kenya has different variants in GT1, particularly GT1a. Comparatively, Ethiopia is affected with GT4, GT2, GT3, GT1a, GT1b, other types in GT1, and mixed genotypes (22).

Prevention

The prevention in East Africa includes increasing the use of safety-engineered syringes for intradermal and intramuscular injections and screening of blood transfusions (90,91). To decrease the HCV infection and decrease the elimination goal by 2030, good and effective medical practices along with the use of safer blood products are mandatory. More studies should be conducted on the prevalence of PWID and IVDU in the Middle East and North African [MENA] Countries (92).

South Africa

Southern African Countries analyzed in this review include Zimbabwe, Tanzania, Mauritius, and Pretoria (6).

Epidemiology

In South Africa, prevalence rates range from 30% among PWID/ID using opioid substitution therapy (93) in Tanzania, 97% in Mauritius, and 72% in Pretoria. PWID/ID carried the highest HCV burden with marked geographic variations in Mauritius (94). HIV infection is a major cause of HCC in Zimbabwe. Young patients have a high prevalence of anti-HIV antibodies and a low prevalence of anti-HCV, while older patients have a high anti-HCV prevalence and low anti-HIV (95). The viremic prevalence of HCV in South Africa was 0.7% (0.4-0.9) in 2015 (22), 1.3% in Mauritius, and 1.6% in Zimbabwe, according to data collected in 2019 (40).

Molecular biology

GT1 was predominant in blood donors and young people less than 30 years of age (34%). GT5a was prevalent in patients (36%) and older subjects (96). GT1 and GT5 were at the highest proportions than other genotypes across all regions in South Africa, especially in blood donors, GT1 was predominant among Caucasians (43%) and GT5a among Blacks (54%) (96). In South Africa, prevalent genotypes include GT5, GT1b, GT3, GT4, GT1, mixed GT, GT1a, and GT2 (22). Specific genotype data is not available for Zimbabwe, Mauritius, Pretoria.

Prevention

The key populations of HCV-inflicted individuals in South Africa are sex workers, PWUD/ID, and homosexual men. Accordingly, South Africa has developed a national action plan to eliminate the global threat by 2030, by targeting these populations. PWUD/ID are provided with education regarding sterility, along with the opportunity for opioid substitution therapy. Preventative measures such as point of care testing and HIV screening should be mandatory and easily accessible as South Africa's standard of care; unfortunately, documentation of the successful implementation of said measures across the region is limited. To achieve their goal of HCV elimination within the next decade, political support and resource allocation for dedicated people in the key populations with proper implementation are imperative (97). According to the WHO hepatitis scorecard, Tanzania is on the path with the National strategic plan for viral and treatment programs but still has to work towards target 2020 testing for HCV. Mauritius is not on track with the national hepatitis strategic plan (81). In Tanzania, the existing OST (Opioid Substitution treatment) and NSP (Needle and needle programs) give a vital possibility to advance the screening, assessment, and linkage to HCV care (93). There are no specific programs and not much data available on prevention in Pretoria.

Central Africa

The countries discussed here are the Central African Republic and the Democratic Republic of the Congo (DRC).

Epidemiology

In 2015, the estimated viremic prevalence in the Central African Republic was 0.3% (0.2-0.4%) in 2015 (22), and 4.3% in the DRC in 2014 (25). The reported HCV antibodies (anti-HCV) prevalence range from 0.2% to 13.7% in the DRC, where the HCV infection is endemic. The subgroup analyses revealed that the prevalence rates of anti-HCV in blood donors and pregnant women were 2.7% and 3.3% (1.4-5.1%), respectively (98).

Molecular biology

The new genotype originated from the DRC is the prototype QC69 virus which is considered as GT7 and is different from GT1 to GT6 (99). The most common type in both the DRC and the Central African Republic is GT4; followed by GT2 and GT7 in the DRC, and GT3 and GT2 in the Central African Republic (22).

Prevention

HCV infection remains an issue of public concern in the DRC, manifesting a need for adequate hepatitis

control programs. A great deal of effort is required to eliminate transfusion-transmitted HCV throughout the country (98). According to the WHO scorecard 2019, the National Strategic Plan for viral hepatitis [HBV/HCV] was on track in DRC. The Central African Republic did not meet the targets of testing for HBV/HCV in 2020 and is not on track with Hepatitis treatment programs (81).

