

Impact case study (REF3b)

Institution: Imperial College London
Unit of Assessment: 01 Clinical Medicine
Title of case study: Improvement in Diagnosis and Management of Tuberculosis in Children.
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>In 2006, new diagnostic tools for tuberculosis (TB) were introduced through the NICE guidelines, assuming they would perform equally well in adults and children. Research conducted by Imperial College researchers proved this assumption to be incorrect and that TB diagnostics needed to be evaluated specifically for children, as performance was different from adults. The Imperial researchers were the first to conduct the evaluations. Their results subsequently influenced the use of diagnostics and overall management of childhood TB, including the design of a public health tool for contact tracing in the community and inclusion of their results and recommendations in national and international guidelines.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Key Imperial College London researchers: Professor Beate Kampmann, Professor in Paediatric Infection & Immunity (2007-present) Dr Robin Basu-Roy, Academic Clinical Fellow in Paediatric Infectious Diseases (2010-present) Dr Elizabeth Whittaker, Academic Clinical Fellow, then PhD student (2008-2013)</p> <p>Tuberculosis (TB) remains a global threat with an estimated half a million children (0-14 years) falling ill and 64,000 deaths attributable to TB in children per year worldwide (1). National and international guidelines or algorithms for management of TB are usually developed for management of adult TB and guideline developers assume that they will also equally apply to children. However, work at Imperial has shown, this is not the case. TB is different in children, due to the underlying immaturity of their immune system and lower bacillary burden, which has an impact on immunological and microbiological diagnostic tools (2). By using “adult tools”, the diagnosis and opportunities for diagnosis and prevention are often missed.</p> <p>One powerful example is the 2006 NICE recommendation for use of interferon-gamma release assays (IGRA) for the diagnosis of TB. Through the unique work at Imperial all available immuno-diagnostic tests were evaluated comparatively in a large paediatric cohort within several NHS Trusts (3). The work at Imperial demonstrated that they do not perform as reliably in children as they do in adults, should be interpreted with caution and certainly not be used to exclude active TB (4). This study has informed many of the International and European guidelines and consensus statements (5).</p> <p>TB in children is the result of transmission from an infected adult. In order to prevent it, contact tracing in TB-affected households has to be conducted. However, these activities were not previously captured by the TB register in the UK and therefore the outcome of children traced and treated in the community was not recorded, unless the children themselves had become TB cases. As part of the Imperial research programme, in collaboration with the National TB register and Public Health England (PHE), Professor Kampmann developed a novel database which enables a link between children exposed to TB, their management in the community and later development of disease. Professor Kampmann designed this contact tracing module which is now implemented as part of the TB reporting system in the UK and can be used to capture the success or failure of TB prevention in children.</p> <p>The evidence gathered from our multi-centre studies has defined the practices of diagnosis and management of childhood TB in the UK and internationally. The contact tracing database has made an important contribution to TB control in the country by enabling follow-up of patients who are TB exposed but not yet diseased. This illustrates how the most current research has driven change in the management of TB in both adults and children. It is facilitated by close links between</p>

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PHE and Imperial researchers.

The research work at Imperial has also led to the establishment of a paediatric TB research network in both the UK and Europe, the ptbnet (www.ptbnet.org). This network has published evidence from a cohort of over 1000 children from 5 European countries on the performance of IGRA for TB diagnosis in children and discovered that BCG vaccination protects against TB infection (6).

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

(1) Newton, S.M., Brent, A.J., Anderson, S., Whittaker, E., & Kampmann, B. (2008). Paediatric Tuberculosis. *Lancet Infectious Diseases*, 8 (8), 498-510. [DOI](#). Times cited: 95 (as at 1st November 2013 on ISI Web of Science). Journal Impact Factor: 19.96

(2) Jones, C., Whittaker, E., Bamford, A., & Kampmann, B. (2011). Immunology and pathogenesis of childhood TB. *Paediatr Respir Rev*, 12 (1), 3-8. [DOI](#). Times cited: 6 (as at 1st November 2013 on ISI Web of Science). Journal Impact Factor: 2.79

(3) Bamford, A.R., Crook, A.M., Clark, J., Nademi, Z., Dixon, G., Paton, J.Y., Riddell, A., Drobniewski, F., Riordan, A., Anderson, S.T., Williams, A., Walters, S., & Kampmann, B. (2010). Comparison of Interferon-gamma release assays and Tuberculin Skin Test in predicting active tuberculosis (TB) in children in the UK- a Paediatric TB Network Study. *Arch Dis Child*, 95 (3), 180-186. [DOI](#). Times cited: 33 (as at 1st November 2013 on ISI Web of Science). Journal Impact Factor: 3.05

