Special Communication

Epidemiology, Disease Burden, and Treatment Strategies of Chronic Hepatitis C Virus Infections in Saudi Arabia in the New Treatment Paradigm Shift

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ABSTRACT

Background/Aims: Around 101,000 individuals are estimated to be viremic for chronic hepatitis C virus (HCV) in the Kingdom of Saudi Arabia (KSA) in 2014; however, only about 20% have been diagnosed. We aim to assess baseline epidemiology, disease burden, and evaluate strategies to eliminate HCV in KSA. **Materials and Methods:** The infected population and disease progression were modeled using age- and gender-defined cohorts to track HCV incidence, prevalence, hepatic complications, and mortality. Baseline assumptions and transition probabilities were extracted from the literature. The impacts of two scenarios on HCV-related disease burden were considered through increases in treatment efficacy alone or treatment and diagnosis. **Results:** In 2030, it is estimated by the base scenario that viremic prevalence will increase to 103,000 cases, hepatocellular carcinoma (HCC) to 470, decompensated and compensated cirrhosis cases to 1,300 and 15,400, respectively, and liver-related mortality to 670 deaths. Using high efficacy treatment alone resulted in 2030 projection of 80,700 viremic cases, 350 HCC cases, 480 liver-related deaths, and 850 and 11,500 decompensated and compensated cirrhosis cases, respectively. With an aggressive treatment strategy, in 2030 there will be about 1,700 viremic cases, 1 HCC case, about 20 liver-related deaths, and 5 and 130 cases of decompensated and compensated cirrhosis, respectively. Delaying this strategy by one year would result in 360 additional deaths by 2030. **Conclusions:** HCV in KSA remains constant, and cases of advanced liver disease and mortality continue to rise. Considered increases in treatment efficacy and number treated would have a significantly greater impact than increased treatment efficacy alone. The projected impact will facilitate disease forecasting, resource planning, and strategies for HCV management. Increased screening and diagnosis would likely be required as part of a national strategy.

Key Words: DAA, disease burden, epidemiology, hepatitis C, hepatitis C virus, mortality, prevalence, Saudi Arabia, treatment

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Hepatitis C virus (HCV) infection is the major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) and is the leading indication for liver transplantation worldwide.[1] HCV remains a major global public health and economic burden. It is estimated that about 130–150 million people are chronically infected with HCV and about 500,000 people die each year from HCV-related liver diseases.[2,3] In Eastern Mediterranean countries there are about 21.3 million

HCV-infected patients.[4] The prevalence in the Kingdom of Saudi Arabia (KSA) is not well established; however, blood donor screening data indicates prevalence rates of 0.4%–1.1%.[5] In a cross-sectional study of a mainly young population, as part of a premarital screening policy, an average prevalence of HCV infection was 0.33%.[6] Genotype (G) 4 is most prevalent and accounts for up to 60%, followed by G1 for up to 25.9%.[7,8] Minimal to moderate (Metavir, F0-2) fibrosis stages constitute about two-thirds of HCV in Saudi patients.[9] The treatment aim in patients with chronic HCV is to eliminate the virus, thus reducing the risk of all-cause and liver-related death, need for liver transplantation, HCC, and liver-related complications. The treatment strategies for HCV infection have progressed considerably during the past 2 years due to the availability of new, highly effective, all oral, direct-acting antiviral (DAA) medications.

Recently, the Saudi Association for the Study of Liver diseases and Transplantation (SASLT) issued a position statement to address concerns related to the feasibility and cost of treating all chronic HCV patients at Saudi health care organizations. It was also intended to be a guide for drug approval at these health care institutions. The statement conclusion was that HCV antiviral therapy should be prioritized for patients in most need of immediate viral clearance.[10]

HCV epidemiology data from KSA are scarce and are often reported in different years from a small sample size. This has made it essential to have a mathematical model that can be used to estimate the HCV-infected populations in the country in a given year. The aim of this study was to estimate the total number of HCV infections, new infections, number diagnosed, treated, and cured as well as mortality and treatment protocols in 2014. Furthermore, we aimed to estimate the current and future disease burden (2014–2030) if the existing treatment paradigm and response rate were continued, and to also develop treatment strategies that consider the actions necessary to control or eliminate HCV infection in the future. The results are not directed to instruct the application of these specific strategies, but rather to present possible outcomes should similar intervention plans be put into action.

MATERIALS AND METHODS

Methods for reporting historical hepatitis C virus epidemiology

The historical epidemiology of HCV was obtained through a literature search of all studies reporting the epidemiology, age, and gender distributions of infected subjects, total number of HCV cases diagnosed, treated, and cured in KSA between January 1990 and December 2014. Embase® and PubMed databases were searched by one individual for terms "Saudi Arabia" and "hepatitis C." Duplicate records were removed and abstracts were reviewed and screened based on exclusion and inclusion criteria. Exclusion criteria included different country population; no relevant data (HCV-related and epidemiological); case studies, opinion letters, and animal studies; high-risk study populations (except for past blood transfusion and injection drug use); and if no abstract or article could be found. Inclusion criteria (required) included Saudi study population and relevant data (HCV-related and epidemiological). Full articles of the studies not screened out were further reviewed with additional eliminations. All remaining studies that reported relevant data for inputs to the computer model were considered.

A panel of Saudi researchers, clinicians, and health systems experts was convened to provide unpublished data, local conference proceedings, and grey literature (eg, government reports) and to assess this body of evidence (including the results of the literature search). Individuals were identified to participate based on contribution to prior published research on the subject and colleague referrals. Factors in deciding the highest quality data included population type and representativeness to the general population; scope and representativeness to the national population, sample size, year of study; and any additional biases as pointed out by the authors. When no input data were available, analogues (data from countries with similar populations and health care systems) or expert estimates based on clinical and research experience were used. All data inputs were decided on by group consensus among the expert panel. Ranges were used when uncertainty existed with inputs, with wider ranges indicating greater uncertainty; these ranges were calculated using sensitivity and Monte Carlo analysis using Crystal Ball®, (Oracle Corp., Redwood City, CA, USA) an Excel® add-in. The term viremic was used to emphasize the presence of HCV virus (HCV-RNA positive). The term incidence does not refer to newly diagnosed cases, but rather absolute number of new infections occurring in a given year, whether diagnosed or not. HCC refers to the total number of viremic HCV-related HCC cases, rather than new cases or HCC related to other etiology. Additionally, all reductions by disease stage were assumed to occur among the viremic HCV population. Because data collection spanned a wide range of years, care was taken to report the year of collection for various data points. Recently, a modeling approach was used to analyze the HCV-infected populations (viremic, diagnosed and treated) in different countries, including KSA, during 2014.[11] In this analysis, United Nations (UN) population data were applied by age, gender, and five-year age cohort.[12] The annual number of liver transplants was collected from the Saudi Center for Organ Transplantation (SCOT) database and adjusted for the percentage attributed to HCV.[13] Since the number of total and newly diagnosed cases in KSA was not available, expert panel input was used. Diagnosis rates from known

countries (analogues) were provided to the Saudi expert panel, and the panel selected one or more countries that had similar profiles to KSA. It was assumed that the viremic rate among the diagnosed population was the same as the total population, and the same viremic rate was used to estimate the number of viremic-diagnosed individuals.