Southeast Asia

The Southeast Asian countries discussed in this present review constitute China, India, Pakistan, Bangladesh, Indonesia, Philippines, Thailand, South Korea, and Malaysia (6).

Epidemiology

The Asia Pacific region displays the highest percentage of Hepatitis C-related deaths, with 74% of global deaths occurring from liver cancer (100). The most prominent HCV feature in China is their dichotomous rates since there is a low prevalence rate in most areas, high prevalence rates in specific regions, and scattered and uneven distribution of cases in between (101). There has been a reported increase in HCV prevalence rates over the years. From 2006 with a national prevalence rate of HCV-antibody being 0.43%, the country's crude prevalence rate in 2015 nearly tripled to 1.4%. Data also shows the male prevalence rate is two times greater than that of females (102,103). Prevalence among populations with high-risk behaviors, especially among IVDU, continues to be higher (104, 105) than non-injection drug users. The prevalence of HCV IVDU is 70% in China (104,106) compared to 60% in the United States (107). The HCV-RNA positive prevalence was estimated as 13.7% for drug users (108) and their HCV viremic prevalence was estimated as 0.7% in 2015 (22).

Pakistan has an estimated HCV prevalence of 3.8% (22) in 2015, comprising 8.74 million people. This represents the second-largest population infected with HCV, after China (109).

In Bangladesh, HCV prevalence varies considerably, from 0.8% among truck drivers to 24.8% among IVDU (110) to 0.9% among women at an STD clinic (111). The overall prevalence for 2014 was reported to be 1% (25).

In India, screening is inadequately regulated, and contaminated blood products continue to be the main source of HCV transmission; the reuse of contaminated needles and syringes is considered unsafe because of inadequate sterilization and poor waste disposal (112). The prevalence in India was 0.50% in 2015 (22), with 70.38% of seropositive individuals older than 35 years, 18.05% aged between 12-35 years, and 5.55% aged less than 12 years (113). According to a West Bengal study, a prevalence of 1.5% was estimated in those greater than 60 years of age as compared to 0.31% prevalence in the age group less than 10 years (113,114).

For Indonesia, the anti-HCV prevalence, based on the National Basic Health Research (RISKESDAS) study in 2007, was estimated to be 0.8% (range 1.7%) in Nanggroe Aceh Darussalam to 1.7% in Sumatra Barat (26). The country had a viremic prevalence of 0.5%, according to data collected in 2016 (25).

In South Korea, the viremic prevalence in 2015 was 0.5% (22), less than the estimated adult HCV prevalence of 1.2% in 2013 and 1.29% in 2009 (26). Risk factors for HCV infection in South Korea, other than blood transfusion and history of acupuncture, have not yet been proven (115).

In the Philippines, according to data in 2015, the viremic prevalence is 0.6% (22). Infection rates are highest in rural areas and low-income populations (100).

In Thailand, 0.7% were infected with HCV according to data in 2015 (22). Epidemiological studies of HCV provide inconsistent data due to the selection of the studied population and areas (100) especially in the southern part of Thailand. High-risk groups like IVDU had 70-90% seroprevalence (100).

In Malaysia, an overall prevalence of 2.5% (743,000 people) was estimated; 1.1% of which were of Chinese descent, 2.9% were of Malaysian descent, and 0.6% were either of Indian descent or other ethnic groups (100). The disproportionate prevalence rates between ethnic groups in the country can be attributed to the uneven rates of IVDU within each subpopulation (100). The specific viremic prevalence of some countries in Europe is represented in Figure 1 and summarized in Table 1.

Molecular biology

China is one of the most affected regions of HCV infection in Southeast Asia. Among the HCV genotypes, GT1b and GT2a are prevalent in the Northern areas. GT1, GT2, GT3, GT6, and the subtype GT1b predominate in the Southern areas of the country (116). In recent years, the GT3 and GT6 are transmitting fast in the southwest and growing towards becoming the prevalent epidemic genotypes. Data suggests that this rising transmission is affected by IVDU and that perhaps the HCV genotypes common amongst IVDU are spilling over to the general population (117,118). In China, four HCV genotypes (119,120) and related 13 subtypes are prevalent, causing a severe public health burden to the government (116, 121). GT1b originated in 1968 and dispersed rapidly between the years 1968 and 1990. Many poorly-trained healthcare workers or non-professional entered the healthcare system throughout the Cultural Revolution (1966 to 1976) and the medical malpractice that ensued during this period has become known as the foremost reason for the overall increase in HCV spread. In 1975, other GT1b clusters began and spread quickly during 1975 and 1985, mainly because of contaminated blood products and blood (117,122,123). Phylogenetic analysis revealed that GT1b and GT2a are the main subtypes of HCV-positive patients from the coast of Putian, part of

central China (101). Moreover, sexual transmission is increasingly becoming the main route of transmission in the country's central region (124).

