Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

IMPROVED TREATMENT FOR TUBERCULOUS MENINGITIS

Summary of the impact:

Researchers at the Oxford University Clinical Research Unit (OUCRU) in Vietnam demonstrated the effectiveness of dexamethasone (a corticosteroid) as an adjuvant treatment for Tuberculous Meningitis (TB meningitis). OUCRU's research persuaded the World Health Organization (WHO) to recommend corticosteroid therapy for the treatment of TB meningitis, and this has been shown to reduce the mortality and long-term disability caused by this devastating disease by 30%.

Underpinning research:

TB meningitis is a life-threatening infectious disease, which causes inflammation of the meninges – a protective membrane that surrounds the brain and spinal cord. It causes up to 50% mortality or severe long-term disability even in patients who are treated with combination antibiotic therapy.

While a number of early studies suggested the use of corticosteroids[1] might be an effective adjuvant therapy, the small scale of these trials lacked evidence for global change to clinical practice and guidelines.

To address this problem, OUCRU Vietnam researchers undertook the first large scale trial of dexamethasone (a type of corticosteroid) in patients with TB meningitis. Published in 2004, this randomised, double-blind, placebo-controlled trial of 545 adults and adolescents (over 14 years of age) showed that adjunctive treatment with dexamethasone improves survival[2].

In a follow-up study to determine the underlying mechanisms behind increased survival rates resulting from dexamethasone, OUCRU Vietnam researchers aimed to determine the effect of dexamethasone on the brains of adults with TB meningitis. This study showed that dexamethasone reduces increased fluid from around the brain and prevents tissue death, leading to improved survival[3].

Increased survival rates were again confirmed in a collaborative study, published in 2011, between Oxford's Vietnam Unit, Imperial College, and Cambridge University. This longitudinal study also showed that adjunctive dexamethasone treatment improves survival in patients with TB meningitis, until at least two years of follow-up[4].

References to the research:

1. Thwaites, G. E. & Tran, T. H. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol* **4,** 160–170 (2005) doi.org/10.1016/S1474-4422(05)01013-6.

This review indicates that while there have been many small scale studies suggesting the use of* corticosteroid therapy (as an additional treatment for *TB meningitis), none were adequate or large enough to encourage changes to clinical management.

2. Thwaites, G. E. *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N. Engl. J. Med.* **351,** 1741–1751 (2004) doi: 10.1056/NEJMoa040573.

The first large scale trial of corticosteroid treatment in patients with TB meningitis,

showing that adjunctive treatment with dexamethasone improves survival.

3. Thwaites, G. E. *et al.* Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study. *Lancet Neurol* **6,** 230–236 (2007) doi.org/10.1016/S1474-4422(07)70034-0.

   In a follow-up study showing the underlying mechanisms leading to increased survival rates resulting from dexamethasone therapy.

4. Török, M. E. *et al.* Dexamethasone and long-term outcome of tuberculous meningitis in Vietnamese adults and adolescents. *PLoS One* **6,** e27821 (2011) doi: 10.1371/journal.pone.0027821.

   A study confirming that adjunctive dexamethasone treatment improves survival in patients with TB meningitis, until at least two years of follow-up.

This research was funded by the Wellcome Trust.

Details of the impact:

The World Health Organization (WHO) estimated there were 8.8 million new cases of tuberculosis, of all forms, in the world in 2010 and 1.45 million deaths. TB meningitis represents 1% of cases but is disproportionately important because it causes such high mortality and severe disability. It affects all groups but peaks in children aged 2-4 years and makes up 5-7% of admissions to specialist paediatric neurology units in some countries. It is also common in untreated HIV infection and the incidence of tuberculosis is increasing in some industrialised countries, for example doubling in London in the last 10 years[5].

Primary research from OUCRU Vietnam showing that dexamethasone treatment, given in combination with existing antibiotic treatment significantly improves survival rates in adults and adolescents with TB meningitis, led the *British Infection Society* and the *WHO* to introduce adjuvant corticosteroid treatment as standard therapy for TB meningitis.

An independent Cochrane review published in 2008 emphasised the importance of the OUCRU trial in providing the first, adequately randomised trial of steroids in TB meningitis with adequate follow-up and blinded outcome assessment. The Cochrane meta analysis, which combined all data, concluded that dexamethasone indeed reduces mortality and disability by 30%[6].

In 2009 the *British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children*, which was authored by Dr Guy Thwaites (first author of OUCRU Vietnam's pivotal 2004 longitudinal study) showed that dexamethasone (corticosteroid) therapy improves survival in patients with TB meningitis. These guidelines cite the key research from OUCRU Vietnam recommending: "Adjunctive corticosteroids (either dexamethasone or prednisolone) should be given to all patients with TBM, regardless of disease severity"[7].

Chapter eight of the WHO's *Treatment of Tuberculosis Guidelines – Fourth Edition*[8], which was last updated in 2010, cites OUCRU Vietnam's primary 2004 paper as key evidence in its guidance for the treatment of TB meningitis, stating: "Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis" [8].

Sources to corroborate the impact:

5. Thwaites, G.E., van Toorn, R. & Schoeman, J. Yuberculous meningitis: more questions, still to few answers. *Lancet Neurol***,** (2013) S1474-4422(13)70168-6. 10.1016/S1474-4422(13)70168-6.

This general review highlights the scale of the problem caused by tuberculous meningitis worldwide and provides a context for improvements by adjunctive therapy.

6. Prasad, K., & Singh, M. B. (2008). Corticosteroids for managing tuberculous meningitis. Cochrane database of systematic reviews (Online), (1), CD002244. doi:10.1002/14651858.CD002244.pub3

Cochrane review emphasising the importance of the OUCRU trial in providing the first, adequately randomized trial of steroids in TB meningitis with adequate follow-up and blinded outcome assessment.

7. Thwaites, G. *et al.* British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* **59,** 167–187 (2009) doi: 10.1016/j.jinf.2009.06.011.

British Infection Society guidelines recommending adjunctive corticosteroid treatment should be given to all patients with Tuberculous Meningitis. These guidelines directly cite key research from OUCRU Vietnam.

8. World Health Organization Treatment of Tuberculosis Guidelines. (2010). Available at http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (Accessed 2013)

Chapter eight of the WHO's Treatment of Tuberculosis Guidelines – Fourth Edition, cites OUCRU Vietnam's primary 2004 paper as key evidence for the use of adjuvant corticosteroid in treating Tuberculous Meningitis.