Statistical analysis, modeling, and methods for reporting hepatitis C virus disease burden

The magnitude of the hepatitis C virus-infected population

We utilized a disease progression model constructed in Microsoft Excel® (Microsoft Corp., Redmond, WA, USA) to quantify the size of the HCV-infected population, by the liver disease stages, from 1950 to 2030. The model was set up for sensitivity and Monte Carlo analysis using Crystal Ball®, an Excel® add-in by Oracle (Oracle Corp., Redwood City, CA, USA). Beta-PERT distributions were applied to all inputs limited by uncertainty. The Excel® optimization add-in, Frontline Systems' Solver®, was used to calculate the number, age, and gender distribution of the annual acute infections.

It started with the annual number of acute infections that progressed to chronic HCV (viremic) infection while factoring out those who spontaneously clear the virus [Figure 1]. These new cases, along with all chronic infections from preceding years, were then followed through the disease progression. The model's scope extended to HCV-RNA positive cases only. Nonviremic (negative HCV-RNA) cases were excluded even though they would test positive to HCV antibodies and may still reach more advanced stages of liver disease.[14] The total number of cases was tracked by age and gender and at each stage of the disease. The model detail was described previously.[15] The age distribution was gathered from previously published data.[16] The HCV-infected population was then aged in the model while removing those who die or achieve a sustained virological response (SVR) from treatment.[11] Further details on age distribution and the birth cohort effect have been described previously.[11]

New hepatitis C virus infections and re-infection

Due to lack of reported estimates, the number of new infections was back-calculated by first calculating the annual number of incident cases, followed by the age and gender distribution of these cases. The annual number of incident cases was calculated from the estimated number of total HCV infections. At any point in time, the prevalence of HCV infections equals all new infections over time after subtracting spontaneously cleared, deceased, and cured cases. The annual number of deaths and cured cases were calculated in the model by applying mortality (all-cause and liver-related) and cure (spontaneous and treated) rates. It was assumed the annual number of new cases varied over time since 1950. Thus, an annual relative incidence value was used to map the changing patterns in incidence over time. Relative incidence was set to one in 1950, and a discussion with the expert panel on common historical and contemporary risk factors in KSA identified the years when new infections increased, peaked, and declined.

In the second step, the age and gender distribution among the total infected population in a given year were used to calculate the age and gender of the acute infections. The age and gender distributions of the new infections in every

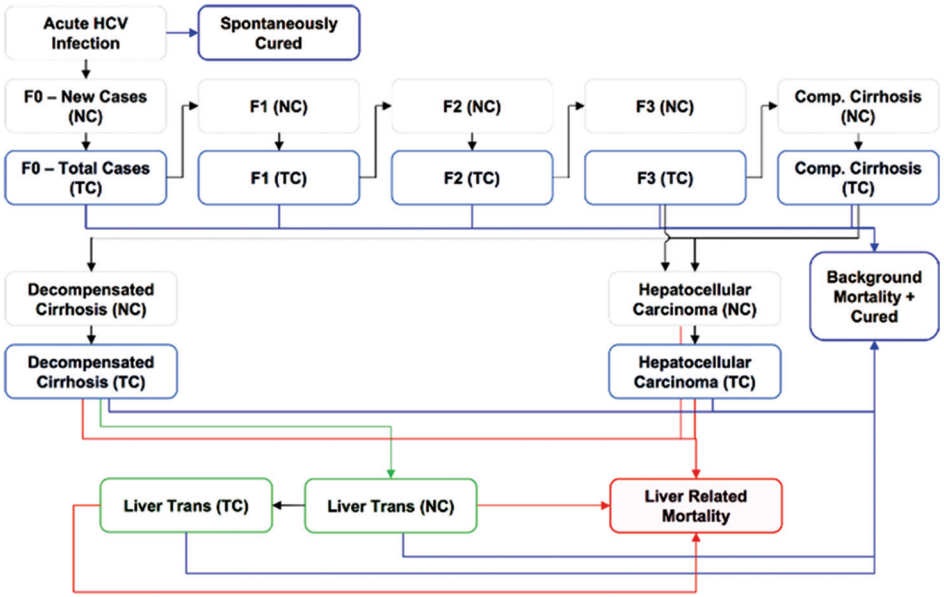

Figure 1: The flow of hepatitis C virus diseases progression model (Adapted from Razavi *et al.*[15])

fifth year from 1966 to 2011 were modified to match the known distribution of the total infected population. The age and gender distributions in years 1950–1965 were set to equal 1966 with linear trends applied between the 5-year estimates going forward.

Due to lack of information on any significant changes in risk factor trends over the last 10 years, it was assumed that HCV infection and re-infection would remain constant in the future. Whereas a dynamic model might assume a reduction in HCV incidence due to treatment of high-risk populations (treatment as prevention), a more conservative approach was believed appropriate in the face of uncertainty regarding HCV epidemiology, particularly with regard to infection and re-infection rates in KSA.

Progression rates

Disease progression from one stage to the next was simulated by applying progression rates to the total number of cases at a particular stage of the disease. The rates, which vary by stage, were gathered from previous studies[17-21] and calculated using known number of HCC cases/mortality, as previously reported.[15] Aging, all-cause mortality, and cases cured in any given year were factored into determining number of new cases at each stage.

