The global elimination of hepatitis C?

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Globally, 71 million people are thought to be viraemic for hepatitis C. The advent of short course all oral direct acting antiviral curative therapy for the virus has put the ideal of the global elimination of this virus within reach. Multiple efforts will be required to achieve this through identifying patients currently infected and preventing further transmission through rapid linkage to treatment while a vaccine remains tenaciously elusive.

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In May 2016, the World Health Assembly of the World Health Organization (WHO) adopted a strategic document entitled 'The Global Health Sector Strategy 2016 – 2021'. The document, adopted by all member states, provided a framework for the elimination of viral hepatitis by 2030.[1] The viral hepatitis document is the first of its kind ever adopted by the WHO and clearly outlines a process towards the elimination of viral hepatitis by 2030. Consequently, a number of targets were developed to achieve this aspirational goal.

The strategy was introduced on the background of data suggesting that over the last 25 years, the global mortality from viral hepatitis has increased, in stark contrast to the declining mortality from other global pandemics such as HIV/AIDS.[2] The 2016 report noted that the global mortality from viral hepatitis increased from the 10th in 1990 to the 7th in 2013, accounting for almost 1.4 million deaths in 2013. This was greater than the respective deaths attributed to HIV, TB or malaria. The paradox is that organisations such as the Global Fund have significantly (and appropriately) invested in diseases such as HIV, TB and malaria while funding to prevent and treat viral hepatitis globally has largely been neglected. To date, only UNITAID have appropriated funding towards the management of hepatitis C but only in those who are HIV co-infected. An additional aspect of the WHO Global Health Sector Strategy is its alignment with the 2015 United Nations Sustainable Development Goals (SDGs). Section 3.3 of the SDGs notes that by 2030 there must be an end to the epidemics of HIV, TB, malaria and other neglected diseases. In addition, it states that hepatitis, water-borne diseases and other communicable diseases should be combatted.[3]

The targets proposed within the plan are that by 2021 there should be a 30% reduction in new hepatitis viral infections, which would equate to a 10% reduction in mortality, and by 2030 a 90% reduction in new infections, which will equate to a 65% reduction in mortality. It must be understood that the global mortality related to viral hepatitis is predominantly due to chronic hepatitis B and C.[4] They account for over 90% of deaths related to viral hepatitis; the remainder are caused by hepatitis A, E and hepatitis D co-infection with hepatitis B. That hepatitis B and C account for the bulk of the burden is not surprising given their propensity to result in chronic infection with an elevated likelihood of progression to cirrhosis, end-stage liver disease and hepatocellular carcinoma.[5,6] Unsurprisingly, half of the world's hepatocellular carcinoma is related to chronic hepatitis B virus infection.[7]

It is apt to pause and consider what is meant by the term 'elimination' with respect to infectious diseases. This is often used interchangeably with the term 'eradication', which has an entirely different context and meaning. Elimination refers to the reduction of an infectious disease's incidence in a regional population to zero or the reduction of the global prevalence to a negligible amount. Eradication, on the other hand, refers to the reduction of an infectious disease's incidence in the global population to zero as we have attempted to achieve with diseases such as smallpox. Hence, the approach is not to achieve eradication, but rather regional elimination with the onus on individual countries to develop viral hepatitis elimination plans, and even further, micro-elimination strategies within targeted communities.

The global hepatitis C landscape

Recent modelling data suggest that 71 million people are actively viraemic with chronic hepatitis C virus infection globally.[8] Approximately 30 countries account for 80% of global HCV infections and of those, 50% are accounted for by a handful of countries that include China, Pakistan, India, Egypt, Russia, USA, Brazil and Nigeria. Other regions with a high burden are parts of western and central sub-Saharan Africa. Six dominant genotypes of HCV account for the vast majority of infections.[9]

