distribution and BCG vaccination coverage. New vaccines should also be tested in animal models against different *M. tuberculosis* strains before progressing to human studies. Finally, vaccine trials in humans should be performed in Asia where the Beijing genotype family predominates. ■

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Optimizing β-Lactams against Tuberculosis

To the Editor:

Although encouraging progress continues to be made in the development of novel compounds against tuberculosis (TB), a significant proportion of patients with TB resistant to various first-

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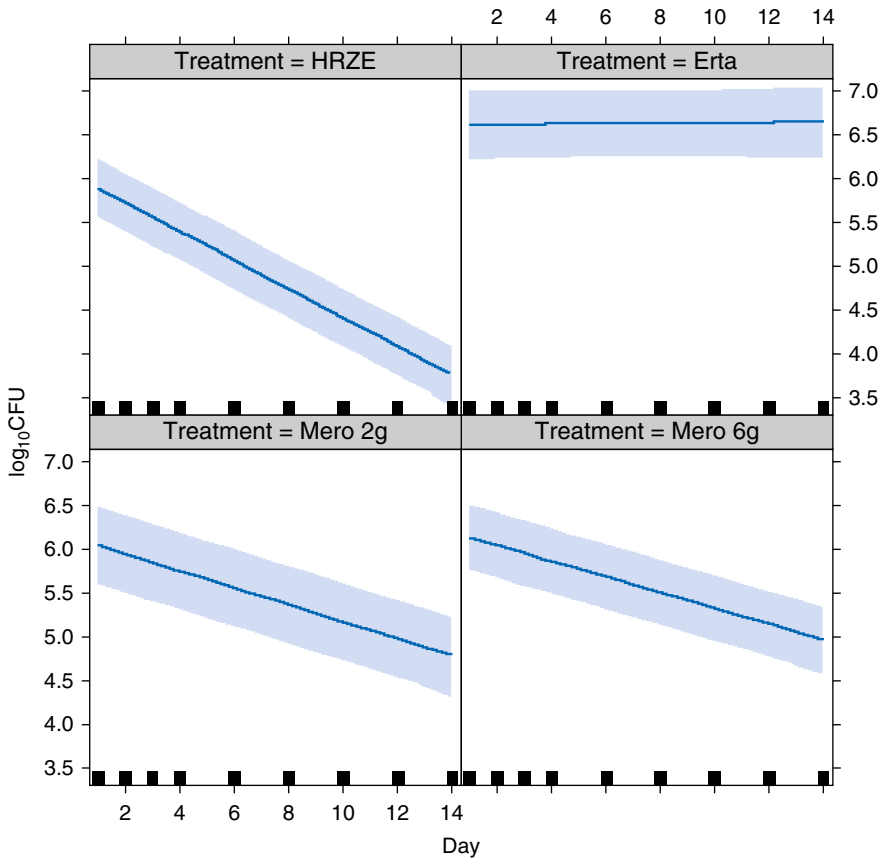

Figure 1. Fourteen-day mycobactericidal activity of intravenous meropenem (Mero) 6 g once daily over 6 hours versus 2 g every 8 hours, compared with that of ertapenem (Erta) 1 g once daily intramuscularly and isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) dosed once daily according to standard weight bands. All Mero- and Erta-containing groups received amoxicillin plus clavulanic acid orally twice daily. The darker blue lines represent the estimated daily on-treatment change in colony-forming units [$\log_{10}$cfu], adjusted for baseline cfu, age, body mass index, sex, and study. The lighter blue shadows are the associated 95% confidence bands. The solid squares represent the time point of sputum collection. We used a single joint linear mixed-effects model, taking into account the correlation between observations from each participant.

and second-line drugs are unable to be successfully treated with the current anti-TB armamentarium. Building on evidence of the early bactericidal activity (EBA) of 2 g meropenem (Mero) administered intravenously every 8 hours combined with oral amoxicillin plus clavulanic acid (Amx/Clv) (1), the World Health Organization recently included Mero-Amx/Clv as an additional drug combination for drug-resistant TB (2).