All-cause mortality

The all-cause mortality rates by age and gender were gathered from the available Saudi national data and from the expert panel's consensus. Mortality rates were adjusted using standard mortality ratios among injection drug users (IDU) and individuals who have received blood products, as described previously.[22] New HCV infections due to transfusion were no longer a risk factor in KSA. A linear declining rate was applied to reduce the proportion of total infections due to transfusion to zero by 2030. Adjustments to all-cause mortality were made for active IDU and transfusion. It was estimated that 9% of the infected HCV population are active IDU and 15% are attributable to transfusion.[23] The IDU estimate was back-calculated using an estimated anti-HCV prevalence among IDU of 14%.[24]

Diagnosed

The total number of diagnosed cases was collected as described earlier in this review and according to what has been previously reported.[16] Current and future total numbers of diagnosed cases were estimated under the assumption that the number of newly diagnosed cases remained constant going forward from the last reported year.

Treated and cured

Reliable Saudi national data on number of patients treated were unavailable. Estimates were derived by applying the average number of units of pegylated interferon (Peg-IFN) or ribavirin (RBV) per patient to the annual numbers of units sold, as reported by IMS Health.[25] Variables used to calculate the average number of units per patient included genotype distribution of the infected population (assumed equal distribution in both the treated and total infected populations), duration of treatment for each genotype, number of Peg-IFN or RBV units per week, and treatment adherence rate. The annual number of units was adjusted using inputs from the expert panel to account for uses other than HCV as well as potential under-reporting. Details of these methods were described previously.[16] Expert input was used for years when IMS data was not available.

It was assumed that the number of patients treated annually remained constant going forward from the last reported year. Furthermore, it was assumed that the genotype distribution was equivalent in both the treated and total infected populations.[16] The annual number of cured patients was calculated by applying SVR rates (by genotype) to the number treated in each genotype in a given year, as shown in Table 1. To estimate the average SVR, we took into consideration a weighted average of different treatment options in a given year-interferon-based therapy in combination with ribavirin (RBV) (dual therapy) or with RBV and a protease inhibitor (triple therapy). We also considered the proportions that were treatment-experienced and treatment-naive for each combination therapy, as well as the disease stages of the patients being treated (eg, F1, F2, F3, and F4).

Treatment protocols

The group of patients who could be treated was determined by the clinical experience of each expert panel member in his center. In 2014, decompensated cirrhotic patients were considered ineligible for treatment in KSA. In this analysis, 60% of the patients were considered treatment-eligible for standard of care [Table 1]. The expert panel provided the most common stages of fibrosis considered for treatment using the Metavir scale [Table 1]. The expert panel also determined the most common age range considered for treatment, as outlined in Table 1. The Metavir score and age parameters do not imply exclusion of treatment but rather serve as ranges for the majority of treated patients.

Future treatment protocols

In this analysis, it was presumed that the future treatment paradigm would remain the same as today, thus all assumptions related to treatment described above were kept constant in future years.

Methods for reporting treatment strategies

The details of the model used to forecast HCV disease burden were described above and have been reported previously in more details.[11,15,16] The model interface allowed for adjusting

inputs related to interventions, including the number of patients treated, the percent of eligible patients for treatment, the rate of treatment restrictions, the average SVR by genotype, the age range and fibrosis stages most treated, the number of newly diagnosed individuals, and the number of new infections at five different points in time (the years in which could also be changed). A variety of new therapies were considered, including DAAs + Peg-IFN + RBV, DAA + RBV, interferon-free all-oral, second-generation DAA combinations, and third-generation combinations.

Table 1: Hepatitis C virus-infected population and treatment forecast in 2014

Category	Value
Country's population (no.)	20,600
Total viremic infections[1] (no.)	101 (75-181)
Viremic prevalence[2] (%)	0.50 (0.4-0.9)
Diagnosed (viremic)[3]	
Total cases	21,500
Annual newly diagnosed[4]	2000
Diagnosis rate[5] (%)	21
Newly diagnosed rate[6] (%)	2.0
Treated and cured	
Annual number treated	380
Annual number cured	190
Average SVR (%)	50
Treatment rate (%)	0.4
New infections	
Total cases	2200
Infection rate (Per 100,000)	11
Risk factors	
Number of active IDU	8700
Percentage active IDU	9
Previous blood transfusion	6800
Percentage previous blood transfusion	7
Mortality	
All cases	1080
All cause mortality	870
Liver related mortality	210
Current treatment protocols	
Treatment age	15-69
Percentage treatment eligible (%)	60
Treated stages - G1	≥F0
Treated stages - G2	≥F0
Treated stages - G3	≥F0
Treated stages - G4	≥F0
SVR - G1 (%)	42
SVR - G2 (%)	90
SVR - G3 (%)	76
SVR - G4 (%)	50

[1]Active HCV infections who are RNA-positive, [2]Prevalence of active HCV infections, [3]Individuals diagnosed with an active infection, [4]Active (viremic or RNA-positive) HCV infections diagnosed for the first time, [5]Total viremic diagnosed cases divided by total viremic infections, [6]Number of new viremic diagnosed cases divided by total viremic infections. IDU: Injection drug use, SVR: Sustained viral response, HCV: Hepatitis C virus

All changes took effect immediately, and the average SVR was modified to account for the co-existence of multiple therapies. The number of patients treated in future years was limited by (1) number diagnosed, (2) number eligible, and (3) unrestricted cases. The latter related to either physician's practice or to treatment guidelines restrictions and could be modified by changing the age range and stage of fibrosis (≥F4, ≥F3, ≥F2, ≥F1 or ≥ F0) for treating patients, as defined by the expert panel. Patients with decompensated cirrhosis, irrespective of genotype, were deemed ineligible for any treatment that involved Peg-IFN. The fibrotic stages eligible for treatment are shown in Figure 2.

