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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REFERENCES

1 Oxlade O, Schwartzman K, Pai M, *et al.* Predicting outcomes and drug resistance with standardised treatment of active tuberculosis. *Eur Respir J* 2010; 36: 870–877.
2 World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva, World Health Organization, 2010. Available from www.who.int/tb/features_archive/world_tb_day_2010/en/index.html
3 Individual country profiles. Anti tuberculosis drug resistance in the world. http://whqlibdoc.who.int/hq/2000/WHO_CDS_TB_2000.278_Annex2.pdf
4 World Health Organization. Treatment of Tuberculosis Guidelines. 4th Edition. Geneva, World Health Organization, 2009.

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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.