Prudent antibiotic prescribing is a key component of efforts to control antimicrobial resistance and to reduce the occurrence of *Clostridium difficile* associated diarrhoea. In this issue of the Journal, Paul et al. report the results of a cluster randomized trial of TREAT, a computerized decision support system. This is a pivotal trial seen from the perspective of the joint BSAC and HIS Working Party on Appropriate Antibiotic Prescribing in Hospitals. We reviewed the literature on interventions to change prescribing published up to November 2003. Sixty-six studies were included that met the eligibility and quality criteria of the Cochrane Effective Practice and Organisation of Care Group. The key issue in our discussion of this evidence base was validity, which is commonly divided into internal validity, external validity and construct validity. The 66 studies that were included in the review used study designs that had internal validity because they provided some protection against bias and confounding. External validity is concerned with the extent to which results can be applied or generalized to people, settings or times other than those that were the subject of the study. Multicentre studies provide reassurance that the intervention effect is not dependent on the structure or staffing of a particular hospital. Only five of the interventions were tested in multiple hospitals and only one of these multicentre studies was of an intervention to reduce antibiotic prescribing. The other four multi-hospital interventions aimed to improve the effective management of patients with bacteraemia or pneumonia. Finally, construct validity is concerned with the relationship between the study results and a theoretical construct of prudent prescribing. The main flaw in construct validity was that very few studies provided any reassurance about the unintended adverse consequences of interventions. For example, clinical outcomes were only reported for nine (16%) of the 57 interventions that primarily aimed to reduce antibiotic prescribing. The lack of clinical outcome data fundamentally weakens any estimates of cost-effectiveness. A second flaw in construct validity was that only one of the 66 studies addressed the decision to prescribe an antibiotic and the aim of this study was to increase the proportion of women who received prophylaxis for caesarean section.

The article by Paul et al. addresses all of these issues. The authors performed a cluster randomized trial of TREAT in three hospitals in Germany, Israel and Italy. The outcomes included length of hospital stay and 30 day mortality with the null hypothesis that the introduction of TREAT would not have adverse clinical consequences. The costs and benefits of the intervention are compared in Appendix II of the article. The intervention aimed to improve decision making by junior doctors, including the decision about whether or not to start antibiotics.

What were the results? The trial was preceded by an observational cohort study that established the impact that TREAT might have if it was used in clinical practice. For infections with an identified bacterial pathogen the empirical regimens recommended by TREAT were found to be appropriate in 70% of patients compared with 57% of the regimens prescribed by physicians. At the same time TREAT advised no antibiotic treatment for 23% of patients, whereas physicians gave antibiotics to all but 19% of patients. In the randomized trial TREAT significantly improved the probability that patients received appropriate antibiotics [odds ratio (OR) 1.48, CI 1.03–2.11]. Antibiotic costs and length of stay were significantly reduced in two of the three sites. There was no significant difference in 30 day mortality overall or within each site for all patients, those...
Leading article

with infectious diagnoses or those with microbiologically
documented infections. All of these results were based on
intention-to-treat analysis, despite the fact that TREAT was
used to manage only 134 (49%) of 273 patients in the intervention
arm. In a per-protocol analysis (restricting the analysis to cases in
which physicians prescribed an antibiotic identical to TREAT
advice) patients in the intervention arm were much more likely
to receive appropriate antibiotics than patients in the control arm
(OR 3.40, CI 1.96–5.90).

What is the next step? TREAT is an example of a complex
intervention in health care, which is built up from a number of
components that include behaviours and methods of organizing
and delivering those behaviours [e.g. type(s) of practitioner,
setting and location]. In 2004, the UK MRC Health Services and
Public Health Research Board published a framework for the
evaluation of complex interventions. They proposed four phases
to the evaluation of these interventions, analogous to the phases of
drug development. The first two phases involve modelling and
exploratory clinical evaluation, which have both been completed
for TREAT. Phase III is the main randomized controlled trial to
evaluate a complex intervention, analogous to the definitive pre-
licensing trials in drug development. Phase IV, the final step in
the evaluation of a complex intervention is a separate study to
establish the long-term and real-life effectiveness of the
intervention outside of a research context in an observational
study. The next step for TREAT must therefore be observational
studies in clinical practice. The randomized trial clearly shows
what experience with TREAT is going to vary between hospitals;
the more hospitals that can evaluate TREAT and report their
experience the more we will learn.

The publication of this trial is timely. The public health
importance of prudent antimicrobial prescribing rises as deaths
from C. difficile associated diarrhoea increase. The BSAC/HIS
Working Party will be revising its systematic review of
interventions to improve antibiotic prescribing to hospital in-
patients in November 2006. This trial of TREAT will make a
significant new contribution to the evidence base.

Transparency declarations

The author is currently in negotiation with Judex, the company
who developed TREAT, with a view to undertaking further
evaluation of the system, but has no commercial or financial
interest.

References

1. Paul M, Andreassen S, Tacconelli E et al. Improving empirical
antibiotic treatment using TREAT, a computerized decision support
system: cluster randomized trial. J Antimicrobial Chemother 2006; 58:
1338–45.
antibiotic prescribing practices for hospital inpatients. Cochrane Data-
com/cochrane/clsysrev/articles/CD003543/frame.html (1 October 2006,
date last accessed).
3. Landgren FT, Harvey KJ, Mashford ML et al. Changes in antibiotic
prescribing by educational marketing. Med J Aust 1988; 149:
595–9.
4. Hoven JL, Haaijer-Ruskamp FM, Vander Stichele RH. Indicators of
prescribing quality in drug utilisation research: report of a European
60: 831–4.
5. Wyatt JC, Paterson-Brown S, Johanson R et al. Randomised trial
of educational visits to enhance use of systematic reviews in 25 obstetric
6. MRC Health Services and Public Health Research Board. A
Framework for Development and Evaluation of RCTs for Complex
Interventions to Improve Health (2004). http://www.mrc.ac.uk/pdf-
report/mrc_cpr.pdf (2 October 2006, date last accessed).
and decision-theoretic methods in treatment and prognosis modeling.
using TREAT, a computerized decision-support system. Clin Infect Dis
2006; 42: 1274–82.
guardian.co.uk/uk_news/story/0,,1885022,00.html (4 October 2006,
date last accessed).