When the number of treated patients exceeded those diagnosed, eligible, and unrestricted, the diagnosis rate was increased or the treatment restrictions were eased. The analysis focused on how many cases have to be diagnosed to achieve a strategy rather than to project the future screening capability. A treatment eligibility of 60% was used for all therapies that included Peg-IFN/RBV. The eligibility was increased in scenarios where Peg-IFN was excluded from the treatment under consideration. The increase in eligibility did not increase treatment in the future, but rather the pool of patients eligible to receive treatment. In this analysis, three principle strategies were considered: Base, increased efficacy only, and increased efficacy and treatment. The base strategy represented the scenario where all assumptions (the number of acute cases, treated patients, percent of patients eligible for treatment, treatment restrictions, the number of newly diagnosed and the average SVR by genotype) reflect today's standard of care and remain constant into the future. This maintenance of the status quo served as the most conservative, but feasible, scenario. Even more conservative scenarios could have been considered (eg, a scenario where no patients are treated), but those were believed to be impractical. In the second strategy, the impact of therapies with greater SVR was considered. All other assumptions, including number of treated patients, remained consistent with the base strategy. The third strategy considered increasing both SVR and treatment rate. The decision for the number of treated patients in the future was driven by a desire to achieve elimination of HCV disease burden (defined as a 90% reduction in total infections) in KSA and was developed in discussion with the expert panel. To achieve this goal, expanding treatment to patients with early stages of fibrosis (F0–F2) was considered. The number of newly diagnosed cases also had to be increased to ensure a large enough diagnosed eligible patient pool for future treatment. Further consideration of this scenario included an analysis of the impact of implementing the strategy one year sooner (2014) and one year later (2016).

Scenario inputs for these three strategies, including number of treated and diagnosed patients, SVR, fibrosis stage and medical eligibility, are provided in Figure 2.

RESULTS

Hepatitis C virus epidemiology

Electronic search revealed 86 studies that were included in analysis. Study selection process was depicted in Figure 3. Estimates from the literature review, unpublished data, and expert input, including antibody and viremic prevalence, genotype distribution, viremic diagnosis, annual treatment, and liver transplants, are shown in Tables 2 and 3. The specific age and gender distribution of the viremic-prevalent population is shown in Figure 4.

Hepatitis C virus-infected population

The prevalence rate of anti-HCV was estimated at 1.08% (0.97%–1.19%) in Saudi nationals aged ≥15 years and 0.19% among children based on expert consensus. The prevalence among all Saudi nationals was estimated to be 0.7% (0.6%–0.9%). A viremic rate of 70% was applied,[26] resulting in a 0.5% (0.4%–1.3%) viremic prevalence rate among all ages and approximately 100,000 (81,000–257,000) HCV-infected individuals in 2011 [Table 2]. The age distribution was drawn from a study on more than 28,000 blood donors in the Jazan region from 2004 to 2009[27] and then modified via expert input, specifically regarding ages >60 years. A gender ratio was applied from a prevalence study of 1,482 screened subjects, also in the Jazan region.[23] Genotype distribution, including genotype 1 subtypes, was determined from local studies and from expert consensus.[7,8]

Diagnosed

There was no specific Saudi data on the number of diagnosed HCV cases. The expert panel estimated that 20% of viremic cases in 2013 had been previously diagnosed and that 10% of those diagnosed had received their diagnosis in the last year. Thus, the total number diagnosed in 2013 was estimated to be 20,100 cases, 2,010 of which were newly diagnosed [Table 2].

Treated

The number treated from 2006 to 2009 was estimated by taking IMS data for standard units of Peg-IFN sold and applying a 5% reduction to factor out expatriate/immigrant patients (expert input). The number treated in 2009 was estimated at 1,900 and assumed to remain constant in future years based on expert consensus. The standard treatment in KSA as of 2014 was Peg-IFN and ribavirin.

Liver transplants

In 2014, 198 livers were transplanted in KSA; with 128 livers transplanted from living and 70 transplanted from deceased donors.[13] According to SCOT report, in 2014, the 70 transplants from deceased donors amounted to a total cost of 24,500,000 Saudi Riyals (SAR), which was equal to 6,532,114 USD, excluding pre- and post-transplant costs.[13] It was estimated that 98% of these transplants were performed on Saudi nationals based on expert input. The expert panel estimated 45% of all liver transplants in KSA are performed on patients with HCV.

Hepatitis C virus disease burden

The results of the analysis for 2014 are shown in Table 1. The age distribution of the HCV-infected population is shown in Figure 5. The change in HCV disease burden between 2014 and 2030 is shown in Table 4. The projected HCV disease burden between the years 1950 and 2030 is depicted in Figure 6. The analysis includes those who received a liver transplant in estimates of decompensated cirrhosis.

Figure 2: The fibrotic stages eligible for treatment by genotype and year

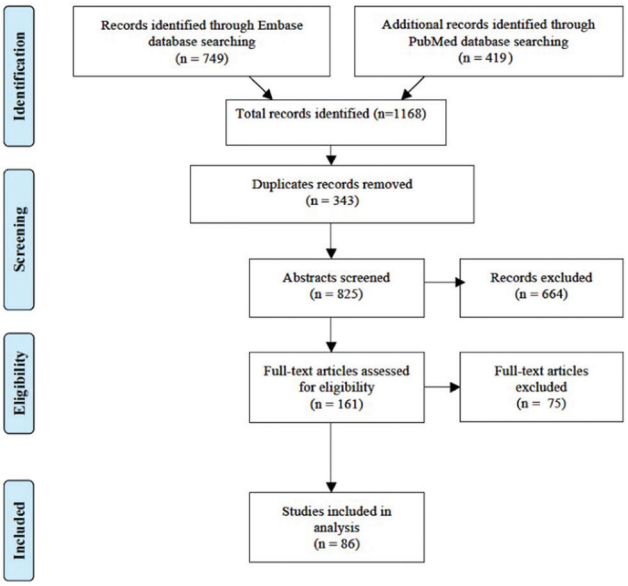

Figure 3: Preferred reporting items for systematic reviews and meta-analyses flow chart summarizing search results

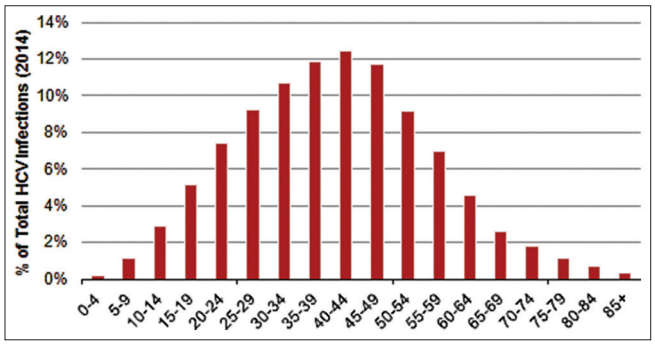

Figure 5: Age distribution in the hepatitis C virus-infected population as percentage of total numbers of cases in 2014

Incidence

The expert panel estimated that approximately 2,700 incident cases of HCV occurred in 2010 (one case per 10,000 persons). The model mapped incidence rising through the 1970s and 1980s before peaking at an estimated 4,800 cases per year in the early 1990s. The development of medical infrastructure in KSA and the consequent increase in the number of subcutaneous procedures and blood transfusions were believed to account for the rise in incidence, while the significant decrease in incidence thereafter was thought to be due to the implementation of blood screening in the early 1990s. It was estimated that there were 2,200 new cases of HCV in 2014.