Genotype distribution in regions or countries demonstrate that high-income countries tend to have a more limited genotype distribution with lower-income areas more pangenotypic. In the USA genotype 1 dominates (75%) with the remainder of genotypes accounted for by genotypes 2 and 3. A similar trend is observed in Europe, although genotype 4 is encountered occasionally. In sub-Saharan Africa, genotypes 1 to 5 all occur, with genotype 5 seen exclusively in South Africa (SA).[9] Interestingly, in SA, genotype 5 still predominates in the general population, with recent data suggesting that in key populations such as people who inject drugs (PWID) and men who have sex with men (MSM), only genotype 1 and 3 are observed.[10] Another aspect in SA is a growing genotype 4 population possibly accounted for by immigration from Central and East Africa to Southern Africa from a genotype 4 predominant area.[11] In other parts of the world, such as South-East Asia including countries such as Bangladesh, Pakistan and Vietnam, genotype 3 is heavily over-represented with genotype 6 seen in Vietnam and in Hong Kong.

Understanding the epidemiology of the HCV globally is crucial to achieving elimination. Important data trends from the USA suggest a bimodal HCV distribution.[12] The data are perhaps similar for many parts of the world and relate entirely to the risk factors for transmission of HCV historically and, currently, factors that are driving the onward transmission for a new generation of HCV infection. Historically, the major risk factors for HCV include the sharing of needles in PWID as well as blood or blood-product exposure prior to 1992.[13] These two factors accounted for the vast majority of patients with HCV infection. Additional risk factors included unsafe medical procedures or dental interventions, tattooing with unsafe equipment, percutaneous needle-stick injuries in healthcare workers, haemodialysis, perinatal mother-to-child transmission and, in sub-Saharan Africa, traditional practices that involve scarification and other potentially transmissible practices. Importantly, injecting drug use and the receiving of blood or blood products prior to 1992 account for the birth cohort HCV peaks seen in many countries. The unimodal distribution of prevalence was typically seen in those of middle age, suggesting acquisition between the years of 1945 to 1965. It is for this reason that countries such as the USA introduced mandatory screening for the so-called 'baby boomer' generation. Similar trends have been observed in sub-Saharan Africa. For example, in Cameroon, HCV infection is seen predominantly in older Cameroonians, which is most likely due to potentially unsafe injection practices used in the eradication of tropical diseases such as trypanosomiasis in Cameroon in the 1950s and 1960s.[14] What is being observed of late are reports suggesting a new wave of prevalence in younger individuals in 20 - 40-year-old people. Two major reports from Massachusetts and California in the USA have noted a clear earlier bimodal distribution of HCV prevalence within the population over the last 15 years.[15] To completely appreciate this, one has to have an understanding of acute HCV case reporting. New HCV is almost exclusively accounted for by the growing epidemic of injecting drug use as well as the onset of potential sexual transmission of the virus in the MSM population. The reasons for this are numerous, but clearly represent a new wave of transmission of HCV that needs to be dealt with urgently in order to avoid further onward transmission into the general population. This has important implications for planning around elimination programmes in a country.

Looking specifically at PWID, there is little doubt that this remains the most significant at-risk population and it is estimated that almost two-thirds of PWIDs have evidence of current or previous HCV. This is critical to appreciate given that without targeted intervention programmes specifically aimed at this key population, the intention of achieving elimination within a country will simply not be achieved as it remains a nidus of active ongoing infection. An important additional dimension to this is the risk of HIV co-infection in this population. In parts of Europe and the USA, reports are that 50 - 75 % of HCV-infected PWID are HIV co-infected.[16] Trends are not much different within the other key population, notably MSM, who also have reported high rates of co-infection. Within SA, very recent data suggests that almost half of PWID in SA are HCV-infected, of whom 25% are HIV co-infected.[10] The HCV sero-prevalence within the MSM group in SA ranges between 5 - 10%, with a significant component HIV co-infected. The third key population, namely sex workers, seemingly have very low rates of HCV.

Why is elimination by 2030 feasible?

