and traditional case-finding) and, second, that such disease can be
diagnosed either radiologically or microbiologically. Both features of
this definition pose difficulties.

First, the concept of subclinical disease is difficult to
operationalize because of its sensitivity to the elements
included in the standardized history—with most studies
rellying on cough ≥2–3 weeks (with or without hemoptysis),
and a minority adding various constitutional symptoms—and
because the art of history-taking yields differential results.
Significantly, studies purporting to demonstrate subclinical TB
consistently rely on “asymptomatic” patients who nevertheless
produce sputum (3, 4). To account for such difficulties, the
authors extend their definition of subclinical TB to those with
symptoms “not recognized in the context of a clinical
interview”—which unfortunately begs the question, whose
interview? Active TB to one clinician may be subclinical TB to
another, and categorial heterogeneity remains. While
diagnosing subclinical disease will always be subject to some
ambiguity because it depends on human insight, studies
deploying a maximally rigorous history are needed to
minimize this ambiguity and determine what proportion of
infectious TB is truly subclinical (i.e., inaccessible to all
symptom screening). Sputum induction or other advanced
methods will be required for diagnosis in such cases.

Second, the information provided by radiologic and
microbiologic assays are of different kinds; in the absence of
symptoms, the latter is diagnostic of subclinical TB, whereas the
former is only suggestive. Radiologic findings in
asymptomatic patients may include stigmata of disease now
resolved, latent, or incipient, but suspicious for activity (e.g.,
fibrocvatary disease), as well as features more suspicious for
active disease (e.g., airspace or endobronchial disease)—yet each
of these would qualify for the authors’ definition of subclinical TB.
Suboptimal performance characteristics make imaging
modalities unreliable for definitively diagnosing subclinical TB;
they have been inadequately studied for that purpose. In
practice, radiologic studies are used to generate pretest
probabilities relative to a threshold for performing microbiologic
studies. The distinguishing feature of subclinical TB, as opposed to
latent, incipient, or active disease, is microbiologic positivity
in the absence of symptoms (4), which, per the authors’
intention, infers the possibility of silent transmission.
Again, prevalence studies employing sputum induction on
asymptomatic patients seem necessary to delineate the
scope of the problem.

As to scope, the authors estimate that missed subclinical TB
(symptom- and radiograph-negative disease) accounts for at least
10% of additional cases in the 2011 Cambodia National TB
Prevalence Survey. Meanwhile, Frassella and colleagues (4), reviewing
these and other data, estimate the same burden at only 0–5%.
Pending further studies, indirect evidence for a more modest figure
may come from the successful treatment of latent TB infection
(LTBI). If subclinical disease were as prevalent as the authors suggest,
monotherapy for LTBI would be expected to drive significant
drug resistance via missed subclinical cases—particularly in that
(unknown) proportion of subclinical disease that is smear positive.
Yet trials of both isoniazid and rifampin monotherapy for LTBI,
using only traditional symptom and radiograph screening to rule out
active disease, have produced no such evidence (5, 6).

Any characterization of subclinical TB must account for
this phenomenon.
In terms of population prevalence, “subtle” symptoms that are either too mild to trigger healthcare-seeking or too nonspecific to prompt clinical TB workup are far more common than “classic” symptoms that lead to rapid care-seeking and diagnosis. As noted by Dr. Pierce, some patients with these milder symptoms might answer “yes” if explicitly asked about the presence of symptoms—and thus would not be classified as having subclinical TB in prevalence surveys (3) or other TB-focused clinical evaluations where TB symptoms are explicitly queried. However, detecting these milder symptoms depends on asking the right questions, in the right way; the presence of symptoms is not a fully standardizable objective measure. Further down the spectrum of symptom severity, people with TB may experience symptoms that are so mild or transient (in comparison with the routine lived experience) that they do not recognize those symptoms as unusual. These individuals would be classified as having subclinical TB in most prevalence surveys—even though symptoms are present. Eliciting such mild symptoms may require more in-depth investigation (e.g., wearable cough monitor or patient diary) than is typical in large-scale surveys, but they can be detected with sufficient effort. Furthermore, the determination that TB is “symptomatic” versus “subclinical” is also context-specific; for example, whether an occasional cough is identified as unusual by a patient or interviewer may depend on the prevalence of unrelated cough related to weather, ambient air pollution, or smoking.

Standardization of methodology (4) and inclusion of objective measurements may help to better characterize both the spectrum of TB symptoms and the prevalence of truly asymptomatic TB. This may be particularly important for cough, given the role that its frequency and character often play in transmission (5). However, objectively based standardization is difficult to employ routinely in large-scale surveys. Ultimately, some dichotomization of TB by symptoms is necessary, both for describing the epidemiology of TB and for deciding who should receive further testing. Still, as Dr. Pierce suggests, we should not confine standardization with conceptual clarity, nor simple dichotomization as “symptomatic” and “subclinical” with either the complex underlying spectrum of TB symptoms or transmission potential.

Similar considerations apply to radiographic findings: dichotomization is sometimes necessary, but radiographic abnormalities of TB exist on a spectrum from easily recognized to very mild or perhaps imperceptible. Furthermore, an individual’s place on this radiographic spectrum can be useful—if imperfect—indicator of the intensity and duration of therapy required for cure (6). As the TB community pursues much-needed investigation of how best to detect and treat subclinical TB, historical data suggest—as Dr. Pierce reminds us—that preventive therapy after widespread X-ray screening likely cures those with asymptomatic or minimally symptomatic TB that is not detectable radiographically.

In summary, we agree with Dr. Pierce that both symptoms and radiographic findings should be conceptualized as falling on a spectrum, even if we must sometimes rely on artificial dichotomizations to help standardize definitions and make binary clinical decisions. Further characterization of the underlying spectra of TB symptoms and radiographic abnormalities—and their correlation with transmission—is an essential step to better understanding the dynamics of TB on a population level in different epidemiological contexts.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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