diagnosis of peripheral nodules be recommended as opposed to direct referral for surgical resection in a patient with acceptable lung function? Will a bronchoscopic technology be developed that will allow for real-time ultrasonographic guided biopsies of peripheral lung nodules, similar to EBUS-transbronchoscopic needle aspiration for central lung masses and lymph nodes? What is the utility of UTB and radial ultrasound for the diagnosis of pure ground glass pulmonary nodules, given that patients with these radiographic abnormalities were excluded from the study by Oki and colleagues?

Of course, initiation of nationwide lung cancer screening with low-dose CT scan presents a number of other concerns; primarily, that nodules identified in the National Lung Screening Trial were smaller than the nodules described in this study, with the majority of them less than 1 cm in diameter (>80% nodules identified measured less than 1 cm and 50% measured less than 5–9 mm) (5). None of the guided technologies in this clinical study, nor those additionally reviewed in the Wang-Memoli meta-analysis, have proved highly reliable in the diagnosis of subcentimeter pulmonary nodules, which are traditionally only accessed by CT-guided transthoracic needle biopsy (3, 4). Single-center retrospective analyses by expert bronchoscopists have demonstrated high diagnostic yield rates for navigational bronchoscopy techniques in small (<1.5 cm) pulmonary nodules, but these have not been confirmed on multicenter prospective clinical trials (6).

One bronchoscopic approach that has shown the theoretical potential for successful biopsy of subcentimeter pulmonary nodules is the recently described bronchoscopic transparenchymal nodule access procedure (7), although this it extremely early in clinical development and only demonstrated a high yield in subcentimeter nodules in an artificial lung nodule model in canines (8, 9).

The pulmonary and thoracic surgery community now has at its fingertips a number of bronchoscopic and percutaneous technologies of varying expense, risk, and yield for the diagnosis of peripheral lung nodules. We are, however, in need of well-designed, randomized controlled clinical trials comparing these interventions with outcomes that are patient-centered and sensitive to increasing concerns of cost-containment in every health care system. These can then inform guidelines for routine clinical management of our patients with this increasingly identified clinical scenario. ■

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# Upper Room Germicidal Ultraviolet Systems for Air Disinfection Are Ready for Wide Implementation

Upper room germicidal ultraviolet (UV) systems consist of luminaires with lamps installed that emit light in the UV-C range (100–290 nm; typically at 254 nm generated by low-pressure mercury vapor lamps). Most luminaires are designed with louvers that limit the light to a narrow region, and are installed in the upper part of the room. These systems are designed to focus the UV-C light in the upper part of the room, thus inactivating airborne infectious agents that reach the lighted zone. The lower part of the room is kept relatively UV-C free, minimizing exposure to persons in the lower part of the room. Inactivation in this context means the loss of the ability to replicate and form colonies.

These upper room UV systems have long been championed by a handful of physicians and engineers for air disinfection.

Why this technology has yet to be widely implemented, as an engineering control strategy to combat airborne disease transmission, is somewhat of a mystery. Upper room germicidal UV has many unique applications, especially for use in high-occupancy settings such as jails, homeless shelters, and emergency rooms, where unsuspected infectious persons may be present. It is most useful against diseases, such as tuberculosis (TB), that are transmitted by the airborne route. It is advantageous in settings with low ventilation rates. It is probably also useful in settings that have high rates of respiratory infections, such as childcare centers or schools, but this application has yet to be investigated compared with use against TB. Overreliance on mechanical ventilation has been the norm for airborne disease transmission control, but in many settings the outdoor air supply flow rate is too low to impact transmission. Upper room germicidal UV has many benefits including low power use, flexibility, and a high rate of air disinfection.

Many have called for epidemiologic studies of upper room UV before wider implementation, despite the obvious efficacy found in laboratory studies. It is difficult to conduct population-based studies of engineering controls because of their excessive cost. Thus few have been done, and those that have been done have focused mainly on ventilation (1–4). This does not mean that engineering controls do not have a place in health care settings (5, 6).

It is exemplary that authors Mphaphlele and colleagues, as described in this issue of the *Journal* (pp. 477–484), repeated with improvement to the study design this controlled trial to further document the efficacy of upper room UV (7). The use of these data to show upper room efficacy against TB infection, and to improve on the guidelines for installations of upper room UV, is important. Comparing their results and proposed guidelines with previous laboratory and field studies validates the efficacy of upper room UV installations for reducing TB transmission.

In laboratory tests of an upper room UV system (five fixtures and a total of 216 W), the room average concentration of culturable airborne bacteria was reduced on UV exposure by between 46 and 98% compared with the original concentration, depending on the room ventilation rate and microorganism (8, 9). This result is consistent with the efficacy to prevent TB infection of 80% found in the current study, and 70% in the work completed in Peru (10). That the results of these studies are consistent shows the robustness of upper room UV germicidal efficacy, even in complicated real-world settings.

Another major deterrent for implementation of upper room UV systems has been the lack of knowledge about how to size these systems. The first guideline that was suggested for sizing upper room UV systems was to install one 30-W fixture for every 18 $m^2$ (200 $ft^2$) of floor area, or one for every seven people in a room, whichever is greater (6, 11). The following update to the guideline was more recently proposed by the National Institute for Occupational Safety and Health (12). The UV-C wattage room volume power distribution should be 6.3 $W/m^3$. The difficulty in this guideline was that it did not take into account the fixture efficiency, meaning how much UV-C light made it out of the fixture.

