location, income, education, and the benefit plan design of the individual's health insurance. The paper's findings on aggregate spending tell us about the magnitude of healthcare payments by Medicare, Medicaid, and private insurance but obscure the details of health plan designs that may affect the scale of spending on respiratory disease and reveal the causes of spending differences among health plans. Indirect costs of respiratory conditions, such as productivity losses associated with allergic rhinitis or the mortality costs of COPD, were also excluded, leaving out essential components of economic burden of the disease. For chronic respiratory conditions with no currently existing cure, a more practical focus would be the cost of uncontrolled category of the disease rather than the cost of both controlled and uncontrolled categories, similarly to the cost of uncontrolled asthma (7).

Despite these limitations, the paper substantially contributes to a relatively small body of literature on the cost of respiratory illness by providing a comprehensive analysis of spending for respiratory diseases. To my knowledge, for the first time in the literature, the authors used DEX data to provide a detailed analysis of expenditures on respiratory diseases, how expenditures varied by demographic group, how they changed over time, and how various factors drive changes.

The results of this study suggest development and implementation of effective programs and policies to improve the quality of care for respiratory diseases while reducing its costs. ■

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References

1. European Respiratory Society. European Lung White Book. Sheffield, UK: European Respiratory Society; 2022 [accessed 2022 Sep 28]. Available from: https://www.erswhitebook.org/.
2. Blaiss MS. Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc* 2010;31:375–380.
3. Yelin E, Trupin L, Cisternas M, Eisner M, Katz P, Blanc P. A national study of medical care expenditures for respiratory conditions. *Eur Respir J* 2002;19:414–421.
4. Ford ES, Murphy LB, Khavjou O, Giles WH, Holt JB, Croft JB. Total and state-specific medical and absenteeism costs of COPD among adults aged ⩾18 years in the United States for 2010 and projections through 2020. *Chest* 2015;147:31–45.
5. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008–2013. *Ann Am Thorac Soc* 2018;15:348–356.
6. Sullivan PW, Ghushchyan V, Navaratnam P, Friedman HS, Kavati A, Ortiz B, *et al.* The national cost of asthma among school-aged children in the United States. *Ann Allergy Asthma Immunol* 2017;119: 246–252.e1.
7. Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M. The projected economic and health burden of uncontrolled asthma in the United States. *Am J Respir Crit Care Med* 2019;200:1102–1112.
8. Zhong W, Bragazzi NL, Kong JD, Safiri S, Behzadifar M, Liu J, *et al.* Burden of respiratory infection and tuberculosis among US states from 1990 to 2019. *Clin Epidemiol* 2021;13:503–514.
9. Palmer S, Raftery J. Economic notes: opportunity cost. *BMJ* 1999;318: 1551–1552.
10. Centers for Disease Control and Prevention. Health expenditures. Atlanta: Centers for Disease Control and Prevention; 2021 [updated 2022 Sep 6; accessed 2022 Sep 28]. Available from: https://www.cdc.gov/nchs/fastats/health-expenditures.htm.
11. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, *et al.* US health care spending by payer and health condition, 1996–2016. *JAMA* 2020;323: 863–884.
12. Byford S, Torgerson DJ, Raftery J. Economic note: cost of illness studies. *BMJ* 2000;320:1335.
13. Duan KI, Birger M, Au DH, Spece LJ, Feemster LC, Dieleman JL. U.S. healthcare spending on respiratory diseases, 1996–2016. *Am J Respir Crit Care Med* 2023;207:183–192.
14. Reinhardt UE. Does the aging of the population really drive the demand for health care? *Health Aff (Millwood)* 2003;22:27–39.

To Err Is Human, to Forgive Is Pharmacodynamic

It was not long after completion of the first controlled clinical trial of a new treatment for tuberculosis (TB) that drug-resistant strains of TB developed (1), dampening the enthusiasm generated by the mortality improvement that had been observed after 6 months of streptomycin (2). This discovery initiated a period of sustained research to identify combination regimens for the treatment of TB that were effective at curing disease and preventing the acquisition of drug resistance (3, 4). Despite a number of options for the treatment of both drug-sensitive and drug-resistant TB, there are large gaps between the proportion of individuals cured when allocated to standard of care in clinical trials (5–8) and comparable figures published annually in the World Health Organization global surveillance reports (9). How robust a new treatment regimen is likely to perform in a programmatic setting in the presence of nonadherence is a critical aspect of drug development; in this issue of the *Journal*, the work by Stagg and colleagues (p. 193–205) to compare the forgiveness of 6- and 4-month regimens using data from clinical trials is welcome (10).

As the authors note, the relationship between dose-taking and treatment outcomes is complex, but they are to be commended for

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using causal mediation analysis to tease out the direct and indirect effects of nonadherence. Their finding that shorter regimens are not more vulnerable, *per se*, to nonadherence is reassuring, particularly in light of recent new collaborations with public, private, and philanthropic funding aimed at further aggressive treatment shortening (11–13). The authors' work also has relevance for national TB programs, as they highlight the importance of adherence in the continuation phase and not just the intensive phase of treatment.