In Pakistan, while genetic heterogeneity most commonly was exhibited by the GT3a subtype, data analysis reveals that Pakistani isolates are also genetically different from the other global variants, due to their worldwide intermixing with various populations (125). The GT3a subtype is the most abundant HCV form in the Mardan population of Pakistan, followed by GT3b, GT2a, GT2b, GT4a, untypeable, mixed, GT1a, and GT1b. The overall prevalence of HCV in the population of Mardan was significantly higher in females (60.2%) than males (39.7%). The most frequently noted mixed genotype was GT3a plus GT1b, which was more prevalent in males (126).

In India, the HCV infection with GT3 was predominant in North, West, and East Indian populations, whereas GT1 was shown to be prevalent in South India (113). Subtype GT3a was found from the outbreak in Anantnag in February 2013, and subtype GT3b spread from the outbreak in Srinagar in May 2015. This geographical distribution of HCV GT3a and GT3b is similar to previous reports from North India (127,128,129,130). Another atypical subtype GT3g was found in one of the Kulgam outbreaks in India (130,131).

The different genotype distribution patterns discussed here are briefly summarized in Table 4. GT1 predominates in Indonesia, followed by GT3; the genotype distribution is as follows: GT1 (68%), GT2 (9%), GT3 (9%), GT4 (4%), and others (10%) (26). In South Korea, the most prevalent form of HCV is GT1b, followed by GT2a (115), GT1a, GT4, and GT6 (22). In the Philippines, GT1a predominates over GT2, GT1b, GT4, and GT6 (22). In Thailand, the principal HCV types are GT3, followed by GT6, GT1a, and GT1b (22). In Malaysia, GT3 (62.3%) is the most common type, followed by GT1 (35.8%), GT2, GT4, and even GT6 (22).

Prevention

A well-known risk factor for the Asian spread of HCV is the overuse of intravenous injections, especially among those cultures that consider injectable medication as more effective than orally administered ones (100).

Some countries have a national plan or strategy to fight HCV infection, such as Pakistan, India, and Indonesia (100,132). An estimated 90% reduction in HCV infections in Pakistan could be achieved by 2030 through an organized and aggressive approach to prevention, screening, and treatment (100,133) to improve awareness, the Pakistan Association for the Study of Liver Diseases called Hepatitis Education, Prevention, Advocacy, Information, Diagnosis (HEPAID), was designed in 2014. Moreover, the Yellow Warriors are a community-based hepatitis patient group in the Philippines whose target is improving the lives of people with hepatitis (100). In Indonesia, the government began a comprehensive 5-year plan to decrease the spread of viral hepatitis (100).

It is of note that the cost of HCV drugs is usually not covered by many health insurance providers (100) and that governments in Asia leave many patients to pay large out-of-pocket expenses (100). Some of the preventative measures that can be employed to control HCV rates in Bangladesh, India, Indonesia, Malaysia, Pakistan, Philippines, and Thailand include the following: policy and advocacy (eg: galvanize a multi-stakeholder advocacy base, elevate viral hepatitis to the ranks of other infectious diseases) (100,134), reliable data to manage policy (e.g. invest in improved surveillance for HCV infection, conduct local studies on the economic impact of different strategies), and harm reduction strategies aimed at prisoners and IVDU (e.g. leverage existing programs aimed at HIV to extend to HCV prevention in prisoners and people who inject drugs) (100). However, due to the diversity in culture and infrastructure, these measures may not be generalized to all of the South East Asian countries.

Western Asia

The Western Asian countries include Saudi Arabia, Iraq, Iran, Lebanon, and Jordan (6).

Epidemiology

As estimated by the WHO, approximately 17 million people in Eastern Mediterranean countries are HCV carriers (46). The occurrence of the HCV epidemic in Egypt affected its genotype distribution pattern in its neighboring country, Libya. In Iran, a viraemic prevalence of 0.2%was noted in 2015 (22). The Arabian Peninsula region has a high inflow of foreign workers, so HCV infection should be treated with utmost caution due to variable genotypic prevalence (72). In 2015, the viremic prevalence was estimated to be 0.3% in Saudi Arabia, 0.2% in Iraq, 0.2% in Lebanon, and 0.3% in Jordan (22) as shown in Figure 1 and Table 1.

