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Finding the right balance between efficacy and tolerability for TB treatment: the search continues

Dear Editor,

The questions raised by Haas et al. has prompted us to describe the precise nature of the problems encountered during the OneRIF trial (Table) conducted in eight clinics in Bangladesh to study the efficacy and safety of double-dose rifampicin (RIF) for first-line TB treatment.[1] Despite 30 years of experience working in and with TB control programmes, we seriously underestimated the difficulty of conducting a randomised clinical trial, rather than an operational study, in a low-income control programme setting in the current climate of ever increasing demands.

The main limitation of our study was the exclusion of patients from 2/8 clinics who had completed treatment and follow-up due to "ambiguous identification". A subsequent substudy on the prevalence of molecularly confirmed resistance to RIF, isoniazid and the fluoroquinolones in new patients using deep sequencing of 100–150 diagnostic sputum samples per clinic organised by registration date showed clustered specimens with identical resistance mutations and spoligotype fingerprints. As regards the two excluded clinics, there were 15 genotypic clusters in one and 16 clusters in the other, each with 2–6 consecutive patients, compared with 0–3 clusters, each with a maximum of two successively registered cases in the six other clinics. A population study in metropolitan Dhaka, Bangladesh, reported only two clusters of two cases among all 56 randomly arranged TB genotypes.[2] Some sputum samples may have been split to replace lost specimens needed for the study; the alternative was to create fake smear-positive cases. In any case, all subjects enrolled at these two clinics were excluded from the analysis.[1] Guided by a recommendation from the committee on research integrity of the Institute of Tropical Medicine (Antwerp, Belgium) that reviewed these findings, a post-hoc on-site investigation by project authorities and an independent investigator could not find any proof for either after a review of the local records and interviews with project staff.

Lost sputum samples may have been faked in an attempt to conceal mistakes caused by the excessive workload at these clinics. Although study procedures had been kept to a minimum to avoid work overload, the impact of unrewarding, time-consuming case detection activities imposed by the Global Fund through the Bangladesh Principal Recipient, the Bangladesh Rural Advancement Committee (BRAC; Dhaka, Bangladesh), had not been sufficiently taken into account when planning and monitoring the trial. Unfortunately, funding had been made conditional to the achievement of certain performance targets, with a strong emphasis on increased case detection. In many low-income countries, a sizeable part of the funding goes into paying for staff salaries or their bonuses. The failure to meet targets means an immediate threat to the livelihood of the field-level staff and their families. The existence of fake TB patients has been known in Bangladesh and elsewhere for decades.[3] Indeed, while the existence of fake TB patients calls into question the accuracy of global TB control data and leads to the risk of unnecessary administration of TB treatment, this is common knowledge and is accepted as a necessary trade-off if targets are to be reached—at least on paper. Right from the inception of its TB activities, Damien Foundation Bangladesh has avoided setting up performance targets, and has instead implemented supportive supervision with attention to effort rather than outcomes, thereby fostering a safe environment to address errors. We fear, however, that after 20 years of relentless pressure to increase case detection, recent charges of falsification are likely to remain unresolved.

The error in the bench aid for dosage, as well as the missed culture samples, is likely the result of the Principal Investigator (PI) falling seriously ill shortly before the study commenced and insufficient oversight by his replacement. The local PI also failed to spot the error. After we became aware of the missing culture samples of treatment failures, none was missed and all samples remained negative. In our post-hoc analysis, on reviewing the smear-based failure cases, we concluded that there was no culture evidence to support failures based on smear as per the protocol. Moreover, all samples that were not culture tested contained scanty bacilli that were negative on vital staining. In failure cases, this test was shown to have a very high negative predictive value for culture negativity.[4] It is well-known among consultants to low-income countries that patients often present late, generally with heavily smear-positive sputum. For this reason, in low MDR-TB prevalence settings with good-quality microscopy performed by well-trained and supervised microscopists, most treatment failures as per the smear-based WHO definition are negative on culture, with

Table Solutions to address concerns related to the OneRIF trail

Concern	Explanation on how this concern was addressed
Due to errors in the bench aid created, the 33–41 kg double-dose RIF group was underdosed for HZE (but correctly dosed for RIF). Adding up the total weight of HZE administered in milligrams and then dividing this sum by body weight in kg to understand factors associated with toxicity is not in accordance with sound pharmacological principles	We agree with Haas et al. that a different approach should have been used to design a study aimed to assess causality between the dosage of first-line drugs and adverse safety outcomes: • First, outcome and safety data were reported by weight band (Maug et al., Tables 2 and 4);[1] • Second, regression models assessing the effect of double-dose RIF on safety and efficacy outcomes included weight bands (33–41 kg vs. other) and HZE dosage (the sum of H, Z and E dose in mg divided by the patient's body weight in kg), in addition to variables already mentioned in the statistical analysis plan as potential confounding factors (Maug et al., Table 3).[1] However, we could not independently assess the effect of H, Z or E due to multicollinearity as a result of the fixed-dose HZE combination formulation. We therefore created a variable for the sum of the dose of H, Z and E in mg and divided it by the patient's weight in kg;
There are insufficient data to support the claim that lower-dose HZE was associated with fewer hepatic adverse events than the standard dose	Adjusted for potential confounders such as weight band (not collinear with dose/kg), the odds of drug-related SAEs doubled (aOR 1.91 for every 10 mg HZE/kg of increase, 95%CI 1.05–3.51), whereas the association between drug-related SAEs and RIF dosage was not significant. We do not claim to have investigated causality, but do believe that this association should be reported;
It is hard to interpret drug-related liver SAEs based on Maug et al. (Table 4),[1] due to the high degree of overlap between line items in the table (ALT > 5x ULN, hepatitis/jaundice, vomiting and Grade 3–4 transaminase increase are all different line items)	As described in the statistical analysis plan, we used the primary safety outcome (any SAE). In the analysis plan, hepatotoxicity was defined as the occurrence of any Grade 3–4 transaminase increase; We described the frequency of different clinical signs by arm and subgroup. There was some degree of overlap between "hepatitis/jaundice" and "Grade 3–4 transaminase increase". However, this overlap was not complete. Two patients with jaundice but without Grade 3–4 transaminase increase were considered not to have had a hepatotoxic SAE;
Primary efficacy outcomes were somewhat problematic. Specifically, not all individuals who were smear-positive at the end of treatment were classified as treatment failures despite the trial definition of failure. Culture results were available for only 9 of these, yet authors considered the remaining 11 patients to be "smear-positive with non-viable organisms"	The trial definition of the primary efficacy endpoint was the occurrence of unfavourable treatment outcomes (relapse, failure, death or loss to follow-up during treatment) against relapse-free treatment success (Maug et al., Table 2). Relapse and treatment failure were defined based on smear results (any number of acid-fast bacilli). The 20 individuals who were smear-positive at the end of treatment were classified as treatment failures in the primary efficacy analysis. Hence, smear-based primary efficacy outcomes were not "problematic" but were made to conform to the statistical analysis plan; The correction of smear-based outcomes was described (and not used in the efficacy analysis) to inform the reader on the interpretation of smear-based outcomes in many low-income countries with late case presentation and low prevalence of multidrug resistance

RIF = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; SAE = serious adverse event; aOR = adjusted odds ratio; CI = confidence interval; ALT = alanine aminotransferase; ULN = upper limit of normal.

only a few dead but stainable bacilli. As we believe that the WHO's definition of treatment failure needs to be revised, our aim was to demonstrate this.

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