The results of this analysis are limited by the data available; in particular, overall percentage adherence could be evaluated, whereas patterns of adherence could not. It has been shown that longer periods of consecutive nonadherence and shorter gaps between periods of nonadherence are independently associated with poor outcomes among patients with multidrug-resistant TB (14), but the granular data were not available for Stagg and colleagues to evaluate these findings in these data; this is a lesson for trialists, that they should attempt to capture adherence data with sufficient detail to permit important secondary analyses. Adherence, as expected, was generally high in these clinical trials, so there were little data to inform how robust shorter regimens might be when adherence is lower, as is often observed in programmatic settings.

The finding that the shorter regimens were reasonably robust to missed doses is encouraging but should be viewed through the lens of what we already know about forgiveness in TB and other infectious diseases. Although the slow doubling time of *Mycobacterium tuberculosis* would theoretically make this infection more forgiving of missed doses, the data suggest that intermittent regimens (twice or thrice weekly) are associated with higher relapse rates (15). There is clearly some threshold at which forgiveness is no longer granted, and it is difficult to find that threshold in cohorts of highly motivated clinical trial participants. Furthermore, forgiveness may well be primarily a pharmacodynamic optimization problem. Current TB treatment includes drugs with relatively short half-lives (30–90 min for isoniazid and 2–3 h for rifampin) that are less robust when doses are missed. It would be interesting to understand how regimens with drugs that have longer half-lives—such as the moxifloxacin (half-life, ∼12 h) and rifapentine (half-life, ∼14 h) regimen used in the recent Study 31/A5349 trial (8)—would fare under real-world conditions of suboptimal adherence. The evolution of HIV therapies over time is informative here; treatment began with pharmacodynamically suboptimal drugs requiring multiple daily doses of several different pills to achieve therapeutic levels, resulting in the frequent emergence of resistance. Now, 25 years later, the current standard of care typically includes drugs with long half-lives and high barriers to resistance, often coformulated into a single pill, that are robust to suboptimal adherence. Pharmacodynamic optimization, even in the setting of a virus that replicates and mutates much more quickly than *M. tuberculosis*, has even made intermittent therapy for HIV possible (16).

The manuscript by Stagg and colleagues provides encouragement that shorter TB treatment regimens for drug-sensitive disease are not necessarily more fragile than the standard 6-month regimen in the face of imperfect adherence. However, the key lesson is that regimens need to be developed that incorporate our understanding of antimicrobial pharmacodynamics while taking human behavior into account. Forgiveness will not be achieved by forgetting the lessons of the past. ■

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References

1. Fox W, Sutherland I, Daniels M. A five-year assessment of patients in a controlled trial of streptomycin in pulmonary tuberculosis; report to the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council. *Q J Med* 1954;23:347–366.
2 . Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. *BMJ* 1948;2:769–782.
3. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999;3:S231–S279.
4. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970;26:28–106.
5. Nimmo C, Lipman M, Phillips PP, McHugh T, Nunn A, Abubakar I. Shortening treatment of tuberculosis: lessons from fluoroquinolone trials. *Lancet Infect Dis* 2015;15:141–143.
6. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, *et al.*; STREAM Study Collaborators. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019;380: 1201–1213.
7. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, *et al.* Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019;7:249–259.
8. Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE, *et al.*; AIDS Clinical Trials Group; Tuberculosis Trials Consortium. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021;384:1705–1718.
9. World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization, 2021.
10. Stagg HR, Thompson JA, Lipman MC, Sloan DJ, Flook M, Fielding KL; Critical Path to TB Drug Regimens. Forgiveness is the attribute of the strong: nonadherence and regimen-shortening in drug-sensitive TB. *Am J Respir Crit Care Med* 2023;207:193–205.
11. Boeree MJ, Lange C, Thwaites G, Paton N, de Vrueh R, Barros D, *et al.* UNITE4TB: a new consortium for clinical drug and regimen development for TB. *Int J Tuberc Lung Dis* 2021;25:886–889.
12. Bill & Melinda Gates Medical Research Institute. PAN-TB Collaboration to advance investigational tuberculosis drug regimens to phase 2 clinical trials. 2022 [accessed 2022 Sep 28]. Available from: https://www.gatesmri.org/wp-content/uploads/2022/08/PAN-TB-JDA-Press-Release-August-17-2022.pdf.
13. USAID. USAID announces up to $200 million for research to combat tuberculosis. Washington, DC: USAID; 2022 [updated 2022 Sep 26; accessed 2022 Sep 28]. Available from: https://www.usaid.gov/news-information/press-releases/aug-04-2022-usaid-announces-200-million-research-combat-tuberculosis.

14. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, *et al.* Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. *J Infect Dis* 2015;211:1607–1615.
15. Johnston JC, Campbell JR, Menzies D. Effect of intermittency on treatment outcomes in pulmonary tuberculosis: an updated systematic review and meta-analysis. *Clin Infect Dis* 2017;64:1211–1220.
16. Landman R, de Truchis P, Assoumou L, Lambert S, Bellet J, Amat K, *et al.*; ANRS 170 QUATUOR study group. A 4-days-on and 3-days-off maintenance treatment strategy for adults with HIV-1 (ANRS 170 QUATUOR): a randomised, open-label, multicentre, parallel, non-inferiority trial. *Lancet HIV* 2022;9:e79–e90.