HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

EDITORIALS

Regional and Global Summary Estimates of Antibody to Hepatitis C Virus Prevalence in Detainee Populations: Seeing the Forest and the Trees?

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Hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States and worldwide.[1,2] Using systematic review and mathematical modeling, Hanifiah et al. recently estimated that the global prevalence of antibody to HCV (anti-HCV) increased from 2.3% (95% uncertainty interval [UI]: 2.1%-2.5%) to 2.8% (95% UI: 2.6%-3.1%) from 1990 to 2005, for an increase in the number of anti-HCV-positive persons from 122 to 184 million.[3] Although this estimate is higher than some previously published studies, the researchers rightly suggest that their estimate may nonetheless be "conservative" or may underestimate the global prevalence of anti-HCV. Their systematic review specifically excluded studies of high-risk populations (e.g., injection drug users, paid blood donors, homeless persons, and detained or incarcerated persons), and their review included national population-based studies (e.g., U.S. National Health and Nutrition Examination Survey; NHANES), which systematically excluded institutionalized persons, including those detained in jails or prisons, who are at increased HCV risk.

The exclusion of penal detainees from national, regional, and global estimates of anti-HCV prevalence is particularly problematic. The International Center for Prison Studies estimated that, as of May 2011, more than 10.1 million people were held in penal institutions worldwide as pretrial detainees/remand prisoners or sentenced prisoners (hereafter, inclusively termed "detainees").[4] Throughout the world, studies of detainee populations have consistently shown elevated prevalence of anti-HCV, compared to noninstitutionalized, local reference populations. In the United States, for example, anti-HCV prevalence in detainee populations has historically been estimated to be 15-20 times greater than nonincarcerated populations. Based on 1999-2002 NHANES data, the estimated anti-HCV prevalence was 1.6% (range, 1.3%-1.9%) among noninstitutionalized persons in the United States.[1] In 12 selected studies of anti-HCV prevalence in U.S. detainee populations conducted from 1985 to 2002, anti-HCV prevalence estimates ranged from 23.1% to 41%.[5] Notably, from these same studies, anti-HCV prevalence estimates among U.S. detainees with a history of injection drug use were exceptionally high, ranging from 32.3% to 82.8%.[5] Given the large estimated number of detained persons worldwide and the consistently high estimated prevalence among detainees in many countries where data are available, estimates of the anti-HCV burden that exclude detainees are likely *underestimates*. National, regional, and global estimates of anti-HCV prevalence in detainee populations are needed to produce better, "truer" estimates of the burden of HCV infection.[6]

In this issue of HEPATOLOGY, Larney et al. provide regional and global estimates of anti-HCV prevalence among detainees in "prisons and other closed settings".[7] Prisons and other closed settings was defined as prisons, jails, juvenile detention facilities, pretrial detention centers, and extrajudicial detention centers for people who use drugs and excluded psychiatric institutions and immigration detention facilities. Estimates were based upon systematic review and meta-analysis of 93 studies reported between 1990 and September 2012. Specifically, regional summary prevalence estimates were produced using meta-analytic techniques, and, in turn, regional summary prevalence estimates were summarized using meta-analysis to produce a global summary prevalence estimate. To produce regional and global estimated counts of anti-HCV-positive prisoners, regional summary prevalence estimates were applied to the number of prisoners reported or estimated in the region. Regional summary estimates were based on varying numbers of studies (from 1 in Central Asia to

Abbreviations: anti-HCV, antibody to HCV; CI, confidence interval; HCV, hepatitis C virus; NHANES, National Health and Nutrition Examination Survey; UI, uncertainty interval.

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View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.26474
Potential conflict of interest: Nothing to report.

39 in Western Europe) and showed considerable heterogeneity (I^2 >94% in all regions). The global summary prevalence estimate for general detainees was 26% (95% confidence interval [CI]: 23%-29%) and for detainees with a history of injection drug use (k = 51) was 64% (95% CI: 58%-70%). The researchers estimated that 2.2 million (range, 1.4-2.9 million) detainees globally are anti-HCV positive.

