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