

Institution: University College London
Unit of Assessment: 2 - Public Health, Health Services and Primary Care
Title of case study: Study A leads to changes in Tuberculosis treatment guidelines
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Prior to the change in WHO recommendations which occurred following this study many patients in Africa and other developing countries were receiving an inferior regimen for the management of tuberculosis, a consequence of which meant that many had to be retreated. Since the implementation of the revised WHO Guidelines in 2010 almost all countries have now switched to the gold standard tuberculosis treatment regimen based on 6 months of isoniazid and rifampicin</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Study A was a multi-centre randomised controlled trial testing two 8-month regimens (one of which was recommended in international guidelines at the time) against the gold standard 6-month regimen for treatment of newly diagnosed pulmonary tuberculosis. The trial was sponsored by the International Union Against Tuberculosis and Lung Disease (IUATLD) and involved 1,355 patients from eight centres in Africa and Asia. This was the first TB trial to utilise a non-inferiority trial design.</p> <p>From 1993 onwards WHO recommended an 8-month regimen without rifampicin in the maintenance phase, in preference to a 6-month regimen with rifampicin throughout. WHO guidelines (issued in 2003) recommended a regimen of daily ethambutol, isoniazid, rifampicin and pyrazinamide for 2 months, followed by ethambutol and isoniazid for 6 months (2EHRZ/6HE). However, that regimen had not been evaluated in a randomised controlled trial. Study A compared that regimen with a 6-month regimen with the same initial intensive phase as the first regimen, followed by four months of daily rifampicin and isoniazid (2EHRZ/4HR).</p> <p>Study A demonstrated that the WHO-recommended 2EHRZ/6HE regimen was clearly inferior to the 2EHRZ/4HR regimen [1]. 12 months after the end of chemotherapy 10.4% treated with 2EHRZ/6HE had unfavourable outcomes, compared to only 4.9% of those treated with 2EHRZ/4HR. At 30 months the failure/relapse rates were 11.7% of those treated with 2EHRZ/6HE and 6.0% of those treated with 2EHRZ/4HR [2]. The study was carried out between March 1998 and June 2004 and the results 12 months after stopping treatment were presented at the IUATLD meeting in Montreal in October 2002, and were published in 2004 [1]; the 30 month follow-up results were published in 2011 [2].</p> <p>Key researchers and the positions they held at the time of the research</p> <p>The International Union Against Tuberculosis and Lung Disease is a long established NGO working to support national tuberculosis programmes world-wide. Its mission is to bring innovation, expertise, solutions and support to address health challenges in low- and middle-income populations. The IUATLD conceived the trial and invited Andrew Nunn at the MRC Clinical Trials Unit (MRC CTU) to be an investigator because of his long-standing involvement in TB clinical trials, as he had been statistician for previous practice-changing trials. The MRC CTU took the lead in statistics, in the non-inferiority design of the study, in the interim analyses for the Data Monitoring Committee and analyses for the published findings. Andrew Nunn was also closely involved in the writing of the papers for publication. IUATLD chose to work with MRC CTU because of the Unit's expertise in trial design and statistical analysis.</p> <p>Dr Amina Jindani and Professor Donald Enarson were both employed by the IUATLD, Professor Enarson as the Scientific director, Dr Jindani was the chief investigator on the study; Professor Andrew Nunn who was at that time Head of Division Without Portfolio, MRC Clinical Trials Unit,</p>

was the senior statistician.

3. References to the research (indicative maximum of six references)

- [1] Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *The Lancet*. 2004 **364**:1244-51. [http://dx.doi.org/10.1016/S0140-6736\(04\)17141-9](http://dx.doi.org/10.1016/S0140-6736(04)17141-9)
- [2] Nunn AJ, Jindani A, Enarson DA. Results at 30 months of a randomised trial of two 8-month regimens for the treatment of tuberculosis. *International Journal of Tuberculosis and Lung Disease*. 2011 **15**(6): 741-745. <http://dx.doi.org/10.5588/ijtld.10.0392>

4. Details of the impact (indicative maximum 750 words)

TB is a major health problem, with 9.4 million new cases and 1.7 million deaths in 2009 [a]. WHO guidelines issued in 2003 [b] recommended a regimen of daily ethambutol, isoniazid, rifampicin and pyrazinamide for 2 months, followed by ethambutol and isoniazid for 6 months (2EHRZ/6HE) as one of the category 1 regimens for the treatment of drug sensitive *M Tuberculosis*. However, that regimen had not been evaluated in a randomised controlled trial. Study A found that this regimen was clearly inferior to a regimen with the same 2-month intensive phase, followed by 4 months of isoniazid and rifampicin.

The results of Study A were published in 2004. It took several years for the results of the research to change international guidelines, perhaps partly because the results were disappointing to international agencies, who would have preferred not to use rifampicin after the initial intensive phase of treatment because of the risk of acquired resistance to this drug in patients who failed treatment. However, eventually the results did begin to influence international policy, as they provided evidence that filled an important gap in knowledge of how to treat TB.

In 2006 the International Standards for Tuberculosis Care cited the Study A results [c], and recommended 2EHRZ/4HR as the preferred treatment regimen, but that 2EHRZ/6HE could be used where adherence through the continuation phase cannot be assessed. It was considered to be of particular relevance for the developing world, where the majority of people with active TB live.

