aspects. It was not fully pragmatic because it was the first multicentre randomised trial of a standardised regimen for MDR-TB; participant follow-up was more intensive and delivery of the regimen was less flexible than in usual care, highlighting two domains from the PRECIS-2 tool.[3] While these explanatory elements do restrict broad generalisability,[4] the answer is not to abandon randomisation, but to conduct follow-up pragmatic trials to evaluate real-world effectiveness without the biases inherent in observational studies. Both explanatory and pragmatic trials are crucial for the generation of high-quality evidence to support treatment guidelines. Randomised trials to improve the treatment of MDR-TB are urgently needed; unfortunately, one trial cannot answer all questions.

Loveday and colleagues[1] further argued that the STREAM trial was unable to address subgroups such as children or those with HIV. Aside from the challenges in avoiding over-interpretation of subgroup effects,[5] no study can be appropriately powered for subgroup analyses unless it is very large. This limitation will apply to any observational study: all require a similarly large sample size and cannot address key effectiveness questions because of a lack of randomisation. Loveday and colleagues also highlight the lack of audiometry, and that delamanid and bedaquiline were not used. The enhanced audiometric measures were not widely available at the time of stage 1 of the STREAM trial, but they are included in stage 2, as are regimens containing bedaquiline.[6]

Observational and qualitative studies have their place within implementation science, and they provide the opportunity to understand why and how the health system affects the delivery of a treatment. This is not a zero-sum game. We need such studies, together with trials. Change affects not just *Mycobacterium tuberculosis*, but people, societies, and systems, and such studies address these issues.

We agree that trials of tuberculosis treatments take an unacceptably long time to complete. There are efforts underway by major funders to streamline processes, such as approvals and reviews, while protecting the delivery of high-quality and safe research. We should all support such initiatives, which could lead to faster, efficient, innovative, and adequately powered trials.[4] The alternative is to perpetuate the belief that MDR-TB trials are too difficult, in which case guidelines will continue to be based on poor evidence.

IA reports grants from the UK National Institute for Health Research, the United States Agency for International Development (USAID), the Medical Research Council (MRC), and the European Commission. SM reports grants from USAID, the MRC, and the Department for International Development. AN and PPJP report grants from USAID and the MRC. IDR reports grants from USAID.

*Ibrahim Abubakar, Sarah Meredith, Andrew J Nunn, Patrick P J Phillips, I D Rusen
i.abubakar@ucl.ac.uk

Institute for Global Health (IA) and the Medical Research Council Clinical Trials Unit (SM, AJN), University College London, London WC1N 1EH, UK; School of Medicine, UCSF Center for Tuberculosis, University of California San Francisco, San Francisco, CA, USA (PPJP); and Division of Research and Development, Vital Strategies, New York, NY, USA (IDR)

1 Loveday M, Reuter A, Furin J, Seddon JA, Cox H. The STREAM trial: missed opportunities and lessons for future clinical trials. *Lancet Infect Dis* 2019; **19:** 351–53.
2 Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; **380:** 1201–13.
3 Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015; **350:** h2147.
4 Phillips PPJ, Mitnick CD, Neaton JD, Nahid P, Lienhardt C, Nunn AJ. Keeping phase III tuberculosis trials relevant: adapting to a rapidly changing landscape. *PLoS Med* 2019; **16:** e1002767.
5 Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007; **357:** 2189–94.
6 Moodley R, Godec TR, STREAM Trial Team. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. *Eur Respir Rev Off J Eur Respir Soc* 2016; **25:** 29–35.

Revolutionary new treatment for multidrug-resistant tuberculosis

Timothy D McHugh and colleagues[1] have highlighted the potential of the newly recommended, all-oral regimen to improve treatment for people infected with multidrug-resistant tuberculosis. We also welcome the potential for all-oral regimens to decrease the toxicity of multidrug-resistant tuberculosis treatment. However, one must recognise that as yet no evidence exists for the efficacy or safety of the recommended combination. The duration of the regimen (20 months) is of specific concern, since ensuring completion of long regimens is a major challenge for programmes and could restrict their usefulness in practice. Incomplete treatment risks both relapse and development of further antimicrobial resistance.

STREAM stage 1[2] is the first randomised controlled trial to show that a shortened regimen of 9–11 months has non-inferior efficacy to the previously recommended long regimen under trial conditions. Retention was good, but disappointingly the proportion of participants who had an adverse event during treatment and follow-up was not reduced on the shorter regimen. In STREAM stage 2 (NCT02409290), we are testing a 9–11 month fully oral regimen that we hope will be of similar efficacy, lower toxicity, and provide a better option for both patients and programmes. The importance of properly conducted clinical trials to drive the development of treatment guidelines should not be underestimated.

All authors report grants from the US Agency for International Development and the UK Medical Research Council.