Molecular biology

Eastern Mediterranean Regional Office (EMRO) countries show a diverse pattern of HCV genotype distribution. An enormous number of Afghan immigrants make frequent trips between Iran, Afghanistan, and Pakistan due to unstable military and political circumstances, which established the grounds for developing diverse HCV genotype patterns in Afghanistan (135). GT1 and GT3 are found to be most prevalent in non-Arab countries (Iran, Pakistan, and Afghanistan) (72). Middle-East Arab countries showed a predominance of GT4 and GT1, with two variable distribution patterns; GT1 was found with higher frequency in Iraq, Jordan, Lebanon, Bahrain, and the United Arab Emirates, while GT4 was the most common in Saudi Arabia, Kuwait, Qatar, Syria, and Palestine (72). In Iran, the dominant genotype is GT1, followed by GT3 (26).

The other common genotypes found in Saudi Arabia, other than GT4, are GT1, GT2, and GT3 (22) as listed in Table 4.

Latin America and the Caribbean

In the mid-1980s, Latin America witnessed its first HCV epidemic outbreak which was linked with HIV emergence when paid blood donation was in practice (136,137). Unfortunately, only less than 2% of infected Latin Americans currently have access to HCV medications, in the scenario of a reduced number of practicing hepatologists that probably reflects the limited resources of the healthcare system against the hazard of HCV (137). Indeed, in many developing countries, including Mexico, for the lack of accessibility to highly effective antiviral drugs, the HCV-related mortality rates seem to persist (138).

Epidemiology

The primary source of transmission identified in Central and South America is parenteral (139). The prevalence of Hepatitis C is studied in these countries based on socioeconomic aspects (140). For Rio de Janeiro in Brazil, cocaine is the drug of choice for IVDU (141), and the viremic prevalence of this niche population was 0.9% in the year 2015 (22). Limited data is currently available on HCV prevalence in Argentina although some studies showed between 0.1% to 5.6% and it was noticed up to 2.2% to 7.3% in highly endemic regions (142).

Prevalence rates of 1.2% and 1.4% have been reported among the general population in Mexico (138), and the viremic prevalence was 0.4% in 2015 (22) as represented in Figure 1 and Table 1. However, in 2007, much higher rates of 2.0% and 1.5% have been documented in North and South Mexico, respectively (138). A cumulative incidence rate of HCV per 100,000 residents peaked at 5.32 in men in the age group 50-59 years and 5.33 in women between 60-64 years (12).

Molecular biology

In the Caribbean and South-Central America, GT1 is the most prevalent (140). HCV subtypes GT1a and GT1b were found in Brazil during 1940-1950 and 1820-1920, respectively.

GT1b infections seemed to be the prevailing genotype in the 1960s, whereas GT1a infections appeared to have emerged in the early 1970s (143). There is a unique risk behavior profile among IVDU subgroups, which could ultimately aid the transmission of non-GT1a subtypes.

The subtype GT1a infections reached a peak in the 1980s (37.5%) and remained stable thereafter (25% in the 1990s and 37.5% in 2000) (143). GT1b was the most common infection in former years, then decreased in prevalence over time (32%, 34%, 18%, and 25% in the 1970s, 1980s, 1990s, and 2000, respectively).

Subtype GT3a infections were the most prevalent in the 1970s (40%) and 1990s (57.1%). GT1a (10%), GT1b (50%), and GT3a (40%) were already seen in IVDUs who started injecting drugs during the early 1960s (141). In Mexico, GT1 continues to be found among blood donors, mostly in patients with tattoos and surgeries (138). However, evidence shows the emergence of GT3 in the North and Center-West region related to HCV transmission due to injection drug abuse (138). Moreover, two non-endemic genotypes, GT4 and GT5, have been recently reported in the East/Center/West regions of Mexico (138). Additionally, GT2 subtypes j, k, and r have also been reported (138), as summarized in Table 4. The advent of these GTs might be due to higher temporal or permanent human migration with concomitant use of highly sensitive DNA sequencing methods (138). GT1b is most prevalent in Argentina with evidence of the existence of GT1a and GT2 subtypes as well (144). Puerto Rico has reported a prevalence of GT1a (39.8%) followed by GT1b (27%) and GT2b (9.8%). Similarly, GT1b (82%) has been reported to be most prevalent in Chile (145). In Venezuela, a decline has been observed in HCV genotype 1b prevalence from 1994-1995 to 2004-2005 period followed by a reduction in HCV GT2b prevalence in the last decade (2014-2015) (28).

