In an investigation using national data sources, Shea et al. (1) estimated the rate of reactivation tuberculosis (TB) to be 0.084 cases per 100 person-years among persons with latent TB infection (LTBI) in the United States. The authors present these findings as the overall rate of reactivation TB in the United States, and they state that the groups identified as having higher rates of reactivation TB “have increased rates of progression and will receive even greater benefit from testing and treatment” (1, p. 223) for LTBI. While this study represents an important attempt to quantify the contribution of reactivation TB to the overall TB burden in the United States, this extrapolation has significant implications for TB control programs, and we urge caution in the interpretation and application of these results.

Shea et al. (1) differentiated reactivation TB cases from primary TB cases on the basis of cluster status, with cases that clustered being considered cases of primary TB. A cluster was defined as “at least 2 cases with indistinguishable TB genotypes reported within statistically significant geospatial zones” (1, p. 217). While using genotyping to distinguish primary TB from reactivation TB is a common molecular epidemiologic technique, limitations with this method, such as sampling bias (2), unknown strain variation (3), and genotyping methods with limited discriminatory power (4), have been documented. The authors accurately acknowledge that there are circumstances in which recently transmitted cases may not cluster. Conversely, clustering among TB cases does not necessarily imply recent transmission, as demonstrated in investigations where reactivation of old TB infections occurred at the same time (5) or where endemic strains in a stable population resulted in large genotypic clusters (6). These examples highlight the critical role of local epidemiology, since knowledge of patients’ demographic and social characteristics, epidemiologic links between patients, and the distribution of local TB strains is crucial to determining whether recent transmission has occurred among genotypically clustered cases.

In addition to misclassification related to the definition of reactivation TB, further bias may have been introduced by assigning cluster status to cases that could not be genotyped. This methodology assumes that recent transmission occurred at equal rates among genotyped and nongenotyped cases (>50% clinical TB cases in the study by Shea et al. (1)). However, risk for recent transmission may differ among clinical TB cases when compared with laboratory-confirmed TB cases. This is exemplified among children, in whom only 30%–70% of TB cases are culture-positive, yet these events typically indicate recent transmission (7). Moreover, a number of factors not available for analysis have been shown to influence the risk of clustering, including alcohol abuse and injection drug use (8, 9).

These limitations add to important concerns acknowledged by the authors—including a restricted period of observation (10) and incomplete coverage of all culture-positive TB cases (11)—that may contribute to further misclassification of TB clustering. Despite these issues, Shea et al. (1) depict their estimate as the national rate of reactivation TB.

Of greatest concern, the authors extrapolate their findings to disease progression and recommendations for targeted LTBI testing and treatment. However, the methodology of this investigation was not equipped to study or support such inferences; it lacks information on established risk factors for disease progression and, more importantly, a comparison between persons with LTBI who progress to TB disease and those with LTBI who do not progress (12). Despite these factors, which cause us to urge caution against broad generalization of the results, we appreciate the authors’ novel approach to a complex and critical question in TB control.

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REFERENCES

In their article on fish consumption and depression, Smith et al. (1) presented interesting and important results. The authors speculated, quite reasonably, that ω-3 fatty acids in fish might be causative in depression. However, the amino acid tyrosine is present in high concentrations—approximately 1%—in many fish (2). For example, the tyrosine content of tuna is approximately 160% that of chicken. Tyrosine is a biological precursor of dopamine, norepinephrine, and epinephrine. A deficiency in dietary tyrosine has been implicated in depression (3).

Tyrosine is also a component of thyroxine and triiodothyronine, and reduced thyroid function has been linked to depression (4). Is it possible that an enhanced dietary intake of piscine tyrosine could explain the observations of their study? I think Smith et al. need to cast a wider net so as to consider other dietary components that might have caused their findings.

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REFERENCES


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FIVE AUTHORS REPLY

Mr. Evans raises an interesting point. It is possible that components of fish other than ω-3 fatty acids may be beneficial for mental health or may be synergistic, as we stated in our introduction (1).

There has been a lot of interest in identifying the key nutrient in fish that is beneficial for mental health. The majority of that research has focused on ω-3 fatty acids. Although the evidence from randomized controlled trials is inconsistent,