As yet, no effective hepatitis C vaccine is available and up until 2012, the standard of care involved 24 - 48 weeks of pegylated interferon and ribavirin. Treatment was limited to those without cirrhosis or compensated cirrhosis and the treatment goal of sustained virological response (SVR) ranged from 40 - 65% and was highly genotype-dependant.[17] Those with decompensated cirrhosis were ineligible for treatment and treatment outcomes in patients who were HIV co-infected were substantially less favourable. However, the long duration of therapy and significant toxicities of interferon and ribavirin precluded many from embarking on therapy or even completing therapy. For those who did complete therapy, it was an arduous process with many adverse effects. Management took a significant step forward with the introduction in 2012 of the first two protease inhibitors, boceprevir and telaprevir.[18] These were oral add-on therapies to PEG-interferon and ribavirin and significantly enhanced SVR rates. However, toxicities remained a major issue and many remained ineligible for the triple combination therapy. The development of these oral HCV antiviral therapies, that eventually came to be known as Direct Acting Antiviral (DAA) therapies, was made possible by the development, a few years prior, of an *in vitro* HCV replicon system which allowed direct assessment of new therapies. What emerged were distinct classes of drug that targeted three major areas of the virus, namely the NS3/4A protease, the NS5A replicase and the NS5B polymerase.[19] The three classes of DAAs became the standard of care by 2014. Combinations of the classes either in tandem or in triplicate are used to enhance efficacy and reduce the emergence of resistance. The fact that the life cycle of HCV favours the development of resistance rather than persistence, unlike HIV and HBV, allows for the potential eradication of HCV, as there is neither a reservoir nor persistent elite sites for the virus.[20]

Another positive aspect of DAA therapies is the development of highly efficacious short-course therapies that achieve SVR rates in excess of 90%. In fact, newer combinations can achieve SVR rates approaching almost 100% in as short a time as 8 weeks. The development of all oral, short-course therapies with a minimal side-effect profile, means that treating our way out of the global epidemic has become a reality. This is a highly unusual approach in the management of infectious diseases as historically vaccination has formed the cornerstone of eradication. Vaccination remains key for the prevention of new infections in the future. However, given the significant efficacy of DAA therapies, treating those who are infected serves as a deterrent in terms of preventing onward transmission. This 'treatment as prevention' strategy is akin to what has been used in reducing HIV transmission.

Several modelling studies have now shown very similar trends in terms of managing high-risk populations. Treating as many people within a high-risk population such as PWID, is key to the elimination ideal, as it is these populations that are mostly responsible for ongoing transmission and new infections. In most modelling studies looking at PWID, treating as little as 40 per 1 000 injecting drug users in such a population has massive gains in terms of reducing onward transmission and elimination of HCV infection. However, an essential aspect when dealing with key populations such as PWID is that treatment alone will not suffice and part of the package of care has to be linkage to harm reduction strategies including needle and syringe exchange programmes as well as offering universal opiate substitution therapy. A recent modeling study suggests that offering harm reduction to 80% of a key population plus treating up to 40 per 1 000 in that key population with DAA therapy results in an excess of 80% reduction in onward transmission in that population.[21] This kind of modelling data has unequivocally demonstrated and suggested that elimination of HCV within a high-risk population is entirely achievable with a combination strategy of both harm reduction and offering treatment.

While the advent of short-course all oral DAA therapy heralded a revolutionary new approach in the management of HCV as well as the potential for global elimination, the costs attached to these new therapies were astronomical. News headlines in 2014 were dominated by the USD84 000 price tag for 12 weeks of Sovaldi (sofosbuvir). This equated to USD1 000 a day per tablet, as 84 days of therapy (12 weeks) are required for a typical course of therapy. As new therapies were developed and approved, price tags remained at high levels and the list price of Harvoni (sofosbuvir/ledipasvir) was USD94 500 per 12-week course. It was quite clear from the outset that the majority of those affected by HCV globally were never going to be able to access these revolutionary therapies at the USA- and European-based pricing structure. Given advocacy and within a short time frame, significant genericisation and transfer of intellectual property patent rights to the Medicines Patent Pool, have allowed for the development of generics at a fraction of the costs of the brand name originator products. Advocacy demonstrated that based on calculated likely production costs, DAAs had profits added on that exceeded 500 - 1 000% in some instances.[22] Countries such as Egypt, which face a massive burden of HCV, began in-country production of generics to kickstart their own elimination strategies and national plans within their country.

