

Predicting outcomes and drug resistance with new standardised treatment

To the Editors:

In their hypothetical cohorts Oxlade *et al.* [1] predicted significant public-health benefits by changing from the 8-month to the 6-month (2HRZE/6HE to 2HRZE/4HR; where H=isoniazid, R=rifampicin, Z=pyrazinamide and E=ethambutol) regimen. Data from 2008 on drug-resistance surveillance from five World Health Organization (WHO) regions, *i.e.* Africa (Botswana), Western Pacific (China), Africa (Mozambique), South-East Asia (Burma) and Europe (Tajikistan), has shown isoniazid resistances among newly diagnosed cases varies from 9.0% to 26.6% and among previously treated cases from 11.7% to 74.4% [2]. India and China carry the greatest estimated burden of multidrug-resistant (MDR)-tuberculosis (TB), together accounting for almost 50% of the total cases worldwide [2]. The incidence of mono-drug resistance among new cases in tuberculosis endemic countries is also high [3]. Relapse cases (from all previously mentioned sites) had 5.5 times higher odds of harbouring MDR-TB strains when compared with new cases (95% CI 4.4–6.8), after adjusting for the clustering effect at the country level [2].

The WHO has recommended discontinuation of the regimen that doesn't have rifampicin in the continuation phase (to replace HE by HR) [2]. Thus, rifampicin should be part of regimen throughout the treatment period; both in the intensive and continuation phase. Again the use of isoniazid and rifampicin in the continuation phase of the 6-month regimen (2HRZE/4HR) could lead to acquired MDR in the areas where the incidence of mono-drug resistance among new cases is high [4]. By using HR in the case of mono-resistance to isoniazid, practically only rifampicin is given during continuation phase. Therefore, the third recommendation of the WHO guidelines states: "In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR" [4]. Thus, in areas with higher levels of isoniazid resistance, newly diagnosed TB patients should receive 2HRZE/4HRE instead of 2HRZE/4HR (three-drug regimen in continuation phase) instead of HR or HE. Therefore, it will be more effective if the authors in their hypothetical cohorts could predict and compare the benefits of the 6-month regimen containing HRE in the continuation phase of the proposed regimen, *i.e.* 2HRZE/4HRE, and predict the outcomes of the new proposed regimen.

Worldwide intermittent regimens are widely administered. The authors only predicted the benefits of daily regimens but remained silent about the intermittent therapy in their hypothetical cohorts.

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From the authors:

We thank P.R. Mohapatra and D.T. Hari for their interest in our article, which predicts the public health improvements of switching from an 8-month standardised regimen (2HRZE/6HE; where H=isoniazid, R=rifampicin, Z=pyrazinamide and E=ethambutol) to a 6-month rifampicin containing standardised regimen (2HRZE/4HR) for the treatment of tuberculosis [1].

P.R. Mohapatra and D.T. Hari suggest that we should consider the benefits of a different 6-month regimen, one that contains ethambutol in the continuation phase (*i.e.* 2HRZE/4HRE), as this regimen may be superior in settings with high levels of mono-isoniazid resistance.

Although we agree that it may be advantageous to use an ethambutol-containing regimen in some areas, the primary objective of our study was to evaluate gains that could be made by switching to the predominant standardised treatment strategy, used globally and recommended by the World Health Organization (WHO). As the authors point out, WHO has since made a policy change and they now formally recommend that the 6-month regimen should be used exclusively, and that the 8-month regimen should be phased out [2]. Evaluating other proposed regimens would certainly be an interesting future exercise; however, evaluating the specific scenario they suggest would be difficult as there is inadequate data available on the development of multi-drug resistance with the use of a regimen containing ethambutol.

P.R. Mohapatra and D.T. Hari also point out that we do not consider the benefits of using intermittent therapy. Again, the primary objective of our study was to consider gains that could be made by switching to a WHO-supported standardised regimen, one in which daily therapy is recommended wherever feasible [2].

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Estimated population prevalence of obstructive sleep apnoea in a community of German third graders

To the Editors:

We read with interest the article by URSCHITZ *et al.* [1] which estimated the population prevalence of obstructive sleep apnoea (OSA) in an urban community of German third graders. This article highlights the fact that OSA is one of the most common chronic respiratory diseases in childhood and requires more attention from paediatric health services and clinicians. However, we are concerned that the methods employed in the study to diagnose OSA were suboptimal.

The authors correctly state that full sleep laboratory based polysomnography is the gold standard for the diagnosis of OSA in children. However, for the purposes of their study, abbreviated home polysomnography (HPSG) without electroencephalography was utilised for a final diagnosis of OSA. This was not referenced to the gold standard in this study.

The most recent American Academy of Sleep Medicine manual on scoring of sleep and sleep-related events emphasises the need to record and score not only respiratory events, but also arousals throughout a polysomnography [2]. The manual states that if hypopnoeas are to be scored (and form part of the apnoea/hypopnoea index), they must be followed by either arousal or desaturation. The abbreviated HPSG used in this study does not have the ability to detect respiratory events that lead to arousal. On this basis, we feel that the authors may have underestimated the prevalence of OSA in their study population.

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From the authors:

We thank D. Finn and P. McNally for their comments on our recent publication in the *European Respiratory Journal* [1].

We agree that full sleep laboratory-based polysomnography (PSG) including electroencephalography (EEG) may have a higher sensitivity in detecting obstructive sleep apnoea (OSA) in children, and that its use may have led to a higher estimate for the prevalence of OSA in our study. However, our study was designed in 2000, long before the relevant guideline of the American Academy of Sleep Medicine (AASM) was published [2]. At that time, there was widespread debate about the way in which hypopnoea and arousals should be scored and about the significance of these events in children. Many authors used definitions for hypopnoea that were based solely on a reduction in airflow or on both a reduction in airflow and desaturation. In a study by McNAMARA *et al.* [3], only 38–39% of respiratory events (including hypopnoea) were followed by cortical arousal, while all hypopnoeas were followed by a desaturation of $\geq 4\%$. In addition, the occurrence of a cortical arousal following respiratory events depended on age. In contrast to the current AASM guideline, the minimal required duration for a cortical