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COMMENTARY

Measuring hepatitis C virus elimination as a public health threat: Beyond global targets

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Abstract

An increasing number of countries are committing to meet the World Health Organization (WHO) targets to eliminate hepatitis C virus (HCV) as a public health threat by 2030. These include service coverage targets (90% diagnosed and 80% of diagnosed patients treated) and impact targets (80% and 65% reductions in incidence and mortality, respectively, compared to 2015 levels). Currently, a dozen countries are on track to reach 2030 WHO HCV targets. However, while striving for the WHO targets is important, it should be recognized that progress on impact targets is derived from mathematical models projecting decreases in incidence and mortality on a global scale. Despite HCV treatment access in many counties for a number of years, limited empirical data are available to evaluate progress towards elimination. In some countries, substantial incidence and mortality reductions based on reaching the WHO service coverage targets may be unachievable. For example, in countries with ageing hepatitis C–infected populations, even if they have a quality hepatitis C response, high hepatitis C–related morbidity at baseline may not be reversible even with increased HCV treatment uptake and diagnosis. Finally, WHO targets are not necessarily easily or reliably measurable. Measuring relative impact targets requires high-quality data at baseline (ie 2015) and longitudinal data to assess temporal trends. In this commentary, we propose alternative additional measures to track progress on reducing the HCV burden, offer examples where the WHO targets may not be informative or achievable, and potential practical solutions.

KEYWORDS

elimination, hepatitis C virus, WHO targets

1 | INTRODUCTION

In 2016, the World Health Organization (WHO) set ambitious targets to eliminate viral hepatitis as a public health threat; they entail reducing hepatitis C virus (HCV) incidence by 80% and HCV-related mortality by 65% by 2030 (compared to 2015).[1] To achieve them, the following service coverage targets must be achieved: (a) 90% of individuals diagnosed (compared to <5% in 2015), (b) 80% of diagnosed individuals treated for HCV (<1% in 2015), (c) harm reduction coverage of > 300 sterile needles and syringes per person who inject drugs per year and (d) 100% of blood donations screened and 90% of injections performed safely (use of engineered devices).[1]

The modelled reductions in incidence and mortality are based on achieving these service coverage targets globally and have

Abbreviations: DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PWID, People who inject drugs; SVR, sustained virological response; WHO, World Health Organization.

been used as main outcomes in regional WHO action plans.[2] WHO recommends each country to develop country-specific targets within their national plans that align with their epidemiological situation.[3] However, this raises the following question: Will achieving the WHO service targets on a regional or sub-population level always lead to local incidence and mortality reduction by 2030?

In some countries, substantial incidence and mortality reductions based on reaching the service coverage targets may be unachievable, as an example from the HIV field shows. Modelling of the HIV epidemic in Australia demonstrated that achievement of the 95% diagnosed—95% on HIV treatment—95% virally suppressed HIV cascade of care targets by 2030 would reduce HIV incidence by 17% compared to 2010—well short of the modelled ~90% global incidence reduction target.[4] This finding is due to the high baseline coverage of services in Australia; the same might be true for countries other than Australia with high baseline coverage of HCV services. In addition, in countries with populations with long-standing HCV infections, high HCV-related morbidity at baseline may not be reversible even with increased HCV treatment uptake and diagnosis.[5] Furthermore, countries or sub-populations with low baseline incidence may be able to dramatically reduce the burden of HCV infection without meeting the 80% incidence reduction target. However, currently only a relative impact target to define elimination of HCV as a public health threat has been developed.

Another issue is whether these targets are measurable. Measuring relative impact targets requires high-quality data at baseline (ie 2015) and longitudinal data to assess temporal trends. Hence, a surveillance system, using data linkage, cohort studies or sample storage, must have existed since before 2015. A country profile survey on HCV elimination among WHO member states found that the majority of countries lacked baseline estimates.[6] Given that data to assess impact targets are more likely to be collected in certain geographical areas or risk groups than nationwide population-level data, measuring the impact targets is probably more feasible within a defined sub-population or at a regional level also known as micro-elimination.

To track progress on WHO impact targets on a local level or develop country-specific targets to reduce the HCV disease burden, it is important to assess whether targets can be measured and whether they are achievable on a local level. For each setting or sub-population, the state of the epidemic and the most suitable disease control framework must be considered.

