including multiplex PCR, bacterial and mycobacterial cultures, and Xpert MTB/RIF were negative. We suggested that cryptococcal antigenaemia with meningitis symptoms is most consistent with early cryptococcal meningitis.

Given the high prevalence of cryptococcal meningitis in Botswana and results from other studies,[5] culture-negative cryptococcosis might be an important contributor to undiagnosed meningitis. Better characterisation of these poorly described populations is warranted to inform better management and improve mortality.

We declare no competing interests.

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Typhoid Vi-conjugate vaccine for outbreak control in Zimbabwe

Joe Bilcke and colleagues[1] investigated the cost-effectiveness of alternative delivery strategies for typhoid Vi-conjugate vaccine (TCV) in each of the 54 countries eligible for financial support from Gavi, the Vaccine Alliance.

For more on **Gavi, the Vaccine Alliance** see https://www.gavi.org/

In settings with a high incidence of *Salmonella enterica* serotype Typhi (S Typhi), routine vaccination of infants and a catch-up campaign for children younger than 15 years seems to be a cost-effective approach and could reduce the number of typhoid cases in Zimbabwe by 68% over the next 10 years.

Zimbabwe carried out a mass TCV vaccination campaign in February to March, 2019, funded by Gavi, that targeted children aged between 6 months and 15 years in communities affected by an ongoing typhoid outbreak.[2] It was the first time TCV was used in Africa and the first vaccination campaign in response to a typhoid outbreak in the continent. Outbreaks of cholera and typhoid in Zimbabwe result from a lack of investment in and management of the country's water and sanitation infrastructure and health-care system.[3] Additionally, low availability of diagnostics and drugs, brain drain (emigration of highly qualified individuals from a country), prohibitive user fees in health facilities, and strikes by medical personnel have contributed to the most recent outbreak of typhoid.

FIEBRE, a multicountry study, has been enrolling adults and children who present with fever at health facilities in Harare, Zimbabwe, since June, 2018, to investigate the causes of fever in sub-Saharan Africa and southeast Asia. As part of the study, multiple diagnostic investigations have been done, inclu-ding automated blood cultures, bacterial identification, and drug susceptibility testing. S Typhi has been isolated from 23 (17%) of 133 blood cultures from children and 38 (21%) of 183 blood cultures from adults. Of the 61 S Typhi isolates, 54 (89%) were multidrug resistant and 49 (80%) displayed diminished fluoroquinolone susceptibility.

3 months after the vaccination campaign, we observed a sharp decrease in one of the worst affected communities in the proportion of confirmed and suspected typhoid cases among children, but not among adults. In this community, 23 (21%) of 109 blood cultures from children were positive for S Typhi before vaccination compared with none of 24 after vaccination. By contrast, 18 (15%) of 117 blood cultures from adults were positive for S Typhi before vaccination compared with 20 (30%) of 66 after vaccination.

Although the TCV vaccination campaign seems highly effective in reducing typhoid incidence among children, a more comprehensive approach—including vaccination of adults and water, sanitation, and hygiene interventions—will be needed to halt typhoid outbreaks.

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Value of observational data for multidrug-resistant tuberculosis

In their Correspondence, Ibrahim Abubakar and colleagues[1] highlighted the crucial role of explanatory and

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