Prevention

Diagnosis of HCV is established by third-generation immunoassays and RNA-HCV nucleic acid amplification tests; these diagnostic techniques have improved blood transfusion safety (137). In Brazil, the STD, AIDS, and Viral Hepatitis Department is a part of the Ministry of Health's Surveillance Secretariat working to decrease HIV/AIDS and viral hepatitis transmission and to promote a better quality of life among patients (147). The main priority is prevention and early diagnosis of viral hepatitis infections and HIV along with amelioration of healthcare networks and lines of treatment of such infections, aimed to improve and develop surveillance, information, research, and promotion of universal access to medication and condoms (147). The secondary prevention methods seek to avoid the progression of the disease in already-infected people (147). The Brazilian Ministry of Health places emphasis on two generations of people: young people because of IVDU and tattoo practice/piercings, and adults over 45 years old due to their late diagnosis with probable exposure to HCV from blood transfusions performed before blood screening in 1993, hospital procedures such as hemodialysis, or history of IVDU (147). Several public campaigns have been organized to increase awareness of viral hepatitis and to encourage individuals with possible exposure to get free diagnostic tests in Counselling and Testing Centres; there has also been the distribution of free testing kits to these centers since 2011 (147). In Puerto Rico, hepatitis C prevention should be set as a priority for public health authorities by maintaining focus on

raising awareness, education regarding prevention, strengthening the reporting system on epidemiology, and making cost-effective diagnosis and treatment more accessible (147)..

The strategies that can be implemented in Latin America to counter challenges include, a massive educational drive and awareness campaigns should be conducted targeting the general population and frontline health workers. It would be beneficial to make rapid diagnostic tests and the first line of care more affordable. Moreover, Screening programs available in each Latin American country must be expanded according to the prevalence rate; b) To provide more healthcare access to the individuals from liver experts, infectious diseases specialists to manage the disease burden efficiently. Specific training can be provided to physicians to effectively increase manforce in the healthcare sector; c) Implementing treatment with increased availability of DAAs is required due to high variability throughout Latin America. Both Brazil and Argentina have national health care programs guaranteeing treatment to all patients with HCV; d) Generic drugs as per WHO standards can help reduce treatment costs. Also, centralized purchase of large-volume drugs and regional purchases through the Pan-American Health Organization could result in lower costs that can help in achieving the goal of affordable treatment (149).

ECONOMIES IN TRANSITION

According to the United Nations definitive report titled, "World Economic Situation and Prospects 2020," some countries with economies in transition include the Republic of Moldova (ROM), Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, and Montenegro (6).

Epidemiology

The prevalence of chronic hepatitis C in 2019 was 2.7% in the ROM, 4.1% in Uzbekistan, and 2.2% Russian Federation (40). Some of the high-risk groups include hemodialysis patients, female sex workers, IVDU, HIV-infected patients, healthcare workers, and blood donors. These high-risk groups have seroprevalences of 43.2%, 22.6%, 53.6%, 34.2%, 4.4%, and 1.44%, respectively (150). A recent meta-analysis and systematic review measuring the epidemiology of HCV in Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan) reported prevalence to be around 9.6% in Uzbekistan, 2.6% in Tajikistan, 2% in Kyrgyzstan, and 0.7% in Kazakhstan (151); no studies were identified from Turkmenistan. Accordingly to Chan et al, there is a lack of studies published that focus on HCV prevalence among active IDUs in Kazakhstan (152). The viremic prevalence in Russia according to data collected in 2015 was 3.3% (22). The viremic prevalence of a few countries is shown in Figure 1 and Table 1.

Molecular biology

The predominant HCV in ROM is GT1b, while HCV types GT2, GT3, and GT4 viruses also circulate in the country at lesser frequencies (1-2%) (150). GT1 (52.6%) and GT3 (38.0%) are the most frequently circulating strains, with some evidence for GT2 (152). The Uzbekistan genotypes are GT1b, GT3, GT2, and GT1a (22). The different genotypes in few countries are listed in Table 3.