While the current WHO impact targets remain the key indicators for HCV elimination as a public health threat, in situations where these targets might not be appropriate or informative, additional supplementary impact targets can be considered to refine local measures of elimination. Below we discuss differences in disease elimination frameworks and two situations that exemplify challenges when measuring the WHO targets and when the impact targets may be unachievable.

1.1 | Defining the HCV disease elimination framework

Over the past few decades, WHO and others have called for targets to eliminate, end, control or combat various infectious diseases. These terms are often used interchangeably but there are key differences in their meaning, which impacts on the work to be undertaken to achieve national or international targets. In the epidemiological literature, 'elimination' is defined as "Reduction to zero of the incidence of a specified disease/infection in a defined geographical area as a result of deliberate efforts; continued intervention measures are required". That is, there is a focus on stopping transmission.[7] In contrast, 'control' is defined as "The reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction".[7]

WHO frames the viral hepatitis targets as 'Elimination as a public health threat'. The addition of 'public health threat' means that the WHO targets seem closer to the formal epidemiological definition of control rather than elimination.[8] This is because elimination as a public health threat focuses on reducing transmission rather than aiming at zero new infections. Nevertheless, the HCV WHO targets are a first step towards epidemiological elimination. Although this terminology exchange might seem trivial, it is important to understand the epidemiological distinction to learn from other disease control programs and elimination programs designed to meet the WHO 2030 targets.

1.2 | The WHO incidence impact target in settings with low baseline transmission

People who inject drugs (PWID) are no longer a significant source of HCV transmission in the Netherlands; their number is declining, incidence has remained almost zero over the past decades,[9-11] and the harm reduction target is well met (414 syringes/PWID/year in 2013).[12] Nevertheless, chronic HCV prevalence was estimated at ~50% in 2015 among PWID participating in the Amsterdam Cohort Studies.[13] In this situation, the WHO incidence reduction target might be unachievable due to a floor effect because baseline incidence is low. Modelling suggests that HCV treatment uptake does not need to increase in Amsterdam for incidence to remain <2/1000 person-years between 2016 and 2026 among active PWID, but increasing direct-acting antivirals (DAA) uptake can significantly decrease chronic HCV prevalence (from ~35% to <1% by 2026).[14] Other modelling of former and active PWID in Amsterdam projected that scaling up treatment uptake to 3% in 2015 and increasing thereafter would decrease chronic HCV prevalence by 19% (to 31% by 2029).[15] Differences in the projected prevalence reduction between these modelling studies can be partly explained by differences in the modelled PWID population (including 'only active' vs 'former and active' PWID). An incidence target may therefore be a poor indicator

of progress in reducing the burden of HCV infection in PWID in the Netherlands.

While relative targets are useful in being achievable in a range of settings in which baseline incidence is high, this example raises the question of whether they apply in settings with low baseline transmission risk. For example, in Ireland the announcement that HCV had been eliminated in haemophiliacs focused on reducing prevalence to zero rather than reducing incidence, which is arguably appropriate given the low incidence of HCV in haemophiliacs in many high-income countries. In the context of minimal ongoing transmission risk, chronic HCV prevalence could potentially be a better target to track progress towards reduced HCV burden.

Nevertheless, irrespective of baseline incidence, chronic HCV prevalence is a core health indicator to monitor the health sector response[16]; also, data to measure incidence may not be available in all settings with ongoing transmission. Therefore, a chronic HCV prevalence target is a useful HCV elimination indicator regardless of the state of epidemic. In addition, a threshold target at which HCV incidence no longer poses a public health threat makes intuitive sense and could function as a target after which relative incidence targets do not apply.