Study A was included in an influential 2009 meta analysis, which said “*The most important finding of this review is that all three treatment outcomes were significantly worse with regimens that used rifampin for the first 1–2 mo rather than throughout therapy. This finding adds considerable weight to similar findings by Jindani and colleagues, who compared regimens containing 2 mo versus 6 mo of rifampin*” [d].

Eventually, in 2010, the WHO guidelines were updated in a periodic review [e]. This involved carrying out a systematic review of the evidence, which included the results from Study A, which were graded as the most convincing of the available evidence. One of the principal investigators of the trial (Professor Andrew Nunn) was a member of the expert advisory group which helped to develop the new guidelines. The new WHO guidelines included the recommendation that “*New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2EHRZ/4HR*”. Indeed, the foreword states the importance of this change: “*The World Health Organization’s Stop TB Department has prepared this fourth edition of Treatment of tuberculosis: guidelines, adhering fully to the new WHO process for evidence-based guidelines. Several important recommendations are being promoted in this new edition.*”

First, the recommendation to discontinue the regimen based on just 2 months of rifampicin (2HRZE/6HE) and change to the regimen based on a full 6 months of rifampicin (2HRZE/4HR) will reduce the number of relapses and failures. This will alleviate patient suffering resulting from a second episode of tuberculosis (TB) and conserve patient and programme resources.”

WHO guidelines are very influential for national TB policy, particularly in African countries, which face a high burden of TB. A survey of national tuberculosis policymakers found that WHO was an

important and frequent source of information to inform TB policymaking in Africa. This means that the WHO recommendation, based on Study A, has influenced which TB treatment regimens are used in many countries. National guidelines for TB have been updated to reflect the new treatment regimes including Ethiopia, South Africa, and Zimbabwe [f]. Routine data collected by WHO shows that in 2011, 196 out of 206 countries reported using the 6 month regimen with rifampicin throughout for new TB patients. The number of new TB cases (excluding multi-drug resistant TB) in these 196 countries totalled 7,883,245 in 2011, so the results of Study A have had a wide-reaching impact (although it should be noted that not all of these countries were previously using the 8 month regimen) [g].

From the perspective of these eight million patients, the 2EHRZ/4HR has several benefits over the previous 8-month regimen. As well as reducing the number of people who have unfavourable outcomes and require retreatment, it also reduces the inconvenience of attending for treatment (whether fully supervised or not) and reduced the time in which they were exposed to toxic drugs.

National Ministries of Health have benefited from the research, as the 2EHRZ/4HR patient kit is US\$ 4–10 less expensive than the 2EHRZ/6HE patient kit [d]. Reducing the number of people requiring retreatment also reduces costs. This allows more people to be treated with the available (limited) resources.

It is difficult to determine the exact impact Study A's findings have had in reducing unfavourable outcomes. However if we assume that the reduction of relapses and treatment failures is the same in real life as in the trial, and that around 7.9 million people were treated with the 2EHRZ/4HR regimen in 2011, then the impact of Study A in that year alone was to prevent over 400,000 relapses and failures, compared to if those people had been treated with the eight month regimen. However, the actual number of relapses prevented directly due to Study A is likely to be lower than this, as not all countries were previously using the 8 month regimen, and some of those countries that did change may have done so for other reasons.

5. Sources to corroborate the impact (indicative maximum of 10 references)

- [a] Figure for TB incidence and deaths in 2011 taken from WHO Global Tuberculosis Report 2012, available at: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf
- [b] World Health Organization. Treatment of Tuberculosis: Guidelines for National Programmes. 3rd edition. Geneva: World Health Organization; 2003. http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf See section 4.8, which contains the discussion of the two regimens.
- [c] Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance; 2006. http://www.who.int/tb/publications/2006/istc_report.pdf See standard 8, page 9. Research [1] is reference 73 therein.
- [d] Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pai M, Vernon A, Lienhardt C, Burman W. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med. 2009 Sep;6(9):e1000146. <http://dx.doi.org/10.1371/journal.pmed.1000146>. See reference 26.
- [e] World Health Organization. Treatment of Tuberculosis Guidelines. 4th edition. Geneva: World Health Organization; 2010. http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf See section 3.5 for references to [d] above. See page 117 the quoted for cost saving.
- [f] Updated National guidelines:
- South Africa, National Tuberculosis Management Guidelines 2009 http://familymedicine.ukzn.ac.za/Libraries/Guidelines_Protocols/TB_Guidelines_2009.sflb.a

Impact case study (REF3b)

[shx](#)

- Zimbabwe, National TB Guidelines, Fourth Edition, October 2010
http://www.who.int/hiv/pub/guidelines/zimbabwe_tb.pdf See page 37
- Ethiopia, Guidelines for Clinical and Programmatic Management of TB, TB/HIV and Leprosy In Ethiopia, Fifth Edition, March, 2013
http://www.moh.gov.et/English/Resources/Documents/FMOH_Guidelines%20for%20TBL_TB_HIV%20March_2013_Final%20Version.pdf See page 28

[g] World Health Organization 2012: Data provided by countries and territories: case notifications & implementing the Stop TB strategy in 2011
<http://www.who.int/tb/country/data/download/en/index.htm> [accessed 14/06/13]. Analysed spreadsheet available on request.