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Screening Strategies for Hepatitis C Virus

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Since May 2016, the World Health Organization (WHO) has advocated for the elimination of hepatitis C virus (HCV) as a public health threat by 2030, defined as an 80% reduction in HCV incidence and 65% reduction in HCV-related mortality compared with 2015. Targets for achieving these goals include reaching service-coverage targets of diagnosing 90% and treating 80% of chronic HCV infections.[1] This elimination goal was driven by recent advances in the development of highly effective HCV direct-acting antivirals (DAAs).[2] However, it is estimated that less than 20% of all chronically infected individuals were aware of their infection status in 2015 (Fig. 1).[1] This highlights that case-finding will be a major challenge for scaling up treatment to reach the WHO elimination goals, especially in low- and middle-income country (LMIC) settings where limitations in resource and health care infrastructure create additional barriers to accessing treatment.

In most countries, higher prevalence of infection and HCV-related comorbidities are usually concentrated in key subpopulations that have risk factors associated with HCV exposure, such as people who inject drugs (PWID), men who have sex with men, prisoners, individuals with high-risk health care or community exposures, and patients with liver conditions. Recent modeling studies in both LMIC and high-income country (HIC) settings have suggested that prioritizing screening and treatment to such populations can facilitate reaching the WHO HCV elimination goals; therefore, identifying these groups is critical for designing targeted screening programs.[3,4]

In this issue of Hepatology Communications, Chemaitelly et al.[5] explore the issue of whom should be tested for HCV, concentrating on the Middle East and North Africa (MENA) region (including Afghanistan, Iran, and Pakistan), which has a disproportionate burden of infection and disease. They estimate the numbers needing to be tested to identify one chronically infected individual for six broad epidemiological subpopulations (categorized by the perceived risk of HCV infection exposure), referred to as the "yield" of testing. These subpopulations were, namely, PWID, those with liver conditions, those with high-risk health care exposures, those at intermediate risk, special clinical populations, and general low-risk populations. The study's strength is that it draws upon a comprehensive, systematically generated database of HCV seroprevalence estimates derived from over 2,500 studies encompassing 49 million persons across 24 countries of the MENA region, most of which are LMICs. The authors distinguish between "generalized" versus "concentrated" HCV epidemics, in which generalized epidemics were defined as having a HCV seroprevalence of 3% or greater among the general population (Egypt and Pakistan) and concentrated epidemics as less than 3% HCV seroprevalence (remaining countries in region). Concentrated epidemics were usually characterized by high HCV prevalence in one or more subpopulations (e.g., PWID or those with high-risk health care exposures), but with little dissemination in the general population. By

Abbreviations: HCV, hepatitis C virus; LMIC, low- and middle-income country; MENA, Middle East and North Africa; PWID, people who inject drugs; WHO, World Health Organization.

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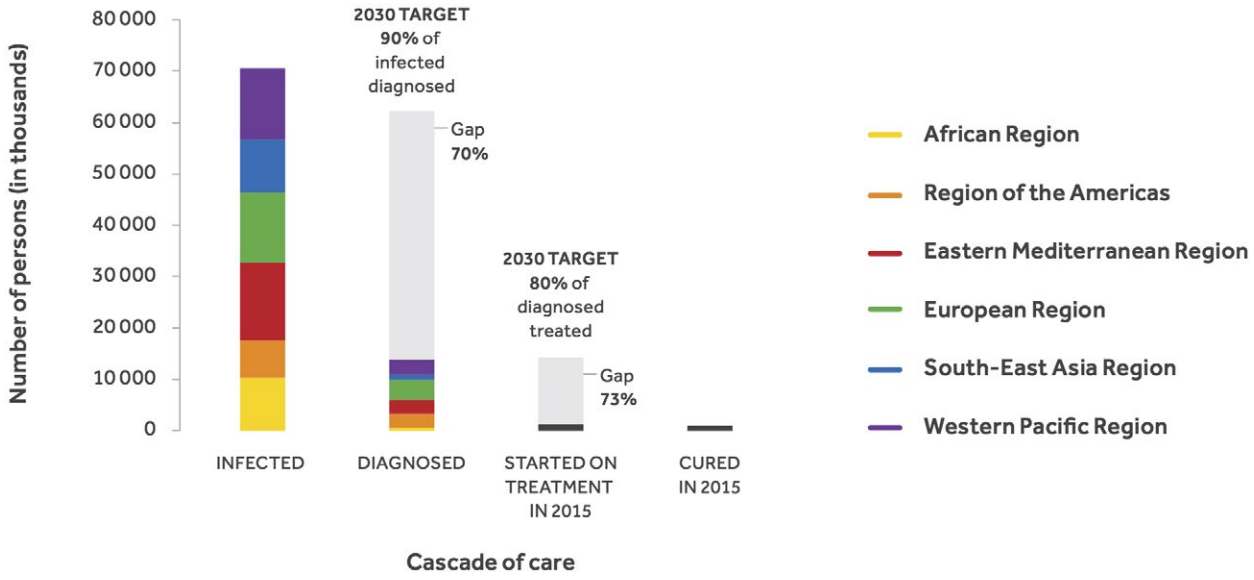

FIG. 1. Cascade of care for HCV infection by WHO region in 2015. Figure reproduced, with permission, from WHO Global Hepatitis Report 2017.[1]

ranking the anticipated yields of chronic HCV cases from screening different subpopulations, the authors identify distinct pathways for how testing programs should expand, depending on the epidemic type.