1.3 | Reducing HCV-related mortality by 65%: the state of the epidemic and the population at risk

Initial high DAA treatment uptake[17-19] could eventually lead to the attainment of the WHO mortality target (65% reduction in liver-related mortality due to *chronic* HCV infections[1]).The population at risk included in the analysis could potentially have a substantial impact on observed reductions in HCV-related mortality. For example, if we compare the mortality rate among individuals living with chronic infection separately in 2015 with that in 2030, individuals who have been cured prior to 2030 would be excluded from the 2030 risk-set. This could potentially lead to a change in the distribution of the duration of chronic infection and liver disease within the chronically infected population in 2030 compared to 2015, both being important predictors of HCV-related mortality. Importantly, individuals with cirrhosis before being cured have a residual risk of liver-related cancer,[20] even after a decade of being cured.[21] If then a relative reduction in mortality is only assessed among those living with chronic HCV, a reduction in mortality may be observed due to removal of those at greatest risk of death from the risk pool. Perhaps, a more sensitive approach to track progress on changes in HCV-related mortality would be to include individuals living with chronic HCV infection as well as those cured in the risk-set. This was illustrated by two recent modelling studies in Australia, which demonstrate that attainment of the WHO mortality target depends on the denominator population (only chronic vs chronic plus cured).[5,22]

Moreover, irrespective of reaching the service targets (ie diagnosis and treatment), decreases in HCV-related mortality may not be observed in some countries due to high baseline levels of severe liver disease. One of these Australian modelling studies projected that a 65% reduction in annual HCV-related mortality among HCV-antibody-positive PWID could only be achieved by 2030 if the annual probability of developing liver-related cancer following HCV cure among people with severe liver disease decreased from 2% to 0.9%.[5] In countries with ageing populations with long-existing HCV infections and few new infections, reaching the WHO mortality target in both chronic and cured individuals will probably be challenging to achieve, and mortality rates could even be higher in 2030 than 2015. For example, most of Amsterdam's PWID acquired HCV during the 1970s–80s, and ~50% screened in 2009-15 with chronic HCV had evidence of severe liver fibrosis or cirrhosis.[23] The same Dutch modelling study of active and former PWID projected that by 2029 hepatocellular carcinoma (HCC) among those with HCV antibodies would increase by 13% in a stable epidemic scenario (ie stable incidence and number of PWID) and 151% in a declining epidemic scenario (ie the observed Amsterdam epidemic among PWID).[13,15]

These examples show that decreasing the burden of HCV disease requires looking beyond HCV cure and considering the state of the epidemic in HCV elimination programs and national plans. The HCV cascade of care should continue following chronic care. A post–sustained virological response (SVR) liver-related screening service target (eg HCC screening) irrespective of HCV cure and/or HCV retesting could be considered when aiming to eliminate HCV as a public health threat.

2 | BEYOND THE WHO GLOBAL TARGETS

While the WHO targets are a strong advocacy tool and provide guidance for HCV elimination as a public health threat, in certain circumstances we must look beyond WHO's global impact targets. Tailoring HCV elimination monitoring to the local epidemic is warranted because the global service coverage and impact targets may not apply in all settings. We propose alternative HCV targets and definitions to track progress on decreasing HCV infection and disease burden. First, without quality longitudinal surveillance, cohort data or baseline estimates before broad DAA treatment access, an absolute threshold for incidence and/or chronic prevalence and mortality targets in addition to or instead of relative estimates must be considered. An incidence rate threshold is particularly important in settings with a low baseline transmission risk where relative reduction targets may be hard to achieve. Second, as the ultimate goal is to decrease the HCV disease burden, looking beyond HCV cure is warranted; hence, a post-SVR liver-related screening target other than mortality could be developed. Further studies are needed to assess the frequency of post-SVR screening needed to reduce liver-related mortality by 65%. Evidence must then guide broad consensus across stakeholders including WHO, policy makers, people living with and at risk of hepatitis, and health and research community. Future modelling or epidemiological studies should guide development of local targets by assessing the impact of the epidemic, baseline service

coverage and the population at risk on local incidence and mortality reductions.

CONFLICT OF INTERESTS

Dr Hellard has received investigator-initiated research grants from Gilead Sciences, AbbVie and Bristol-Myers Squibb, outside the submitted work. Dr Doyle has received investigator-initiated research grants from Gilead Sciences, Bristol-Myers Squibb, AbbVie and Merck Sharp & Dohme, as well as honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead Sciences and AbbVie. Dr Scott has received investigator-initiated research grants from Gilead Sciences, during the conduct of the study. Dr Prins, Dr Sacks-Davis and Dr van Santen have nothing to disclose.

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