Different population groups from the Novosibirsk region of Western Siberia were examined for the prevalence of HCV infection. GT1 prevailed in an older age group (75% among 51-60 years), and GT3 was most prevalent in young people (51.4% in 16-20 years) (153).

Acute and chronic hepatitis C are registered separately in the Russian Federation. A low incidence of HCV cases in all territories of the country was reported, while a notable rise in the cumulative rate of chronic hepatitis C cases was observed, which was higher especially in groups aged 30-49 years (154). Several HCV genotypes are reported to be circulating in different regions of the country; GT1b had a prevalence of 55-80% in almost every part of the country, and GT3 had an expanded circulation among the youth due to increased intravenous drug abuse (154). A recent Bayesian analysis showed that the most prevalent subtype in IVDU in Montenegro was GT3a (155).

Prevention

Republic of Moldova (ROM)

To decrease prevalence, morbidity, and mortality of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma, the Ministry of Health, in alliance with the National Center for Public Health of ROM, has developed a National Program for control of viral hepatitis C (including B and D) (150).

Kazakhstan

Kazakhstan has employed Peg-IFN for the treatment of the majority of the country's HCV cases (156), but the prevalence of chronic HCV is still projected to remain relatively static and morbidity and mortality are still projected to increase significantly (157). As a way to combat these projections, Kazakhstan has implemented needle and syringe programs (NSP), which has proven to have a good reach amongst IDU (158).

Kyrgyzstan

In 2016, at the request of Kyrgyzstan's Ministry of Health, the WHO provided an assessment on the country's hepatitis-related surveillance, national policies, and services. The WHO reported that it is not clear whether the country's surveillance system is adequate to monitor

HCV trends. It also reported that while the Prevention and Treatment of Viral Hepatitis in the Kyrgyz Republic for 2011-2015 were implemented, it was only done to a limited extent. The primary reason for this was attributed to a lack of financial backing. The WHO also noted that Kyrgyzstan has attempted to implement a new program targeting HCV for 2016-2022, but the implementation has been delayed due to a lack of guidance, time, and motivation from leadership (159).

Turkmenistan

In 2018, WHO announced the first-ever Turkmenistan national strategic plan on achieving elimination of viral hepatitis, via a coordinated and comprehensive national effort (WHO) (160). Specifics of the strategy are not readily available.

Uzbekistan

While the WHO has acknowledged Uzbekistan leadership's strong commitment to establishing a national viral hepatitis program, Uzbekistan's strong political commitment and the Research Institute of Virology's great technical leadership. These attributes will enable the quick establishment of a successful long-term national viral hepatitis program. Limited sources are detailing any organized national strategy to prevent HCV. However, insufficient funding has been identified as a significant barrier to achieving WHO HCV elimination targets in Uzbekistan. As such, in 2019, the country's Research Institute of Virology and Ministry of Health, in partnership with the Center for Disease Analysis Foundation, launched a pilot program in Tashkent of an innovative catalytic funding model focused on HCV elimination via a low upfront investment and reduced overall cost (161).

Montenegro

There are limited to no resources specifically detailing Montenegro's national efforts towards HCV prevention.

HCV Treatment

Significant research and developmental innovations have transformed the area of viral hepatitis in recent years. Pangenotypic HCV antivirals are being introduced. Products that would similarly quicken elimination include more cost-effective point-of-care, new virological tests for HCV, and vaccines to prevent viral infection (4). The discovery of HCV therapy became viable in 1989; several types of interferon, along with ribavirin (RBV) have proven to have an increased cure rate between 40-65%, though they have been related to severe adverse effects.

Having been shown to cure the greatest number of people with HCV infection, a huge improvement was specifically seen with the advent of new oral DAA therapy (1,4). Beginning in the year 2011 and onwards, more promising DAA drugs have been introduced; the first generation (e.g telaprevir and boceprevir) and second-generation (e.g sofosbuvir and simeprevir) DAAs target specific molecules of the HCV life cycle, eradicating it in more than 90% to 95% of the patients who receive the antiviral treatments regardless of GT (162). In 2013, sofosbuvir was first registered in the U.S. Not later than October 2015, eight separate DAAs had been approved by the WHO to treat HCV infection (4).

