pragmatic randomised controlled trials (RCTs) in the generation of high-quality evidence to guide the treatment of patients with multidrug-resistant tuberculosis (MDR-TB), in addition to complementary observational research.[1] We wholeheartedly agree, and we would like to highlight the reasons for use of observational studies and the ways to increase their contribution to MDR-TB research.

RCTs remain the gold standard for determining the clinical efficacy of a treatment. Randomisation and inclusion of a concurrent control substantially decrease risk of bias. Nevertheless, the high cost and long duration of RCTs preclude them from addressing every outstanding question. The limitations of long, explanatory MDR-TB trials, which were acknowledged by the STREAM investigators, are well known; proposals to overcome these limitations, including confirmatory pragmatic trials, have been described and should be vigorously pursued.[1,2] Additionally, inadequate funding for MDR-TB research, dynamic research priorities, and changing standards of care demand other approaches to address many urgent questions that cannot or will not be answered by RCTs.

Observational studies, as Abubakar and colleagues note, are subject to many of the same risks faced by RCTs, and more. However, observational research is often more rapidly adaptable to changing practices than are RCTs, and it offers tremendous untapped potential to generate robust, valid, generalisable evidence. Using observational data to produce such evidence hinges upon investments in high-quality data and the application of appropriate analytic methods to resolve biases introduced when a treatment is not randomly assigned. There is no better example of this than in HIV research. Despite nearly 1500 phase 3 and phase 4 HIV/AIDS-related clinical trials registered on ClinicalTrials.gov and higher budgets for HIV trials than for tuberculosis trials, for two decades, HIV researchers have invested in observational cohorts to fill key knowledge gaps. Evidence generated from these cohorts has informed HIV treatment recommendations. Much of this success is attributable to the availability of large, cross-regional partnerships such as the International Epidemiology Databases to Evaluate AIDS and the HIV-CAUSAL collaboration, which have facilitated access to large observational databases. A second crucial component of observational studies in HIV is the development and application of statistical methods to resolve complex biases arising from non-randomised treatments.[3] These attributes permit production of generalisable evidence in response to research questions that could not or would not be answered with an RCT (at a fraction of the cost). For example, ample observational evidence on when to initiate antiretroviral therapy was available before RCTs confirmed these findings.[4]

Programmatic and large-scale observational data are ideally suited to contribute evidence that informs MDR-TB treatment policy and practice. National tuberculosis treatment programmes routinely collect standardised treatment data, which can be exploited to produce timely knowledge. Regional and multinational efforts have attempted to pool these data for generalisable information.[5] Known weaknesses in these data restrict the inferences that can be drawn from them;[6] however, these weaknesses are surmountable with investments in the quality of longitudinal data and building of cross-regional partnerships. Considering RCTs as the sole source of evidence on MDR-TB treatment will restrict the generation of valid, timely evidence. Along with RCTs, improved observational studies will be essential to accelerate our understanding of treatment for patients with MDR-TB who need safer, shorter, and more effective drugs and regimens.

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Bloodstream infections and carbapenem-resistant Enterobacteriaceae in South Korea

We read with interest Andrew Stewardson and colleagues' study[1] of carbapenem-resistant Enterobacteriaceae associated with bloodstream infections (BSIs) in low-income and middle-income countries. South Korea is a high-income country and was therefore excluded from the study. To investigate the effect of carbapenem resistance on patient outcomes, we analysed clinical and microbiological information for 1492 *Escherichia coli* and 579 *Klebsiella pneumoniae* BSI cases in the Global

Antimicrobial Resistance Surveillance System in South Korea.[2–4]

