Comparative-effectiveness research (CER) is a hot topic. There are several definitions for CER, but the Institute of Medicine defines CER as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care” [1]. Comparative-effectiveness research focuses more on effectiveness than efficacy; that is, how well something works when implemented in a real-world setting and on comparing alternative treatments, prevention, or diagnostic strategies. Comparative-effectiveness research also seeks to develop evidence that improves health by focusing studies on outcomes that matter to patients.

Comparative-effectiveness research is receiving a lot of attention right now and, frankly, a lot of money. The American Recovery and Reinvestment Act in 2009 devoted over $1 billion to CER. The Patient Protection and Affordable Care Act led to the creation of the Patient-Centered Outcomes Research Institute, which, as of 2014, has awarded over $400 million in CER research.

The conduct of CER studies involves a range of methodologies including randomized controlled trials (RCTs), cluster randomized trials, observational studies including those that use large administrative databases, as well as cost-effectiveness analysis and decision analysis [2]. Although randomization remains the gold standard for controlling unmeasured confounding in comparative studies, randomized trials have inherent limitations including power and feasibility (especially when studying rare events), high costs, and poor generalizability to real-world care. Advanced methods to control for confounding using observational data, including multivariable modeling, propensity scoring and weights and instrumental variables improve the reliability of observational studies and can greatly improve the ability to do CER when randomized trials are neither available, feasible, nor affordable. These methods of special importance for pediatric infectious disease (ID) research, because children are underrepresented in therapeutic clinical trials [3].

The emerging prominence of CER is in part a response to the fact that healthcare delivery in the United States is highly variable. At the heart of the issue of variability are at least 3 domains: (1) economics: there are geographic differences in reimbursement that create financial incentives to provide more or less care; (2) evidence-base: there is a lack of comparative evidence to support the best and most cost-effective treatment, prevention, or delivery strategies for many common conditions; and (3) implementation: there is failure to translate established evidence into practice, often leading to overuse of unnecessary treatments and services.

The field of pediatric IDs is well positioned to embrace CER. All 3 domains mentioned above are relevant for our field. A prominent example is the variability in antibiotic prescribing observed by region [4], across health plans [5], and between hospitals [6]. As pediatric ID physicians, we often seek to understand clinical outcomes for diseases that in some cases are relatively rare and the evidence base is weak. Comparative-effectiveness research therefore represents a natural approach to addressing the types of clinical research questions that we face. Other important examples include comparing shorter versus standard courses of antibiotics for common infections, prolonged intravenous versus early conversion to oral therapy for a variety of serious infections, and preemptive versus prophylactic antiviral medications after transplantation. Regarding implementation, despite clinical guidelines and evidence supporting the use of narrow-spectrum therapies for conditions including pneumonia and pharyngitis, guideline implementation and successful translation to clinical practice has only been modestly successful [7, 8].
In this issue of *Journal of the Pediatric Infectious Diseases Society*, Ambroggio et al [9] used contemporary CER methods to address a clinical question: do steroids, as an adjunct to antibiotics, benefit children with community-acquired pneumonia (CAP)? This is a real-world clinical question that addresses an aspect of clinical practice that is variable, where overtreatment (with steroids) could cause harm, but any difference in outcomes between the comparison groups is likely to be quite small and difficult to detect. As a result, it would require a large RCT to achieve sufficient power. As an alternative approach to address this question, the authors assembled a cohort of over 2000 children diagnosed with CAP from an outpatient practice network. The main outcome was the occurrence of treatment failure—defined as a follow-up respiratory visit within 14 days during which antibiotic therapy was modified—which was compared between those children that received corticosteroids and those that did not. Because the treatment assignment was not made at random, the authors used the method of propensity score matching to account for patient level differences in the tendency for physicians to either prescribe or not prescribe steroids in addition to antibiotics. This procedure had the effect of “balancing” the exposure groups in terms of other key characteristics besides treatment assignment. The study found no overall difference in the rate of treatment failure between the groups and, in a subgroup analysis, a higher rate of failure among children treated with steroids who did not have asthma. The authors conclude that (1) there is no apparent benefit to the routine use of corticosteroids for children with CAP and (2) there is a possibility that children actually fare worse when they do not have underlying asthma.

This study is an excellent example of the power of using large existing data sources to evaluate competing treatment strategies where there is uncertainty about the best approach. This study addresses a clinical research question that would likely be prohibitively expensive to address as a randomized trial due to the sample size requirements. It highlights the analytic strengths of CER methods and casts some doubt on the benefits of steroids for CAP in outpatients. However, it also brings up a key limitation to retrospective studies, which is the availability of data to study the most important clinical outcomes, especially those that matter most to patients and their families. Treatment failure for outpatient CAP is a relatively rare occurrence in part because many cases are due to viral infection. From the perspective of the patient and their families, the most important outcome may not be “will this treatment fail?” but “how soon will this treatment make me better?” Unfortunately, the data source did not allow measurement of time to resolution of symptoms. If this were designed as a prospective study, the primary outcome may have been chosen to be response rate or time to improvement rather than treatment failure.

Pediatric ID specialists can be leaders in CER. Many of us are skeptics by nature, leery of expensive new therapies, and troubled by waste and overuse. Just in the area of CAP alone, there are many opportunities to use CER methods to address unmet needs across all 3 of the key domains: economics, evidence-base, and implementation. These include comparing standard 10-day treatment courses to shorter courses (ie, 5 days or fewer), use of diagnostic testing to identify patients with a viral etiology who do not need antibiotics, and identifying effective implementation strategies to promote greater use of guideline concordant antibiotic prescribing regimens. The tools to address these questions are available and the funding opportunities are substantial. If we rely solely on RCTs to define and build the evidence base for pediatric ID, we, our patients, and society will wait too long for answers that matter to us all.

**Acknowledgments**

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

**References**