In 2015 HCV infection was diagnosed in 20% of the population worldwide, the Americans had the greatest (36%) and Africans the lowest prevalence (6%), although the latter percentage may be considered not so reliable, probably due to the reduced accessibility to HCV screening opportunities among the African population. Unfortunately, only 7% of diagnosed individuals globally undergo antiviral treatment (4). The Eastern Mediterranean Region accounted for the largest proportion of those who started on treatment (12%), also boosted by the large-scale elimination plans in Egypt (163); among those who started treatment in 2015, about half received DAAs. Given that more people were initiated on treatment the following year, namely 2016, the WHO global report on access to HCV treatment estimated that about 1 million people had accessed DAAs in selected countries (164). Accordingly, the WHO updated its guidelines in 2018, and now recommends DAAs for HCV treatment (1).

Currently, most of the DAAs available are inhibitors of NS3/4A protease, the NS5A protein, and NS5B polymerase. Glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir are HCV protease inhibitors. Sofosbuvir is a nucleotide polymerase inhibitor and Dasabuvir is a non-nucleoside polymerase inhibitor. NS5A are generally elbasvir, ombitasvir, ledipasvir, velpatasvir, pibrentasvir, daclatasvir. Several DAAs are available as fixed-dose combinations such as elbasvir-grazoprevir, sofosbuvir-velpatasvir, glecaprevir-pibrentasvir, ledipasvir-sofosbuvir, ombitasvir-paritaprevir-ritonavir, and sofosbuvir-velpatasvir-voxilaprevir [1]. DAA treatment duration is short, as it usually ranges from 12 to 24 weeks, based on the presence or absence of liver cirrhosis (4). However, it is important to note that there is a wide variation in terms of access to DAAs from country to country. The projected proportion of those with a sustained virologic response (SVR) was the highest in the Region of the Americas (88%) and the lowest in the Western Pacific Region (63%). These regional differences in SVR reflect more probable differences in access to newer DAAs (4).

HCV Treatment by region

The following information presents distinct treatment modalities to the specified regions.

Asia and Pacific

In Australia, the treatment experience differs from most other countries, as it was one of the first countries that allowed subsidized access to DAAs therapy for the entire population (165).

The country of New Zealand has implemented PLATINUM C, an HCV treatment registry and research platform for assessing the comparative effectiveness of alternative interventions for achieving virological cure (166), and has successfully used generic DAAs, such as sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, and ribavirin, to treat the condition to a level of safety and efficiency comparable to branded DAAs (167).

Europe

In Europe, all-oral therapy with NS5A inhibitors in combination with nucleoside analog inhibitors of NS5B can reach a complete HCV clearance (SVR) in 85-100% of patients regardless of HCV stage of disease, genotype, pre-existence of viral resistance, and response to previous therapy (168, 169, 170, 171). This includes the combinations of sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, sofosbuvir with daclatasvir, and a combination of ombitasvir, paritaprevir and dasabuvir (172).

Africa

The standard treatment protocol available in EMRO countries is a combination therapy of pegylated interferon (Peg-IFN) α-2a and RBV. The use of new DAAs is not routinely adopted in most of the countries belonging to this region. Response rates to the standard treatment protocol are higher among those infected with genotypes 2 and 3 while GT4 and GT1 are the most resistant forms and need greater effort to improve the treatment strategies since they are highly prevalent in EMRO countries (69).

In the North African Arab Countries, GT2 and GT3 show higher response rates to treatment with Peg-IFN α-2a and RBV; GT4 and GT1 are hard to treat with the available combination therapies (69).

Southeast Asia

In Southeast Asia, the SVR rates obtained with Peg-IFN plus RBV treatment are high, despite the significant proportion of untreated patients with HCV infection (173). In Indonesia, Peg-IFN and RBV as well as generic sofosbuvir will be available soon in government-funded programs (174). These are the standard treatment regimens in the following countries since 2013: Pakistan, interferon alfa, Peg-IFN, and RBV; Thailand, Peg-IFN and RBV; India, interferon-α, Peg-IFN, and RBV; Bangladesh, interferon-α, Peg-IFN, RBV, boceprevir, and telaprevir; Malaysia, Interferon-α, Peg-IFN, and RBV (174).