As is noted in the study by Mphaphlele and colleagues, some germicidal luminaires are inefficient in their current design for releasing UV-C light. This is because they are designed with louvers to direct the light horizontally and not to allow it to disperse vertically; thus much of it is absorbed. Mphaphlele and colleagues recommend that upper room systems provide 15–20 $mW/m^3$ total fixture wattage to each room.

An additional guideline is proposed in the current study to install fixtures that produce an average room fluency rate of at least 5–7 $\mu W/cm^2$. Although this is a good recommendation, it is difficult to determine the fluency rate in a hospital room. Some methods are available to measure the fluency rate, and Mphaphlele and colleagues estimate it through modeling (13, 14).

In conclusion, this newest controlled trial of upper room UV to interrupt TB transmission convincingly shows again that germicidal UV is an effective treatment against airborne infection. It is clear that to move toward wider implementation guidelines are needed, and this study provides these much needed data-driven guidelines. It is essential to dose a room on the basis of UV-C output from the fixtures. This will optimize designs from manufacturers as well as drive system designs to be more comparable and efficacious. It will also ensure that the correct amount of UV-C light is applied to settings. I hope that these most recent rounds of field studies from Peru and South Africa will give upper room UV systems the data-driven support they need to be more widely implemented. ■

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# Diagnosis of Tuberculosis in Children Using Mycobacteria-Specific Cytokine Responses

## Are There Reasons for Hope?

Recently there has been renewed interest in childhood tuberculosis (TB), and in 2012, World TB Day focused on children for the first time. The World Health Organization estimates that 550,000 cases and 80,000 child deaths are attributable to TB (1), but other estimations using different models almost double these numbers (2).

The confirmation of active TB through culture of *Mycobacterium tuberculosis* is achieved in only 30–40% of children with probable TB (3). Nucleic acid amplification testing does not improve the sensitivity (4), and the rapid GeneXpert *M. tuberculosis* rifampicin assay (Cepheid, Sunnyvale, CA) only detects around 70% of culture-positive cases (5).

The immunodiagnosis of TB relies on the detection of a cell-mediated immune response. The tuberculin skin test (TST) is the standard test, but can have low specificity in bacillus Calmette-Guérin-vaccinated children and nontuberculous mycobacteria infections and suboptimal sensitivity in immunocompromized children (6). Interferon-γ release assays (IGRAs) measure the concentration of interferon-γ in blood exposed to specific *M. tuberculosis* antigens, improving specificity. However, a significant limitation of both TST and IGRAs is their inability to discriminate between latent TB infection (LTBI) and active TB (7). Furthermore, IGRAs have contradictory results in young children, are solely licensed for the diagnosis of LTBI (not active TB), and are not recommended in resource-limited, high-burden TB countries, where their sensitivity is lower than that of TST (8).

In this scenario of difficult diagnosis of TB, the WHO-sponsored *Roadmap for Childhood Tuberculosis* highlights the need to prioritize the evaluation of new diagnostic methods suitable for a pediatric population (9). Biomarkers can provide information about disease status and risk for progression. Because of the frequent paucibacillary nature of the disease in children, a highly sensitive test based on a biological sample other than sputum or gastric aspirate could in theory improve the diagnosis of TB in children (10).

In this issue of the *Journal*, Tebruegge and colleagues (pp. 485–499) investigated 140 children with possible TB, aiming to identify *Mycobacterium*-specific cytokine biomarkers that could allow the distinction between TB-infected and TB-uninfected individuals, as well as between LTBI and active TB (11). All participants underwent a TST, QuantiFERON-TB Gold assay, and cytokine detection by Milliplex human cytokine/chemokine kits (Millipore Corp., Billerica, MA) after ESAT-6 (secretory antigenic target 6), CFP-10 (10-kD culture filtrate protein), and PPD (purified protein derivative) stimulation.

Although considerable overlap between different groups of patients was observed for the majority of cytokines studied, IP-10 (interferon-inducible protein-10), tumor necrosis factor (TNF)-α, and IL-2 responses achieved high sensitivity and specificity for the distinction between TB-uninfected and TB-infected individuals and exceeded the sensitivity of the IGRAs. Furthermore, TNF-α, IL-1ra, and IL-10 responses had the greatest ability to distinguish between LTBI and active TB cases, and the combinations of TNF-α/IL-1ra and TNF-α/IL-10 achieved correct classification of 95.5% and 100% of cases, respectively.

Interestingly, in this study, patients were classified according to stringent criteria: LTB infection was only considered if TST was ⩾10 mm and IGRA was positive, and the child was classified as "uninfected" if TST was 0 mm and IGRA was negative. Four more groups of children were defined according to IGRA results and diameter of TST induration. This categorization allowed a more certain diagnosis of LTBI as well as an analysis of the discrepant results. Thus, some children presented a "common discordance" (negative IGRA with TST ⩾10 mm), and this was attributed to a lack of sensitivity of IGRA based on stimulation with RD1 antigens for the detection of all cases of LTBI. The authors stated there was probably a heterogeneous group comprising both TB-infected and TB-uninfected individuals, but other possibilities, such as the potential effect of nontuberculous mycobacteria exposure on the TST, should be also considered as a cause for the discrepancies (12).

In addition, for children to be classed as having active disease when microbiological confirmation was not achieved, clinical, radiological and epidemiological data had to be present (two of these three), as well as a response to antituberculous therapy.