*Sarah Meredith, Andrew Nunn, I D Russen
s.meredith@ucl.ac.uk

MRC Clinical Trials Unit at UCL, University College London, London WC1V 6LJ, UK (SM, AN); and Vital Strategies, New York, NY, USA (IDR)

1 McHugh TD, Honeyborne I, Lipman M, Zumla A. Revolutionary new treatment regimens for multidrug-resistant tuberculosis. *Lancet Infect Dis* 2019; **19:** 233–34.
2 Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019: **380:** 1201–13.

Pertussis immunisation in newborn babies

We read with interest the Article by Daan Barug and colleagues,[1] and the accompanying Comment by Kirsten Maertens and Elke Leuridan,[2] on maternal pertussis immunisation combined with delayed primary infant vaccination using reduced doses of acellular pertussis vaccine.

The randomised trial confirms the effectiveness of maternal pertussis immunisation to protect against pertussis infections in infants during the first few months of life via increased transplacental transfer of maternal vaccine-specific antibodies. The results also confirm the interaction between increased concentrations of maternal antibodies and active immunisation in the infant (ie, the blunting effect[3]), and show that antibody concentrations were similar to those in the control group during the first 3 months of life. These results indicate that changing the primary vaccination schedule for infants is feasible.

The findings are useful for health-care experts and policy makers who define vaccination schedules in high-incomes countries. However, some questions need to be answered before the most effective schedule is established.

Immunity against pertussis is multifactorial. In addition to specific antibody production, cellular immunity is involved in the elimination of bacteria that escape humoral defence mechanisms. The concentrations of some IgG antibodies are associated with clinical protection: anti-pertussis IgG concentrations seem to be the most important and are most commonly used as a specific marker of immunity against pertussis.[4] To date, the range of antibody concentrations that effectively confer protection against pertussis in newborn babies and in children has not been established. Previous studies testing different vaccination schedules have not been helpful in this regard because the effectiveness of reducing the number of pertussis cases was not assessed as an outcome. Published trials have also been limited by small sample size.

In terms of immunogenicity of vaccines and schedules, the antibody concentrations observed by Barug and colleagues in newborn babies in the maternal tetanus, diphtheria, and acellular pertussis (Tdap) group at 2 and 6 months of life are similar to those reported by Wood and colleagues[5] in newborn babies who received a monovalent acellular pertussis vaccine at birth. Which of the two schemes is more effective remains unclear. We hypothesise that vaccinating the mother before birth and the child at birth, and delaying subsequent vaccinations, might be the best approach.

These questions could be answered by a large, international, prospective study that overcomes the limitations of previous studies and includes the measurement of antibodies against different pertussis vaccines, antibody responses (concentrations and half-life), and vaccine interference, with follow-up that lasts through infancy and monitors susceptibility to pertussis.

We declare no competing interests.

*Maurizio Bonati, Antonio Clavenna
maurizio.bonati@marionegri.it

Laboratory for Mother and Child Health, Department of Public Health, Mario Negri Institute for Pharmacological Research, 20156 Milan, Italy

1 Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *Lancet Infect Dis* 2019; **19:** 392–401.
2 Maertens K, Leuridan E. Maternal pertussis immunisation as the first infant dose. *Lancet Infect Dis* 2019; **19:** 342–44.
3 Halpin SA, Langley JM, Ye L, et al. A randomized controlled trial of the safety and immunogenicity of tetanus, diphtheria, and acellular pertussis vaccine immunization during pregnancy and subsequent infant immune response. *Clin Infect Dis* 2018; **67:** 1063–71.
4 Storsaeter J, Hallander HO, Gustafsson L, Olin P. Low levels of antipertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to *Bordetella pertussis*. *Vaccine* 2003; **21:** 3542–49.
5 Wood N, Nolan T, Marshall H, et al. Immunogenicity and safety of monovalent acellular pertussis vaccine at birth: a randomized clinical trial. *JAMA Pediatr* 2018; **172:** 1045–52.

Diagnosis and treatment of human sparganosis

We thank M Teresa Galán-Puchades[1] for her comments on our Clinical Picture reporting a 50-year-old woman with a recurrent eyelid swelling.[2] We agree that the exact species of plerocercoid should in most cases be identified by PCR. We had no doubt, however, that our case was caused by plerocercoid larvae belonging to the *Spirometra* genus on the basis of morphological features, although the exact diagnosis of the species by morphology alone can be difficult.[3] Identification can be done by inoculating the larvae into a susceptible host, collecting the adult worm in the intestine, and examining the eggs in the faeces,[3] or alternatively in the current era, by PCR.

The first diagnosed case of sparganosis in a human was identified in Xiamen, China, in 1882, and was found to be caused by *Spirometra mansoni*.[3] Sparganosis has now been reported worldwide, although occurs mainly in Asia, and *S mansoni* is considered to be the predominant species in this region.[4] Although PCR identification was not done in our case, sparganosis in China is commonly perceived to be caused by *S mansoni*, and our parasitologist therefore also concluded that this was the species in our case.

Regarding the treatment, we agree that clinicians such as ourselves should be careful to use albendazole in view of potentially causing neurocysticercosis in a region with endemic cysticercosis