Disease burden

In 2014, the total number of viremic cases of HCV was estimated at 101,000 (75,400–181,000). By 2030, this prevalence was projected to increase by 2% to 103,000 (75,900–186,000). HCC prevalence was projected to increase 190% from an estimated 160 cases in 2014 to 470 by 2030. Liver-related mortality was expected to increase by 225%, from 210 deaths in 2014 to 670 deaths in 2030. Decompensated and compensated cirrhosis cases were projected to increase to 1,300 and 15,400 respectively, by 2030 [Table 4].

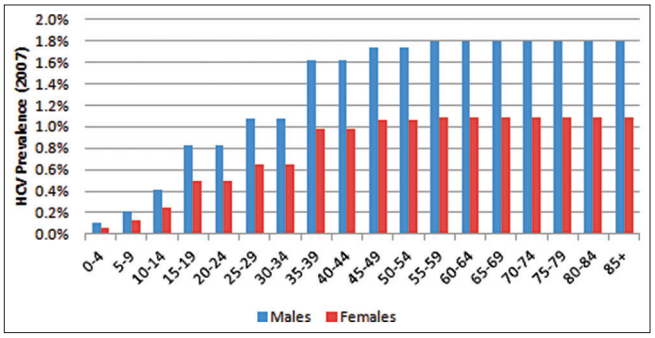

Figure 4: Viremic hepatitis C virus prevalence by age and gender in 2013

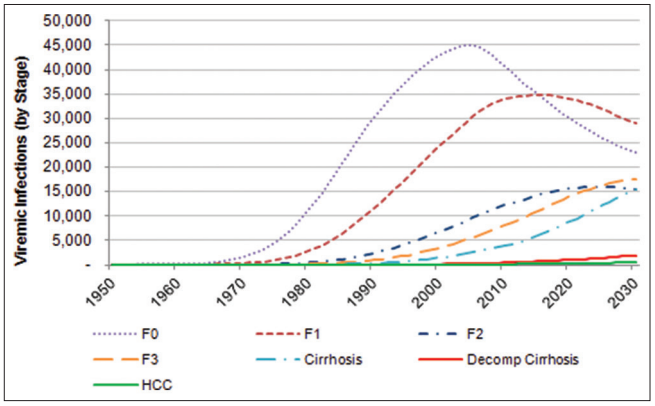

Figure 6: Change in hepatitis C virus disease burden over time by base scenario

Strategies to manage hepatitis C virus infection disease burden

The birth cohort effect in the HCV-infected population revealed that 73% of infected Saudi populations were born between the years 1960 and 1990. The specific scenario results of treatment strategies in KSA are as given in the following sections.

Base Scenario

If the current treatment strategy continues, the HCV incidence and disease burden will increase as the population ages. Tables 1 and 4 and Figures 5–7 illustrate this scenario.

Increased efficacy only

A higher SVR with the same number treated would result in 80,700 viremic cases in 2030, 21.4% fewer cases than the base scenario projection. HCC cases would reach 350 in

Table 2: Hepatitis C virus historical epidemiology

Category	Value
Country's population (no.)	19,300
Year	2011
HCV antibody positive[1] (no.)	
Total case	143 (116-368)
Prevalence (%)	0.7 (0.6-1.9)
Year of estimate	2011
Viremic Infections[2] (no.)	
Total viremic cases	100 (81-257)
Viremic (HCV-RNA positive) prevalence (%)	0.5 (0.4-1.3)
Viremic rate[3] (%)	70
Year estimate	2011
Genotypes (%)	
1a	13
1b	26
1 other	N/A
1 (total)	39
2	4
3	5
4	53
5	N/A
6	N/A
Other	N/A
Year of estimate	2003
Diagnosed (viremic/HCV-RNA positive)[4]	
Total cases	20 100
Annual newly diagnosed[5]	2000
Year of estimate	2013
Treated	
Annual number treated	1900
Year of estimate	2009
Liver transplants	
Total liver transplants	198
HCV liver transplants	89
Percentage due to HCV	45
Year estimate	2014

Prevalence of [1]Past or active HCV infection, [2]Active HCV infections, [3]Percentage of past or active infections who have an active infection, [4]Individuals diagnosed with an active infection, [5]Active HCV infections diagnosed for the first time. N/A: No available data, HCV: Hepatitis C virus

2030 (26% fewer than the base scenario), and liver-related deaths would number 480 in 2030, 28% fewer than the base scenario projection. Decompensated and compensated cirrhosis would reach 850 (34% fewer than the base scenario) and 11,500 (26% fewer) cases.

Increased efficacy and treatment uptake

With an aggressive treatment strategy, viremic prevalence would decrease to 1,700 cases in 2030, a more than 98% decrease compared with the base scenario. Similarly, cases of HCC would decrease by more than 99% to about 1 case by 2030. Liver-related deaths would drop to 20 in 2030, 95% fewer deaths than in the base scenario. Cases of decompensated and compensated cirrhosis would be 5 and 130 in 2030, respectively, nearly 100% reductions compared with the base scenario. The detailed results of the analyses are summarized in Table 5 and Figures 2, 7, and 8.

The annual liver transplants due to HCV were projected to decrease from 80 in 2014 to 11 in 2030 under the most aggressive scenario, or an 88% decrease compared with the base scenario in 2030. This would result in an estimated 451 fewer liver transplants between the years 2014–2030 than if it were kept at 80 transplants per year. At an estimated SAR 1,000,000 cost per liver transplant, the resulting total cost savings by the aggressive scenario would be about SAR 451,000,000 by 2030 [Table 5].

Time sensitivity of the aggressive scenario

Accelerating the implementation of the aggressive strategy by one year would result in 330 fewer HCV infections in 2030 (19% less) and 115 fewer total liver-related deaths from 2014 to 2030 [Figure 9]. Delaying the implementation by one year would result in 68% more HCV infections in 2030 and 360 additional total deaths from 2014 to 2030 [Figure 9].

