Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

IMPROVING THE DIAGNOSIS OF TUBERCULOSIS

Summary of the impact:

Developed in 2001, the University of Oxford's T-SPOT test is capable of detecting both latent and active TB infection more rapidly and accurately than the tuberculin skin test (TST). Since its commercial release in 2004, T-SPOT has been adopted by public health agencies for TB control and prevention in the US, UK and Europe. Tuberculosis (TB) is the second leading cause of death from an infectious disease, killing an estimated 1.5 million people worldwide each year. One-third of the approximately 9 million people infected with TB each year are asymptomatic, yet many go on to develop active TB if left untreated.

Underpinning research:

In 1993, the World Health Organization (WHO) declared tuberculosis to be a global health emergency, estimating that around 35 million people would die from TB between 2000 and 2020, if control measures were not significantly improved. A notoriously difficult disease to diagnose, the tuberculin skin test (TST) has been the standard method of detecting TB infection for over 100 years. One of the biggest problems with the TST method is its inability to differentiate between TB infection and patients who have been vaccinated against TB with the related strain, bacillus Calmette–Guérin (BCG). In addition, the TST method cannot detect latent TB infection, greatly affecting diagnostic yields.

In the mid 1990s, Professor Adrian Hill and his team at Oxford University responded to the WHO's declaration of emergency, by applying a method they had previously used in detecting malarial infection, to identify TB-infected patients. By stimulating blood cells from malaria-exposed patients, they had been able to identify key malaria proteins recognised by the immune system. Applying the same method to patients suffering from TB, this simple overnight ELISPOT (enzyme-linked immunospot assay) or "T-SPOT" test involved mixing blood cells from test subjects with TB proteins, allowing the number of TB protein-specific T cells to be counted. After performing clinical trials over a 16 month period (October 1997 to January 1999) the Oxford University researchers found that their T-SPOT test could not only rapidly diagnose TB-infected patients, but was also far more specific and sensitive than TST[1]. Their findings indicated that the T-SPOT assay detected 96% of TB infections, compared to the TST method, which detected only 69%[1]. In clinical trials performed on TB-vaccinated subjects, 85% of TST-tested patients respondent positively to TB infection, while none of the patients tested positive by the T-SPOT method[1].

The research also showed that the T-SPOT method of diagnosing TB enabled rapid (overnight) detection of the infection, in comparison to the TST, which is read 48 to 72 hours[2] after administration. The T-SPOT test is also far more accurate in detecting TB in asymptomatic patients who are at a high risk of active infection[3]. The T-SPOT assay was licensed across Europe in July 2004 and received FDA premarket approval in July 2008[4]. The T-SPOT test has brought accurate and effective TB testing to many new patient groups where the skin test had previously given poor or unreliable results[5].

References to the research:

1. Lalvani, A. *et al.* Rapid detection of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. *Am. J. Respir. Crit. Care Med.* **163**, 824–828 (2001). ***Primary paper reporting results from Oxford clinical trials for the T-SPOT.TB test.***

2. Centers for Disease Control and Prevention. Tuberculosis TB. Fact Sheets - Tuberculin Skin Testing for TB. Page last reviewed June 20, 2011. [Available from] http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm (accessed 26th March 2013). ***United States CDC Fact Sheet with information about how to administer TB Skin Test.***

3. Lalvani, A. *et al.* Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. *Lancet* **357**, 2017–2021 (2001) http://dx.doi.org/10.1016/S0140-6736(00)05115-1. ***Paper reporting primary results from Oxford study comparing the efficacy of the T-SPOT assay in comparison to the Tuberculin Skin Test.***

4. Oxford Immunotec. T-SPOT®.*TB* test [[available from]] http://www.oxfordimmunotec.com/T-SPOT_International (accessed 26 March 2013). ***Product Information about the T-SPOT.TB test can be found on the Products and Services page of the Oxford Immunotec website.***

5. Chapman, A. L. N. *et al.* Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of Mycobacterium tuberculosis-specific T cells. *AIDS* **16**, 2285–2293 (2002). ***Paper reporting Oxford study into the specificity and sensitivity of the T-SPOT.TB Test when compared to the TST method.***

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Details of the impact:

One of just two interferon-gamma release assays (IGRAs) recommended by the Centers for Disease Control and Prevention[6] the T-SPOT test has had a significant impact on the accuracy of TB diagnosis worldwide since its commercial release in 2004.

Accurate Diagnosis:

The ability to diagnose TB more rapidly, specifically and sensitively than the alternative TST method is a major impact of the T-SPOT test[1 7 8]. The TST method of diagnosis involves injecting an extract of TB into a patients skin, waiting two to three days[2], then examining the skin for lesions – with an inflamed lesion indicating exposure to TB. Diagnosing TB with the T-SPOT test is faster, easier to administer, and easier to read than the TST method[7].

By taking a small blood sample from the patient, the T-SPOT test can give a result in under 24 hours[1]. The T-SPOT test is also easy to read and, because it measures cell numbers, it is highly quantitative. In contrast, the TST test is frequently difficult to interpret, particularly in patients where the swelling is difficult to read, such as children with sensitive skin[9] or patients with conditions like rheumatic disease (which can cause skin swelling)[10]. Interpretation of the TST test is a significant issue, particularly for doctors in developed countries, who are less experienced in examining the skin lesions produced by the TST method. By using proteins that are specific to TB infection, rather than BCG, the T-SPOT test is more effective than the TST method in distinguishing between patients infected with TB and those who have simply been vaccinated [1,11]. The T-SPOT test is also far more accurate than the TST method in identifying individuals who have latent TB infection[5,12] .

