Possible pitfalls of the 2017 ECIL guidelines

We read with interest the Series papers by Catherine Cordonnier and colleagues[1] on the 2017 European Conference on Infections in Leukaemia (ECIL) guidelines for vaccination of haemopoietic stem-cell transplant (HSCT) recipients and by Malgorzata Mikulska and colleagues[2] on ECIL guidelines for vaccination of patients with haematological malignancies. These papers are very useful for everyday practice, but in our opinion, some points should be further discussed (appendix).

Cordonnier and colleagues[1] based vaccine recommendations on laboratory endpoints. However, some weaknesses exist in the use of antibody assessments for evaluation of pre-existing immunity or vaccination efficacy, and for some pathogens (eg, pertussis), no true immunological correlate of protection exists.[3]

Regarding anti-pneumococcal vaccination, the assessment of antibody titres against pneumococcus should help to define the best individual option at a given time. On the one hand, these antibodies, which are often measured by ELISAs, tend not to be opsonophagocytic.[3] On the other hand, the assessment of the functionality of pneumococcal antibodies by opsonophagocytosis assays is complicated and not widely available.

Likewise, Cordonnier and colleagues based their recommendations for revaccination against *Haemophilus influenzae* type b (Hib) on laboratory criteria. Serum titres of anti-purified polyribosylribitol phosphate antibody decrease quickly after vaccination, and the absolute concentration does not correspond to the functional activity of the antibody.[4]

Cordonnier and colleagues ask if individual vaccine responses should be assessed in HSCT recipients.[1] The answer is that serological testing is futile when the expected response is close to 100%, but it can be useful to evaluate the need for specific vaccines. In our opinion, all patients (seropositive and seronegative) should be completely revaccinated against hepatitis B virus (HBV) and measles, mumps, and rubella.[5] For this reason, serological screening before vaccination is always useless. At least for HBV, antibody titres should be measured after a complete course to decide whether revaccination is needed.[6]

Moreover, Cordonnier and colleagues recommend the measurement of antibody titres to decide on booster administration during long-term follow-up (eg, at 5–10 years after the initial series for Hib; and every 3–5 years for diphtheria, pertussis, and tetanus).[1] We do not understand the reasons behind the timings indicated and question the appropriateness of using antibody titres to make a decision on whether a Hib booster dose is needed.[4]

Finally, Cordonnier and colleagues suggest measuring pneumococcal antibodies at 24 months after vaccination,[1] although the practical consequences of such assessments are yet to be evaluated. We agree with this statement, but it seems contrary to the contents of table 2 and the text, which says "the assessment of antibody titres should help in defining the best individual option at a given time".

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See **Online** for appendix

STREAM: a pragmatic and explanatory trial for MDR-TB treatment

In their Comment, Marian Loveday and colleagues[1] delivered a harsh critique of clinical trials, and the STREAM trial[2] in particular. We welcome a critical assessment of the STREAM trial if the end goal is to improve the design and conduct of ongoing and future clinical trials for the treatment of multidrug-resistant tuberculosis (MDR-TB). We agree that well done, programmatic observational studies are valuable to inform treatment guidelines, but these studies are most appropriate when supporting rather than replacing trials. While identifying the putative limitations of the STREAM trial, Loveday and colleagues failed to highlight the limits of observational data. Any observed benefit in a cohort study could also arise from improved processes leading to better outcomes. It is unclear to us how Loveday and colleagues can conclude that improved processes are a strength of observational studies and a limitation of trials.

The STREAM trial[2] was designed with both explanatory and pragmatic

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.

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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.

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