With this article, Larney et al. make a significant contribution to the literature. The search strategy and selection criteria for the review cast a broad, inclusive net, bringing together a large, international sample of anti-HCV prevalence studies among detainee populations. They identify and highlight national and regional differences in the availability of anti-HCV prevalence data from detainee populations, as well as variability of anti-HCV prevalence estimates from detainee populations within and across countries and regions. Perhaps most importantly, they demonstrate and underscore the problem of elevated prevalence of anti-HCV in detainee populations and begin to quantify the global scope of the problem at a critical time in history. New, emerging treatments for HCV, though increasing treatment costs in both correctional and community healthcare systems, hold the promise of improving individual outcomes and reducing HCV-related morbidity and mortality and associated costs.[8]

However, the study is not without problems. Two key issues are discussed here to enhance readers' interpretation of the main study findings. First, the broad, inclusive search strategy and selection criteria—although useful for the descriptive purposes of a systematic review—may be too broad and inclusive for the purposes of meta-analytic summarization. For example, inclusion of all otherwise eligible studies from a nearly 23-year time period (1990 through September 2012) increased the heterogeneity of included studies, understanding heterogeneity to be some combination of "true" variation in prevalence and "artefactual" variation related to differences across studies in design or execution.[9] Moreover, given the reported evidence of decreasing prevalence over time (see Table 1 in Larney et al.[7]), inclusion of studies over this broad time span likely produced summary prevalence estimates that are higher than the "true" current anti-HCV prevalence. There is a trade-off here between the inclusiveness of studies and the current validity and usefulness of summary prevalence estimates. One method of handling this trade-off might have been to include and describe all eligible studies for the systematic review, but to generate summary estimates using only studies published after a reasoned, justifiable date.

Second, it is methodologically questionable to use regional summary prevalence estimates as inputs in a meta-analysis to produce a global summary prevalence estimate. Conceptually, this approach may be thought of as a "meta-analysis of meta-analyses." Statistically, the approach involves using the *results* of several random effects models as *inputs* for a random effects model. Random effects models for meta-analysis can be considered a special case of multilevel analysis because they account for sampling/within-study variance (level 1) as well as systematic/between-study variance (level 2) of included studies.[10,11] Thus, directly inputting regional summary estimates from several random effects meta-analytic models into a random effects meta-analytic model ultimately produces a global summary estimate and associated standard errors that do not fully account for, or accurately reflect, the considerable within- and between-study variance introduced by the population of all included studies. The ideal approach here would be a multilevel or "nested" analytic approach that can accommodate at least four levels (persons within studies and studies within regions). Indeed, several methodologists have advocated using multilevel approaches to meta-analysis because it affords the flexibility of adding further levels to the model and a range of possible methods for estimation and testing.[10,11] Arguably, however, there do not appear to be specific guidelines for conducting multilevel meta-analysis,[12] and even general guidance from the literature appears to be limited.[10,11]

Short of conducting a multilevel meta-analysis, a simpler and sounder approach to producing a global prevalence estimate in this case would have been to take the sum of the anti-HCV-positive counts in each of the regions (produced by applying the regional summary prevalence estimates to the detainee population in the respective regions) and dividing these sums by the total detainee population (see Table 2 in Larney et al.[7]). This would produce a global estimate of 21.5% (range, 14.2%-29.1%) and is consistent with the reported numbers of anti-HCV-positive detainees (2.2 million; range, 1.4-2.9 million). Notably, this point prevalence estimate is lower than that produced by the meta-analysis of meta-analyses (26%). Of course, this revised approach does not address the issues previously discussed here related to heterogeneity of studies or the decrease in anti-HCV prevalence over time.

A commonly used idiom in American English is "can't see the forest for the trees," referring to when one becomes too focused on, or involved in, the details of a given problem to be able to understand the problem as a whole.[13] Although the study by Larney et al. is not without problems, the study

nonetheless helps us to begin to see both the "forest" and the "trees" of anti-HCV prevalence estimates in detainee populations and, in turn, a truer picture of the global burden of HCV infection. Indeed, in and of itself, the identification and collection of 93 studies of anti-HCV prevalence from detainee populations (the trees, if you will) represents a major step forward in quantifying the regional and global burden of HCV infection in these populations (seeing the forests). More generally, the study points toward the challenges of producing useful regional and global anti-HCV prevalence estimates, the need for improved primary collection of anti-HCV data in several regions, and the opportunities for primary, secondary, and tertiary prevention in high-risk detainee populations.

Acknowledgment: The author thanks Sandi L. Pruitt, Ph.D., for providing critical feedback on an earlier draft of this editorial.

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