DISCUSSION

This analysis was designed to develop consensus estimates for the epidemiology of HCV infection in KSA using all available data in KSA and relying on expert input to compensate for a lack of proper epidemiological studies in certain areas. Data sources included indexed and nonindexed publications as well as unpublished data, including hospital and national-level data, when available. Those results were then discussed and reviewed with the expert advisory panel in direct meetings. This method of developing consensus estimates allowed for a more thorough picture of HCV epidemiology to be developed, and the indepth review of all data served to increase the accuracy of the analysis. Given the detrimental effect on public health and financial resources associated with HCV, it is crucial that reliable epidemiological data are available and used by policy makers to most effectively manage the HCV disease burden.

As higher efficacy treatments (SVR > 90%) with fewer side effects and shorter treatment durations are brought to market, countries, including KSA, are faced with reassessing public health policies around the national treatment paradigms for HCV, such as the impact of limiting treatment to patients in more advanced disease stages. This has led to the formulation of a position statement by the SASLT to address this issue.[10] Data from this study can be used by physicians, researchers, and policy makers in KSA to address these public health policy questions on how to most

Table 3: Hepatitis C model input's values and sources

Model input	Value (%)	Year of estimate	Source
Anti-HCV+prevalence rate	0.7	2011	Expert panel estimate
Viremic rate	70	2009	World Health Organization 2009[26]
Percentage infected population who are active IDUs	8.6	2003	Back-calculated from Shobokshi *et al*. 2003[24]
Percentage of infected population with past blood transfusion	14.80	1995	Al-Faleh *et al*. 1995[23]
Genotype distribution	G1/other - 38.6	2013	Al Traif *et al*. 2013[7]
	G2-3.6	2013	Abozaid *et al*., 2013[8]
	G3-5.2		
	G4-52.6		
Annual liver transplants	146	2014	SCOT 2014[13]
Percentage transplants due to HCV	45	2015	Expert panel estimate
Diagnosis rate (among all infections)	20	2015	Expert panel estimate
Annually treated	1900	2014	IMS Health 2014[25]
HCV prevalence by age	N/A	2007	Mohammed Abdullah 2013[27]
Male to female ratio	1.64	1995	Al-Faleh *et al*. 1995[23]

HCV: Hepatitis C virus, IDUs: Injection drug users, SCOT: Saudi Center for Organ Transplantation, NA: Not available data

Table 4: Comparison of hepatitis C virus disease burden between 2014 and 2030 if current treatment strategy continues

Category	Value
Viremic HCV infections	
2014 estimation	101,000
2030 estimation	103,000
Change (%)	2.0
HCC cases	
2014 estimation	160
2030 estimation	470
Change (%)	190
Liver related mortality	
2014 estimation	210
2030 estimation	670
Change (%)	225
Decompensated cirrhosis	
2014 estimation	210
2030 estimation	1300
Change (%)	510
Compensated cirrhosis	
2014 estimation	5400
2030 estimation	15,400
Change (%)	185

HCV: Hepatitis C virus, HCC: Hepatocellular carcinoma

effectively combat HCV through further use of modeling, analysis of risk factors including the impact of immigration, and the development and assessment of various prevention, screening, and treatment interventions. As mentioned earlier, due to lack of better information, treatment estimates were based on drug sales data and expert input, and the genotype distribution of the infected population was used to estimate treatment rates by genotype. In some cases, these values still might over- or underestimate the true treatment numbers by genotype due to preferential treatment of specific genotypes.

Despite the identification and use of the best available data for this analysis, the limitations inherent in these consensus estimates emphasize the need for additional epidemiological research to further assess the burden of HCV in KSA.

We used a modeling approach to estimate the HCV morbidity and mortality in KSA at any point in time. The HCV prevalence reported here is likely lower than other estimates because our analysis focused on the viremic population and not for those testing positive for HCV antibodies. The model factored out those who cleared the virus either spontaneously or through treatment from the infected population. This analysis focused on Saudi nationals as the inclusion of migrant workers, a typically younger population, could skew the age distribution, resulting in a different estimate for total HCV infections [Figure 5]. As illustrated in Table 1, viremic HCV prevalence is 0.5%, with a diagnosis rate of 21% and treatment rate of 0.4%. The treatment rate is considered lower than most countries such as Europe (3.8% in England, in 5.2% France, and 4.7% in Germany), Asia (1.9% in South Korea, 2.6% in Japan), Arab countries (2.2% in Lebanon, 1.3% in UAE, and 1.1% in Egypt).[11,28] All-cause mortality was adjusted by age [Figure 5] and risk factors (IDU and transfusion) [Table 1], with older and high-risk individuals at greater odds of an early death. Disease progression rates increased with age accounting for and additional increase in liver-related mortality in older individuals.

Details of the current treatment protocols were determined through literature review and from discussions with the expert panel. All treatment assumptions (including the number of treated patients, treatment eligibility, the number of newly diagnosed cases, SVR, and treated patient segments) were set constant from now until 2030 to represent what the outcome would be if the current paradigm were to continue

Table 5: Impacts of different treatment scenarios on hepatitis C virus-related disease burden in 2030

Category	2014	2030		
		Base scenario (%)	High efficacy treatment only (%)	Aggressive scenario (%)
Viremic prevalence	101,000	103,000 (2 increase)	80,700 (21 reduction)	1700 (>98 reduction)
Compensated cirrhosis	5400	15,400 (185 increase)	11,500 (26 reduction)	130 (>99 reduction)
Decompensated cirrhosis	210	1300 (510 increase)	850 (34 reduction)	5 (>99 reduction)
Hepatocellular carcinoma prevalence	160	470 (190 increase)	350 (26 reduction)	1 (>99 reduction)
Liver-related mortality	210	670 (225 increase)	480 (28 reduction)	20 (>95 reduction)
Liver transplant	90	90	90	10 (88 reduction)