Neglected components of elimination

DAA therapy is highly efficacious, but, as is described with key populations, preventing new infections is crucial. The tap of new infection literally must be turned off. In several countries the safety of blood products for transfusion is still suboptimal, and needs to be comprehensively addressed. Fortunately, this has improved significantly over the last decade. For example, in the late 1990s, only 19% of blood was screened for HCV in sub-Saharan Africa given the costs of laboratory testing.[23,24] The high HCV prevalence in sickle cell disease patients (17%) who receive multiple transfusions, bears testament to this. The President's Emergency Plan for AIDS Relief, in conjunction with the Global Fund and WHO, funded blood safety programmes in 36 African countries. Comparing the periods from 2000 to 2004 and 2010 to 2011, the median annual number of units of blood donated per country increased, with almost almost 95% of units screened for HBV and HCV. Overall HCV screening increased from 34 - 86% with the median positive blood donations decreasing from 1.4 - 0.9%.[24]

Possibly the most important component of the elimination strategy is the need to target and screen at-risk populations as well as identifying those in the general population who have HCV infection. This component of elimination is the entry point into a continuum of care whereby people ultimately access treatment. This continuum of care must be seamless and smooth and most importantly rapidly transit people from screening, confirmation and linked to the initiation of care. The question regarding who to screen is highly variable for various regions and countries around the world. In the USA for example, a birth cohort screening programme has been undertaken where all people born between 1945 and 1965 are advised to screen at least once for HCV. This so-called targeting of the 'baby boomer generation' is based on known epidemiology. However, as indicated, there is a second wave of new infection within key populations that also needs to be addressed. In sub-Saharan Africa there is also the potential for birth cohort screening in countries such as Cameroon, where the majority of transmission is likely related to programmes within the 1950s and 1960s and related to the use of antiparasitic therapies for trypanosomiasis. Here, unsafe injection practices as well as the reuse of needles and syringes in the programme allowed for the effective transmission of HCV.

The screening and testing of individuals needs to be rapidly upscaled. To achieve this, easy access to point-of-care rapid diagnostic tests (POC RDTs) is key. The WHO makes evidence-based assessments of *in vitro* diagnostic products to help countries when purchasing such tests and then lists the recommendations as prequalified. In 2017, 2 POC RDTs have been prequalified by the WHO and the prequalification of an HCV RNA confirmatory platform is awaited. While prequalification certainly allows for the maintenance of quality, cost of these RDTs remains an issue that warrants global attention and funding to address. In terms of a confirmatory RNA test, the development of cheaper point-of-care confirmatory technologies is also key. Here, a desktop point-of-care system, such as the Xpert System (Cepheid Technologies, USA) or GeneDrive (Epistem, UK) are possible solutions, although again, cost is crucial. The last component of care prior to initiaiting therapy, is liver fibrosis assessment. Non-invasive approaches are paramount as a biopsy-based approach is neither practical nor feasible. Serum-based tests such as the APRI or FIB-4 are very useful and have a reasonable predictive value for cirrhosis. Vibration-Controlled Transient Elastography (VCTE) technology such as Fibroscan (Echosens, France), provides an easy point-of-care assessment of fibrosis with very good predictive value.[25]

Conclusion

The global elimination of HCV by 2030 has become a distinct possibility with the advent of highly effective fairly simple-to-use treatments. The real challenges lie in identifying those infected and linking them to care. Addressing key populations is fundamental to achieving success. Clear, target-focused and government-supported individual country-based plans are required to achieve the elimination ideal.

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