For both generalized and concentrated epidemics, prioritization of screening in key populations should come first and continue in order of diminishing yield. In the case of generalized epidemics, identifying chronically infected individuals through screening higher-risk groups will be effective at program initiation (e.g., requiring 2.5 tests per chronic infection among PWID), whereas reasonable yields should still be possible when testing is expanded (e.g., 15 tests per chronic infection). In contrast, concentrated epidemics demonstrated starker diminishing returns, with rapidly decreasing yield from 2.8 tests per chronic infection diagnosed among PWID to over 220 in the general population. This suggests that widespread testing may not be cost-effective in lower prevalence settings.

However, despite the conclusions of Chemaitelly et al. that a general population screening approach in concentrated epidemics may not be efficient, it may still be necessary to reach the WHO HCV elimination goals in many settings, as the higher HCV prevalence groups may not contain sufficient numbers of infections. This highlights the need for further studies to assess the yield, reach, cost-effectiveness, and budgetary implications of different screening strategies, including those that use more detailed risk-based algorithms. For instance, in Pakistan we showed a clear trend for increasing HCV prevalence with accumulation of multiple medical and community risk factors.[6] Linking such analyses with economic modeling is particularly crucial in LMICs, where resource prioritization is necessary to ensure the greatest impact with limited resources. As prices of DAA treatments fall and generic drugs become more widely available,[2] an increasing proportion of costs will be attributed to testing. Even in generalized epidemic settings where general population case-finding can effectively identify chronic HCV infections, as prevalence declines, so does the yield, which will lead to a substantial increase in the strain on resources.

Treating high-risk subpopulations that are considered difficult to engage with, such as PWID, is still effective,[7] and the work by Chemaitelly et al. emphasizes that treatment programs should be targeted to these marginalized individuals to maximize the screening yield. Although there are many estimates of HCV prevalence among high-risk subpopulations, especially PWID, what is often not well-known is the size of these populations and how important they are to the

overall epidemic. For instance, whereas PWID play a prominent role in many HICs with concentrated epidemics, their role in most LMICs and more generalized epidemics is less understood. Further studies are needed to give clearer estimates on the numbers of infections present and their distributions, which will elucidate the extent of testing required in each group. More broadly, a greater amount of high-quality data will improve the estimates of risk, yield, and hierarchy of testing strategies, particularly for specific subpopulations but also in the general population.

Better data on how HCV prevalence varies within countries are also needed, as this can exhibit a great deal of heterogeneity, with some experiencing generalized HCV epidemic characteristics, while others hosting concentrated epidemics. An example of this is Pakistan, where Punjab and Sindh provinces have generalized epidemics, with provincial HCV seroprevalence estimates of 6.7% and 5.0%, respectively, whereas Balochistan and the northwestern province of Khyber Pakhtunkhwa have far lower HCV seroprevalences (1.5% and 1.1%, respectively) and concentrated epidemics.[8] These variations highlight the need for efficient screening strategies that are tailored to the subregions of each country.

Stakeholders, including governmental health departments, nongovernmental organizations, and other health care providers, need to navigate the concept of "micro-elimination."[9] This strategy seeks to break down country-level elimination goals into smaller and more manageable targets that are geared toward achieving elimination in defined subpopulations. Lessons learned from micro-elimination strategies in diverse contexts can then be applied more widely to alternative contexts within the same country or to other countries. For instance, from 2015-2016, the Egyptian Liver Research Institute and Hospital launched a community-based micro-elimination project to educate, test, and treat HCV in a village in northern Egypt. The findings were used to complement not only the national government HCV elimination program, but also provide insights that could help inform planning in other high HCV-prevalent countries with large rural populations, such as Pakistan, Mongolia, or Indonesia.[10] Egypt's national HCV screening and treatment program is an exemplar for other countries to follow, not only in the MENA region, but also worldwide. Notably, since launching the "100 Million Health" initiative in October 2018, approximately 23 million people in Egypt have been screened in a period of 90 days in 2018 (Government of Egypt State Information Service, Press Release on December 29, 2018), accounting for almost one-quarter of the country's population. The HCV screening program in Egypt demonstrates the scale that can be achieved in LMICs if there is the political will to act.

As HCV treatment is now highly effective, the main priority and challenge is to efficiently identify infected individuals to treat. The study by Chemaitelly et al. presents the best available data for HCV screening in the MENA region, suggesting potential strategies for efficiently scaling up active case-finding of HCV. The findings highlight the need to prioritize high-risk populations such as those with liver conditions and high-risk health care exposures, as well as marginalized populations such as PWID and prisoners. Further research expanding the ideas in this study, especially on using epidemiological data and cost-effectiveness analyses to tailor screening strategies to the context and resources available in different countries, could pave the way for establishing effective strategies for HCV elimination that can serve as examples in other contexts.

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