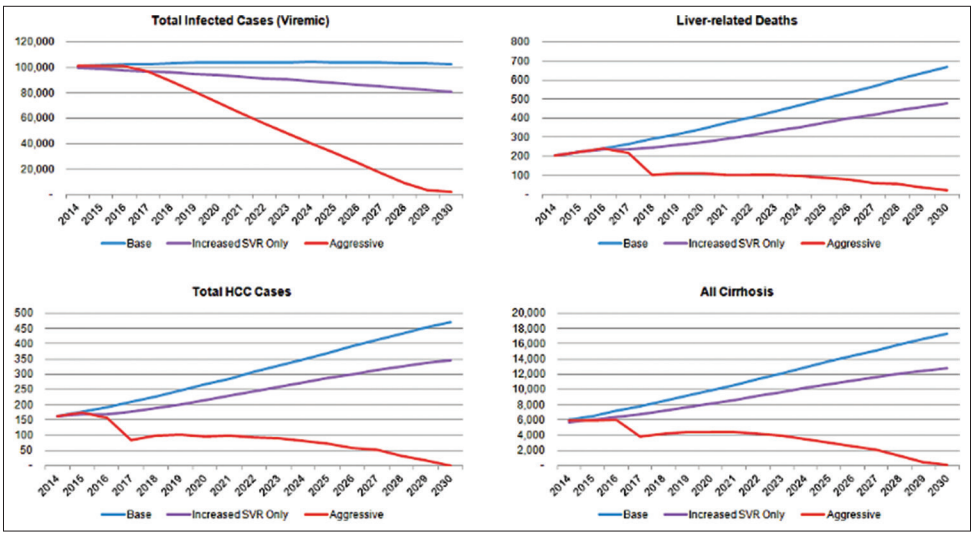

Figure 7: Change in hepatitis C virus morbidity and mortality, by scenario, 2014–2030

unchanged. As such, this scenario was not intended as a realistic scenario, nor does it imply that the current treatment paradigm will remain as it is today. Rather, it serves as a baseline that could be used to compare the influence of new strategies to manage the future disease burden.[29]

Applying the current treatment paradigm (base scenario) projects the total number of HCV-infected individuals to remain stable through 2030 [Figures 6 and 7]. The flat-lining of total infections is explained by the assumption that the number of new annual infections will equal approximately the number of deaths in the infected population in a given year. And while the incidence rate is moderate (11 cases per 100 000 persons), this is likely only partially offset by a low treatment rate (2%). However, this does not mean that the burden of HCV will remain constant. It is expected that patients currently in the early stages of disease will advance over time. HCC, cirrhosis and liver-related deaths in particular are all expected to increase significantly [Figures 6 and 7]. As individuals progress to these stages, the proportion of individuals with advanced liver disease would increase in the total infected population as depicted in Figure 7. The increase in the number of more advanced patients requiring medication, chemotherapy or radiation, liver transplantation, lost work production, etc., would add significant public health and economic burdens.

As part of this analysis, two strategies were investigated: Disease control and HCV elimination. In the former case, the future SVR was increased to reflect the impact of availability of new DAAs, while all other assumptions remained the same as in the base scenario. This scenario achieved modest decreases in total HCV infections (21%), cases of HCC (27%), decompensated cirrhosis (34%), compensated cirrhosis (26%), and liver-related mortality (28%) compared with the base scenario in 2030.

In the HCV elimination case, increased SVR was combined with the gradual expansion of treatment and diagnosis over time to reduce the total number of infections below 10% of 2014 values. By increasing the number treated to 5,180 patients in 2017 and 9,780 patients in 2020, a 98% reduction in prevalence and >95% reduction in advanced stage HCV as compared to the base scenario in 2030 would be achieved.

The current strategy in KSA for HCV treatment prioritizes patients according to their fibrosis stage. Fibrosis stages

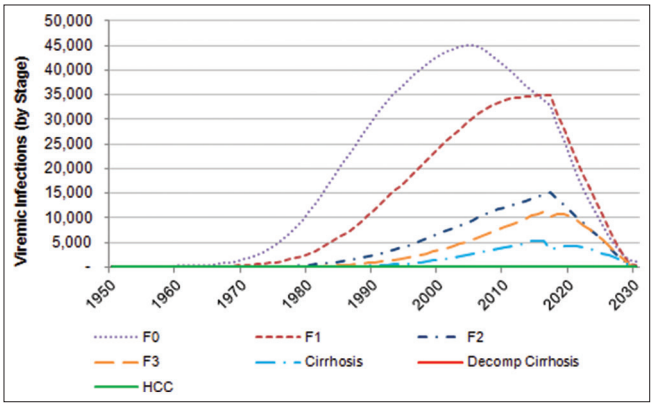

Figure 8: Disease stage distribution over time by aggressive scenario

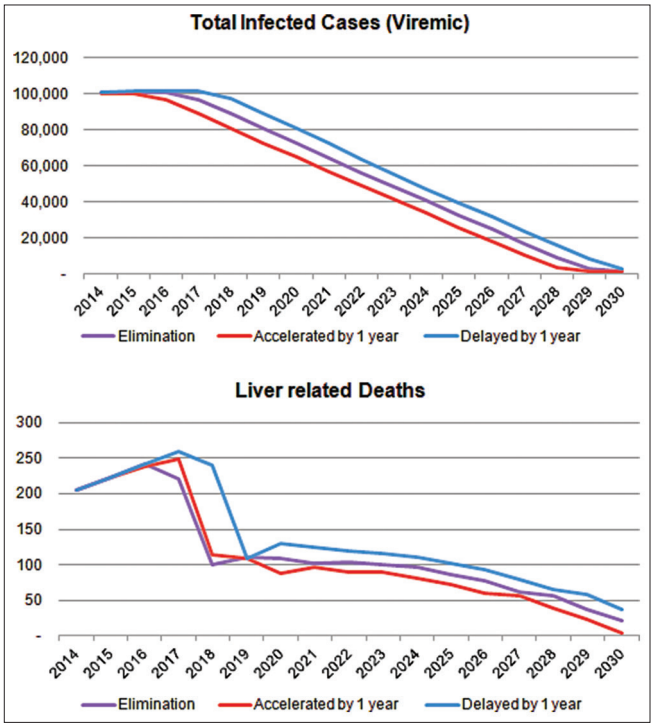

Figure 9: The impact of accelerating and delaying the elimination strategy by one year on total hepatitis C virus infections and liver-related deaths

