Commentary: Modelling the epidemiology of hepatitis C and its complications

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Hepatitis C virus (HCV) was well adapted to emerge worldwide in the late 20th century. Transmitted primarily through percutaneous routes, it took advantage of two emerging epidemics: an epidemic of recreational injection drug use in industrialized countries and an epidemic of unsafe injections primarily in developing countries, made possible by the expanded use of parenteral therapeutics and declining injection equipment prices after the World War II. The result at the beginning of the 21st century is a large pool of HCV-infected people, many of whom are asymptomatic, slowly progressing liver disease.

The greatest burden from HCV infection will come from the long-term complications of this chronic liver disease, namely cirrhosis and hepatocellular carcinoma, which in any individual may take decades to develop. Whether increases in HCV infections in the 20th century will lead to increases in HCV-related complications in the 21st will depend on three factors: the number of people currently infected with the virus, the stage of disease in these individuals, and the natural history of HCV infection.

These determinants are often difficult to measure directly and have not been well characterized. Only the first, the size of the infected population, has been estimated on a global scale. One recent review of published and unpublished literature puts this number at 130 million worldwide, though the precision of this estimate is limited by the paucity of data from representative, population-based surveys of HCV infection and from important regions such as the Indian subcontinent (CDC, unpublished data). The other two determinants of future burden are even less certain. Data from natural history studies suggest that progression to cirrhosis is much slower in people infected as children or young adults, of whom fewer than 5% have progressed to cirrhosis in the first 20 years, than in people infected as older adults, of whom 10–20% have progressed to cirrhosis in the first 20 years. Beyond 20 years there are few data on what to expect and no data to suggest whether disease progression will accelerate or decelerate. In addition, co-morbidities such as alcohol use and human immunodeficiency virus infection may substantially alter the natural history of chronic hepatitis C. Where currently infected individuals are along this natural history is even less well understood and depends in part on how long these 130 million individuals have been infected, a function of past trends in incidence of HCV infection. With few direct data about these trends, mathematical modelling provides an appealing means of inferring them.

Several countries have used modelling to examine trends in hepatitis C and its complications. Australia, in the accompanying paper by Matthew Law and colleagues, has approached this task by assuming that injection drug use has driven the epidemiology there and that infections from other sources have been proportional to infections from injection drug use. They first estimated past trends in injection drug use and then, assuming a certain incidence of infection among drug users, estimated the number of HCV infections by year. To project the current and future burden of HCV-related cirrhosis and liver cancer, they applied to these estimates a natural history model that assumes the rate of progression to cirrhosis will be 5.3% at 20 years and 15.3% at 40 years. Their model fits existing data well and shows a monotonic increase in HCV infections over the past 30 years, portending a monotonic increase in HCV-related complications in the near future.

Groups working in other industrialized countries have used different approaches to infer past trends in incidence and to project the burden of disease. In the US, the Centers for Disease Control and Prevention (CDC) has estimated the past incidence of hepatitis C cases identified by sentinel surveillance represent a fixed proportion of all infections and then using national prevalence data to estimate the value of that proportion. More recently, another group has used these data, including mortality rates, in a more comprehensive model of hepatitis C in the US. A third group used the same prevalence data together with data on the stage of liver fibrosis among HCV-infected patients presenting for treatment to estimate the number of people currently at each stage of infection. With this estimate and a model of the natural history of HCV infection, they estimated future trends in the burden of disease. These US models are consistent in showing an increase in incidence of HCV infection in the past half century and an increase in HCV-related liver disease in upcoming decades. Separate models of the epidemic in France show the same general trends in that country. In Egypt, where unsafe injection practices during a disease eradication programme may have inadvertently led to the largest known epidemic of HCV infection, the current prevalence of infection correlates with what would be expected if incidence of infection had increased in the 1960s and 1970s commensurate with the expanded use of parenteral antischistosomal therapy.

Molecular virologists, approaching the task of reconstructing the emergence of HCV, have come to similar conclusions about past trends in the incidence of HCV infection using completely different data and methods. By examining the genetic diversity of currently circulating viruses and modelling their phylogenetic tree, they have inferred the population size of viruses circulating over time. These analyses have shown genotype 1 HCV emerging in the US in the 1960s and 1970s, coincident

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with the epidemic of heroin abuse, and in Japan in the mid-20th century. In Egypt, the current genetic diversity of genotype 4 is consistent with the spread of HCV during the era that parenteral antischistosomal therapy was in use. The emergence of HCV infection in the 1900s has been a consistent conclusion of these models. This fits with our understanding of the epidemiology of this virus and its most important modes of transmission. Naturally, there are variations in the epidemiology from country to country, but on a global scale, it is safe to say that HCV infection has expanded greatly in the mid- to late-20th century.

There is less certainty about projections in the burden of HCV-related complications in the 21st century. The models are indeed consistent in projecting an increase in cirrhosis and liver cancer, but these generally assume a constant rate of progression to cirrhosis after 20 years of infection, which is speculative. In addition, the magnitude of a future epidemic of cirrhosis and liver cancer will depend in part on trends in incidence of infection in the recent past, which are poorly estimated by many models, as well as incidence in the future, which no model can forecast reliably.

Nonetheless, we can conclude that coming decades will likely bring increases in HCV-related complications. These may be inevitable in the short term without improvements in the efficacy and dramatic decreases in the costs of therapy for chronic disease, both of which are unlikely in the near term. In the long term, preventing HCV infection is the best means of preventing HCV-related complications. In industrialized countries, lowering injection drug abuse rates and slowing transmission among those who continue to abuse drugs are clear priorities. On a global scale, there is an even more urgent need to end injection overuse and unsafe injection practices.

References