Aiming to simplify carbapenem treatment for TB, we evaluated the 14-day EBA of Mero or ertapenem (Erta), combined with oral Amx/Clv, in patients with rifampicin-susceptible pulmonary TB. We conducted a prospective two-phase randomized trial at a single site in Cape Town, South Africa. Approvals were obtained from the local regulatory authority and ethical review board before study initiation. Participants received either Mero 6 g once daily administered intravenously over 6 hours or a once-daily dose of Erta 1 g intramuscularly, along with two tablets of Amx/Clv 1,000/62.5 mg every 12 hours. A smaller control group received standard-of-care combination therapy with daily isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE). We collected serial sputum samples from each participant before and during study treatment. We used linear mixed-effects modeling to estimate EBA as the daily change in colony-forming units ($\log_{10}$cfu) per milliliter of sputum plated onto 7H11S agar plates. A total of 39 participants were recruited, with 18 and 17 participants enrolled in the Mero and Erta groups, respectively, and 4 in the HRZE group. Overall, 69% of the participants were male, with a median age of 32 years and body mass index of 19.2 kg/m^2. All participants were HIV-negative. The mean baseline cfu count was similar between treatment groups.

We also evaluated the data from the previous β-lactam study performed by our group in 2015 (1). Finding no statistically significant differences between baseline and control variables for these two studies, we combined the data and directly compared treatment outcomes (Figure 1). Mero-Amx/Clv 6 g once daily showed significant EBA with a daily decrease of 0.094 (95% confidence interval [CI], 0.075 to 0.115; $P < 0.0001$), which was not different from the Mero-Amx/Clv 2 g 8-hourly EBA decrease of 0.095 (95% CI, 0.073 to 0.118; $P < 0.0001$). Erta-Amx/Clv showed no EBA (increase of 0.010; 95% CI, −0.010 to 0.031; $P = 0.3480$). There were no unexpected or severe adverse events.

A prolonged once-daily dose of Mero with similar activity to the World Health Organization–recommended every-8-hours dose may prove more practically implementable in low-resource settings where treatment is provided on an outpatient basis. Long-term

hospitalization for an every-8-hours overnight administration of intravenous therapy is prohibitive in many areas with a high incidence of TB that is resistant to current orally bioavailable medicines. Based on time above the minimum inhibitory concentration as the driver of carbapenem activity, pharmacokinetic modeling has further predicted that a single 6-g dose of Mero could safely be infused in an even shorter time without critically reducing bactericidal activity (data not shown). Erta administered intravenously and/or at higher doses needs further investigation, as has been suggested by other investigators based on *in vitro* data and pharmacokinetic studies (3, 4). Meanwhile, the search for an orally bioavailable carbapenem with anti-TB activity must continue. ■

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Electronic Cigarette Use and Chronic Respiratory Symptoms among U.S. Adults

To the Editor:

E-cigarette use is rising in the United States, especially among adolescents and young adults (1). Although limited evidence suggests that e-cigarettes may contribute to a higher respiratory symptom burden, the role of age and concurrent tobacco smoking in this relationship remains unclear (2–8). We examined the association of e-cigarette use with chronic respiratory symptoms, specifically focusing on young adults and never tobacco smokers—groups traditionally at low risk for respiratory symptoms.

Methods

We analyzed data on noninstitutionalized U.S. adults (≥18 years old) from the 2017 Behavioral Risk Factor Surveillance System (BRFSS), a national health-related telephone panel survey conducted annually by the CDC. In 2017, 11 states collected data on both respiratory health and e-cigarette use. We included individuals who responded to at least one respiratory symptom question plus the e-cigarette use question.

E-cigarette use was defined as responding "every day" or "some days" to "Do you now use e-cigarettes or other electronic vaping products every day, some days, or not at all"? We considered individuals who responded "not at all" as unexposed. We excluded individuals who responded "don't know" or refused to answer.

Our primary composite outcome was chronic respiratory symptoms, defined as responding "yes" to at least one question assessing daily cough, sputum production, or breathlessness during the past 3 months. We considered missing responses to individual questions as negative responses, provided that the respondents answered at least one question. Secondary outcomes included cough, sputum production, or breathlessness separately. For these secondary outcomes, we excluded participants who refused the respective question.

We used multivariable log-binomial regression to estimate adjusted prevalence ratios for the association of e-cigarette use with respiratory symptoms. We applied BRFSS weights (9) to minimize potential bias from differential survey response rates and selection probabilities. Given our clinical question, we stratified the models by tobacco smoking status (current, recent-former [quit ⩽ 1 yr], remote-former [quit > 1 yr], and never) and age group (18–34, 35–54, and 55+ yr). The final models adjusted for sex, obesity (body mass index ⩾30 vs. <30 kg/m^2), and cardiac or respiratory disease. We prespecified sensitivity analyses excluding individuals at high risk for respiratory symptoms (current inhaled-marijuana users and participants who reported chronic obstructive pulmonary disease, asthma, or heart disease).

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