F3 and F4 were given the priority among other indications believed to affect the progress of the disease.[10] This model showed that expansion of treatment to F0 and F1 patients was necessary if the goal of the strategy was to eliminate HCV. In fact, the aggressive strategy identified the need to expand treatment to all patients once the >F2 patient pool was depleted after only a few years. However, delaying treatment of early-stage patients did have a major drawback in that some would be too old to be treated. The age of the infected population is one of the key variables for not being able to feasibly achieve zero infections in the country. Even with the expansion of treatment to patients of all disease stages, the number of newly diagnosed patients would still need to be increased to find yet more patients to treat in order to eliminate HCV infections. The aggressive scenario in our model required the number of new annual diagnoses to increase from the baseline of 2,010 in 2014 to 4,020 in 2017 and 8,030 in 2020. An aggressive national screening program would hence be required to identify these additional patients. As shown previously,[11,16] diagnosis of HCV remains low in KSA, as well as in many other countries. Targeting definable high risk populations for screening allows for more efficient identification of cases, and in the United States, the Centers for Disease Control and Prevention have targeted birth cohorts with higher prevalence rates.[30-32] As discussed earlier, this analysis identified 73% of the infected population in KSA as being born between 1960-1990. A national screening strategy targeting this cohort, especially in lieu of a significant IDU population, could provide an efficient way to identify new patients.

Successful diagnosis and treatment, even of a small percentage of patients, can contribute significantly to the reduction in HCV disease burden in KSA. Switching to high SVR therapies would reduce HCV-related morbidity and mortality. Not surprisingly though, the scenario where higher SVR treatments were combined with an increase in treatment resulted in the largest reduction in HCV-related morbidity and mortality. While this will require approximately a 4-5-fold increase in diagnosis and treatment, implementing this gradually would require an annual treatment rate of approximately 10% of the total infected population. Strengthening the public health and clinical provider capacity for improved diagnosis and treatment will still likely be necessary to achieve this. It is important to note that an estimated 451 liver transplants could be avoided by the aggressive strategy as progression to end-stage liver disease would be greatly reduced, resulting in an estimated cost savings of SAR 451,000,000 between now and 2030. Therefore, any spending in the implementation of the strategy would at least partially be offset. Timing of the implementation of the scenario is a factor, particularly with regard to reaching goals in a given year. The model estimates that accelerating the scenario by one year results in 115 fewer deaths and delaying the scenario by one year results in 360 more deaths. There would be more to lose by delaying the implementation than there is to gain by accelerating the implementation.

There are several limitations to consider when interpreting the findings of this study. Projecting the incidence of new cases in the future is difficult to estimate. Relative incidence, past prevalence, and historical age and gender distributions could be used to back-calculate the distribution of new cases from 1950 to the most recent year of available data, however an estimate of current incidence after the year of known

prevalence relied on an analysis of key risk factors, including IDU, nosocomial infection and immigration. Without data on the trending of these risk factors, the expert panel was left to assume that the number of new cases would remain constant after 2014. On the other hand, if the incidence were actually increasing in 2014, a higher total prevalence than the current estimate in 2030 could result. A second limitation is the difficulty in determining the resources needed to increase the diagnosis rate in order to provide a pool of patients available for treatment. In reality, there is a diminishing margin of returns that would come with diagnosing each new patient, making it more difficult to find additional patients. Moreover, receiving a diagnosis does not guarantee that patient will be treated due to various burdens to accessing care. Thus, the feasibility to expand treatment of HCV patients may be restricted no matter what efforts are made toward a national screening program. Some estimates used in this analysis relied on the consideration and agreement of the advisory panel and therefore do not represent the actual HCV epidemiology in the country with complete certainty and may be subject to some biases. Additionally, the data used from national or hospital databases or specific epidemiological studies may have the potential for selection bias. SVR rates for the current treatment protocol were based on clinical data and clinician expertise based in large centers experienced in treating patients and limiting adverse outcomes. Hence, these SVR rates may not reflect potentially lower rates in other treatment locations, resulting in larger differences in projections between the base case and each of the scenarios. The relative impact of each scenario may also be more or less pronounced if the prevalence in this analysis was over- or underestimated. A further limitation was that the interventions for each scenario were assumed to take effect immediately. In reality, the successful development and implementation of a disease management strategy at the national level would likely take several years. However, analyzing the impact of accelerating or delaying the HCV elimination strategy demonstrated that desired outcomes were more likely to be achieved when the strategies were implemented earlier and less likely to be achieved when delayed. A final limitation of this study is that disease progression was assumed to stop in cured patients. However, it has been shown that elevated risk of advanced liver disease and liver-related mortality persist among cured patients, but at a significantly lower progression rate than in those with HCV infection.[15] Therefore, the model could overestimate the impact of curing patients and consequently underestimate HCV liver-related morbidity and mortality. This potential underestimation is likely to be minimal, as most of the prevention of HCV progression occurred in less advanced patients where progression to advanced liver disease is unlikely in the near future anyway.

CONCLUSIONS

This study demonstrates that the overall viremic prevalence in KSA is expected to remain constant; while cases of advanced liver disease and mortality are expected to increase as the current infected population progresses to advanced stages of liver disease. The increased disease burden will likely not be controlled without significant changes to the current overall treatment paradigm, including increases in screening, diagnosis and treatment efficacy and number treated. This would have a significantly greater impact than increased treatment efficacy alone. This implies that in KSA, reducing HCV disease burden is quite possible, however distinctive and rigorous strategies must be adopted and implemented in a timely manner to best manage and control HCV-related disease burden. The projected impact will facilitate disease forecasting, resources planning, and strategies for HCV management and eradication in the country. Increased screening and diagnosis would likely be required as part of a national strategy. A potential HCV prevention/treatment strategy for a public health program is feasible through a multidisciplinary approach. This strategy should ideally include: Enhancing health care provider's knowledge and community awareness; consolidating community health surveillance; improving risk estimation; increasing access to testing and treatment; and enforcing infection control measures in healthcare facilities. It should also include proper clinical evaluation and appropriate referral for care and treatment, advocating about available treatment opportunities, planning to commence treatment and maintaining effort on reduction in diagnostic and medication costs for HCV. Such a strategy should be able to properly identify HCV epidemiology and prevention plans, recognize any remaining barriers to HCV management and develop strategies for overcoming such barriers. Highly efficacious, pan-genotypic, well-tolerated, interferon-free HCV treatment has strong potential for cure of HCV infected people. With these new medicines, the elimination of HCV is quite achievable.

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Conflicts of interest

There are no conflicts of interest.

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