Policy and Guidelines:

The commercial availability and superior diagnostic value of the T-SPOT test has had an impact on global health policy and guidelines. Since its commercial approval in 2004 the T-SPOT test has been included in TB control guidelines in the USA (Centers for Disease Control and Prevention) and Europe, with more than 20 countries now recommending the T-SPOT test to diagnose and screen patients for TB infection[6 13]. In 2011 the UK National Institute for Health and Clinical

Excellence (NICE) updated their guidelines on control and prevention, recommending interferon-gamma release assays, such as the T-SPOT test, for use in a number of diagnostic situations[14], including:

- In a TB outbreak, when large numbers of individuals need to be screened;
- For migrants between 16 and 34 years of age, coming from high incidence countries;
- Patients who suffer from immunodeficiency;
- NHS employees who have had contact with patients in a high incidence setting; and
- For individuals who have been vaccinated against TB, and those who have tested positive in a TST test.

Commercialisation and Reach:

Manufactured by Oxford Immunotec Ltd, the T-SPOT.*TB* test was commercially approved for sale in Europe in 2004. T-SPOT.*TB* sales have substantially increased since their first year on the market, growing from 2,000 tests sold in 2004 to 500,000 in 2011. While the cost of the T-SPOT.*TB* test is £30, in comparison to the TST (which is sold for around £2), the accuracy of the T-SPOT.*TB* test effectively eliminates wasted resources in following up patients with false positive TST results, avoiding greater costs related to the treatment of TB in those who receive false negative TST results[15]. Tests have been sold predominately to developed countries such as the USA, Germany, UK, Switzerland and France, and have been requested by clinicians from a variety of specialties including: pulmonology, occupational health, public health and infectious disease[15].

Sources to corroborate the impact:

6. Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection --- United States, 2010. MMWR **5(**RR-05), 1-25 (2010). [available from] http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm (accessed 26 March 2013). ***United States Government updated CDC guidelines recommending the use of T-SPOT.TB test in addition to the QuantiFERON-TB Gold in tube test, to detect TB infection.***

7. Thomas, M. M. *et al.* Rapid diagnosis of Mycobacterium tuberculosis meningitis by enumeration of cerebrospinal fluid antigen-specific T-cells. *Int. J. Tuberc. Lung Dis.* **12**, 651–657 (2008). ***Paper outlining rapid diagnosis of TB using ELISPOT (T-SPOT.TB) test.***

8. Meier, T., Eulenbruch, H.-P., Wrighton-Smith, P., Enders, G. & Regnath, T. Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice. *Eur. J. Clin. Microbiol. Infect. Dis.* **24**, 529–536 (2005) DOI 10.1007/s10096-005-1377-8. ***Paper showing sensitivity of T-SPOT test.***

9. Liebeschuetz, S. *et al.* Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. *Lancet* **364**, 2196–2203 (2004) http://dx.doi.org/10.1016/S0140-6736(04)17592-2 ***Paper showing diagnostic sensitivity of the ELISPOT (T-SPOT.TB) test to be higher than the TST and less affected by health factors associated with childhood tuberculosis in developing countries.***

10. Xie, X. *et al.* A T-cell-based enzyme-linked immunospot assay for tuberculosis screening in Chinese patients with rheumatic diseases receiving infliximab therapy. *Clin. Exp. Med.* **11**, 155–161 (2011) doi: 10.1007/s10238-010-0123-4. ***Paper showing the T-SPOT.TB test to be more specific than TST in detecting tuberculosis during infliximab therapy in Chinese patients with rheumatic diseases.***

11. Sun, L. *et al.* Interferon gamma release assay in diagnosis of pediatric tuberculosis: a meta-analysis. *FEMS Immunol. Med. Microbiol.* **63**, 165–173 (2011) doi: 10.1111/j.1574-695X.2011.00838.x ***Paper showing the far greater specificity of interferon-gamma release assays (eg.T-SPOT, QuantiFERON-TB) in comparison to TST, particularly in children with previous BCG vaccination*.**

12. Soysal, A. *et al.* Diagnosing latent tuberculosis infection in haemodialysis patients: T-cell based assay (T-SPOT.TB) or tuberculin skin test? *Nephrol. Dial. Transplant.* ***27***, 1645-1650(2012).doi:10.1093/ndt/gfr516 ***Paper showing the T-SPOT.TB test's enhanced diagnosis of latent TB in patients with haemodialysis.***

13. Oxford Immunotec Guidelines. *Many countries have developed guidelines, which incorporate the use of interferon gamma release assays (IGRA) such as T-SPOT.TB...* [Available from] http://www.oxfordimmunotec.com/Guidelines_International (accessed 26 March 2013). ***List of worldwide guidelines recommending the use of the interferon-gamma release assays for the diagnosis of TB.***

14. National Institute for Health and Clinical Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (NICE clinical guideline 117). Developed by the National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice at NICE. Issued March 2011. [Available from] http://www.nice.org.uk/nicemedia/live/13422/53638/53638.pdf (accessed 26 March 2013) ***Updated NICE Guideline recommending the use of the interferon-gamma release assays in a number of specific diagnostic circumstances.***

15. *Oxford Immunitec Sales Statement*. Chris Granger: Director Global Professional Relations. Oxford Immunotec Ltd. 2012. ***Sales Statement in email received from Chris Granger, Director Global Professional Relations, Oxford Immunotec Ltd on 1st February 2012. (available on request)***