Latin America and the Caribbean

In the Latin American countries, they have licensed the use of DAAs such as boceprevir, telaprevir, simeprevir, and sofosbuvir in limited regions (51, 162). Treatment in Brazil is usually based on the combined antiviral therapy that was introduced in 2015 (175). In Mexico, there is limited access to new generation DAA agents, and currently, only boceprevir and simeprevir have been approved as triple therapy in combination with Peg-IFN plus RBV in patients with GT1 chronic hepatitis C (176). For a decade in Argentina pegylated interferon (PEG) with ribavirin (RBV) has been used as standard drugs for HCV treatment. As per recent updates, there has been an addition of Protease inhibitor (PI) therapy to the PEG-RBV regimen, for HCV GT1 treatment boosting the SVR from 40%-50% to 67%-75% (177, 178).

HCV Treatment outlook

In the nine countries of Iceland, Hungary, Iran, Indonesia, Latvia, Lebanon, Lithuania, Pakistan, and Saudi Arabia, the total number of HCV-infected individuals are either expected to increase or continue to remain flat until 2030. It has been predicted the achievement of HCV elimination with a treatment rate of nearly 10% (over a 90% drop in total infections) by 2030 (133). Also, it highlights that switching to high SVR percentages antiviral therapies would reduce HCV-related morbidity and mortality in many countries. This impact is magnified in countries with higher treatment rates of more than 2.0% (e.g. Estonia, Iceland, Japan, Hungary, Iran, Latvia, Slovenia, and Lebanon) (133).

Recent data from the ASTRAL 1 and ASTRAL 2 studies showed high-level efficacy and tolerability in patients from the UK, Australia, and New Zealand with GT1, GT2, GT4, GT5, and GT6 undergoing a 12-week regimen with sofosbuvir and velpatasvir (179). The ASTRAL 3 study indicated complete virus clearance in 95% of patients with GT3 infection by a 24-week course of sofosbuvir and velpatasvir with a similar safety profile (180). The ASTRAL 4 study also provided evidence of safety and effectiveness (>80% efficacy, <20% severe side effects) in patients with decompensated liver disease (180). The combination of sofosbuvir with other NS5A inhibitors such as daclatasvir proved to be beneficial and safe in HIV-infected people (181, 182).

Unusual subtypes

Despite the goal of HCV eradication by 2030 is ever closer to fulfillment, the increasing emergence of rare/unusual subtypes of genotypes 1, 2, 3, or 4 in the next future could slow down the process of elimination of HCV due to failure of achieving SVR especially in low-

and middle-income countries (183). Indeed, Africa and Asia harbor a high genetic diversity of HCV strains (183).

Some HCV subtypes display genetic polymorphisms that give high-level resistance to DAAs, making them unresponsive to at least several of the currently available antiviral regimens.

Epidemiological studies reporting the prevalence of these rare/unusual HCV subtypes in their regions of origin, as well as in migrants from these regions, are needed. Pending definite data on their susceptivity to pan-genotypic dual therapies (e.g. sofosbuvir/velpatasvir and glecaprevir/pibrentasvir), patients infected with rare/unusual genotypes should be treated with a triple combination of sofosbuvir plus an NS5A inhibitor plus a protease inhibitor.

HCV vaccination

Vaccines represent the most cost-effective strategy to prevent infectious diseases. Indeed, research development for a specific vaccination even to Hepatitis C is still currently ongoing (183).

However, HCV is a challenge for vaccine development due to the high RNA viral sequence variation, requiring the ability to provide full protection from all seven HCV genotypes, including the more than 50 subtypes identified worldwide.

In detail, many prophylactic vaccines are in clinical and preclinical development, with the most advanced involving the T cell-based approach (184,185).

The current results imply that an HCV vaccine, even if not completely efficacious, will play an adjuvant role in HCV elimination over the next 15-20 years (186, 187).

Author Contributions

Guntipalli, Pakala, Gara, Ahmed, and Shahini were the guarantor of the study; Guntipalli, Pakala, and Gara contributed equally to this study; Guntipalli, Pakala, Gara contributed to study conception, design, and data acquisition; Guntipalli and Ahmed supervised the manuscript; Sarfraz, Solimando and Shahini provided critical reviews to the manuscript; Ahmed, Coronel, Sarfraz and Shahini, assisted in formatting, editing and revising the manuscript; all authors interpreted the data and wrote the first and final draft of the manuscript; all authors revised the article critically for important intellectual content and they gave final approval of the article to be published.

Statement of Ethics

Compliance with ethical standards.

Disclosure Statement

The authors declare no conflict of interests for this article.

Funding sources

This work was not funded.

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