Among 1492 patients with BSIs due to *E coli*, 141 (10%) died within 30 days after BSI onset. Of the 1492 *E coli* blood isolates, 359 (24·4%) belonged to sequence type (ST) 131, 140 (9·5%) belonged to ST95, and 126 (8·6%) belonged to ST69. ST131 was a risk factor for 30-day mortality. Carbapenem resistance was observed in three (0·2%) of 1492 *E coli* blood isolates devoid of carbapenemase production. All patients with BSIs caused by carbapenem-resistant *E coli* took inadequate empirical antimicrobial therapy, and all survived until the end of follow-up. The proportion of patients receiving improper empirical antimicrobial therapy was 347 (23·3%) of 1489 patients with BSIs due to carbapenem-susceptible *E coli*. Notably, resistance of *E coli* isolates to third-generation and fourth-generation cephalosporins was high (35·1%, 524 of 1492 isolates), the associated bla_{CTX-M} extended-spectrum beta-lactamase genes were widespread (31·0%, 463 of 1492 isolates), and the high proportion of inadequate empirical antimicrobial therapy (52·7%, 276 of 524 isolates) and 30-day mortality (12·8%, 67 of 524 patients) were affected by the third-generation and fourth-generation cephalosporin resistance.

Of the 579 *K pneumoniae* blood isolates, 81 (14·0%) were ST23, 32 (5·5%) were ST86, and 31 (5·4%) were ST65. The hypervirulent K1 (13·5%, 78 of 579 isolates), which was associated with liver abscess, and K2 (20·9%, 121 of 579 isolates) were the predominant capsular types.[3] The 30-day mortality rate of patients with BSIs because of *K pneumoniae* was 16·9% (98 of 579 patients), and the capsular type wzi50, which is associated with neither K1 nor K2, was a risk factor. The proportion of carbapenem resistance in *K pneumoniae* isolates was 18 (3·1%) of 579 isolates of which 13 (72·2%) of these 18 isolates were associated with improper empirical antimicrobial therapy and eight (44·4%) of 18 patients with associated BSIs died within 30 days. These results were much higher than for those patients with BSIs due to carbapenem-susceptible *K pneumoniae* of which 72 (12·8%) of 561 isolates were associated with improper empirical antimicrobial therapy and 88 (15·7%) of 561 patients with associated BSIs died within 30 days. Eight (44·4%) of 18 carbapenem-resistant *K pneumoniae* isolates possessed the bla_{KPC} gene; six (75·0%) of these eight isolates were associated with inadequate empirical antimicrobial therapy, and five (62·5%) of eight patients with associated BSIs died within 30 days.

The overall incidence of carbapenem-resistant Enterobacteriaceae and carbapenemase-producing Enterobacteriacea in South Korea is still modest among blood isolates. However, their growing dominance necessitates a close look because antimicrobial resistance is a public health concern for all countries. International travel has an important role for the worldwide spread of antimicrobial resistance,[5] and carbapenem-resistant Enterobacteriaceae and carbapenemase-producing Enterobacteriacea spread intercontinentally at an enormous speed.[6] The time to call for collaborative action to prevent the spread through a systematised plan, including antimicrobial stewardship led by specialists worldwide, is now.

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Carbapenem-resistant *Klebsiella pneumoniae* with low chlorhexidine susceptibility

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is an emerging pathogen of nosocomial outbreaks. In 2018, in our 1400-bed hospital, we identified eight patients colonised with CRKP by rectal screening, of whom four were epidemiologically related. All isolates were sequenced by Illumina MiSeq (San Diego, CA, USA). Six isolates were closely related (sequence type 258, complex type 123) and harboured the plasmid-encoded β-lactamase bla_{KPC-2} carbapenemase, as well as $bla_{TEM-122}$, bla_{SHV-12}, and bla_{OXA-9}. On the basis of genetic distances and the epidemiological data, we detected a nosocomial cluster in the intensive care unit (ICU) in July, 2018.

Subsequently, we sequenced six stored isolates from a local outbreak in 2017. All isolates were clonally related to the cluster in our hospital (appendix). We investigated the biocide susceptibility of all isolates by analysing their minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs).

See **Online** for appendix