(4) Kampmann, B., Whittaker, E., Williams, A., Walters, S., Gordon, A., Martinez-Alier, N., Williams, B., Crook, A.M., Hutton, A.M., & Anderson, S.T. (2009). Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. *European Respiratory Journal*, 33 (6), 1374-1382. [DOI](#). Times cited: 57 (as at 1st November 2013 on ISI Web of Science). Journal Impact Factor: 6.35

(5) Mack, U., Migliori, G.B., Sester, M., Rieder, H.L., Ehlers, S., Goletti, D., Bossink, A., Magdorf, K., Hölscher, C., Kampmann, B., Arend, S.M., Detjen, A., Bothamley, G., Zellweger, J.P., Milburn, H., Diel, R., Ravn, P., Cobelens, F., Cardona, P.J., Kan, B., Solovic, I., Duarte, R., Cirillo, D.M., Lange, C., TBNET. (2009). LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J*, 33(5), 956-973. [DOI](#). Times cited: 152 (as at 1st November 2013 on ISI Web of Science). Journal Impact Factor: 6.35

(6) Basu Roy, R., Sotgiu, G., Altet-Gómez, N., Tsohia, M., Ruga, E., Velizarova, S., & Kampmann, B. (2012). Identifying predictors of interferon- γ release assay results in pediatric latent tuberculosis: a protective role of bacillus Calmette-Guerin?: a p TB-NET collaborative study. *Am J Respir Crit Care Med*, 186 (4), 378-384. [DOI](#). Times cited: 11 (as at 1st November 2013 on ISI Web of Science). Journal Impact Factor: 11.04

Key funding:

- Wellcome Trust (1999-2003, £378 000), Principal Investigator (PI) B. Kampmann, Training Fellowship.
- Wellcome Trust (2005-2009, £705 000), PI B. Kampmann, Career Development Fellowship.
- NIHR (2009-2014, £1.3 million), PI B. Kampmann, Senior Research Fellowship.

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

Impacts include: public policy and services, practitioners and services, health and welfare

Main Beneficiaries include: Patients, practitioners, NICE, PHE, NHS, UK and nternational Government, ECDC, WHO, NIH

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The World Health Organisation (WHO) currently estimates that half a million children (0-14 years) falling ill and 64,000 deaths are attributable to TB per year worldwide ([WHO figures](#)). Research at Imperial College has developed the evidence base for the diagnosis and management of childhood TB nationally and internationally.

In May 2012 the NICE guidelines were changed to a pathway approach. The guidelines now contain separate guidelines for the management of children in separate age groups. The work performed at Imperial informed the age stratification [1]. The contribution of IGRA to the diagnostic process has been downgraded significantly and the approach advocated by Professor Kampmann and colleagues at Imperial for synergistically using IGRA and a tuberculin skin test to increase sensitivity has been adopted and the need for childhood-specific management internationally acknowledged.

At a European level the European Centre for Disease Prevention and Control (ECDC) has utilised Imperial research in the ECDC guidance for the use of interferon-gamma release assays for TB diagnosis [9]. The algorithms resulting from the Imperial research have been used to develop several European consensus statements from the [Tuberculosis Network in Europe](#) [2, 3]. The ECDC conducted a campaign for advocacy in childhood TB, which included an extensive review of the burden of childhood TB in Europe and a feature broadcasted on Euronews in March 2011 in 22 languages. (World Tuberculosis Day 2011: Three key messages on childhood tuberculosis [9].

The notion of TB as a family disease has been adopted by many centres now holding joint adult and paediatric TB clinics, including the establishment of family clinics for TB in Prof Kampmann's international TB work linked to The Gambia. The Stop TB partnership now specifically mentions the concept [4].

The ability to link exposed, infected and diseased individuals on the UK TB register has been facilitated by Imperial research and development of the contact tracing module by Professor Kampmann. The TB register has important ongoing implications for TB control in the UK. This UK TB Register and the contact tracing module are now utilised by other international organisations and settings [5].

Imperial research has also influenced and directed policy and guidance documentation produced by the WHO and National Institutes of Health (NIH). The research has impacted the TB diagnosis methodologies undertaken and the policies employed internationally in the following ways:

- Use of interferon- γ release assays (IGRAs) in tuberculosis control in low and middle income settings [6].
- Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income Countries [7]
- Development of a novel case definition for childhood TB by the NIH [8]

Many of the policies and practices now embedded in the NHS have been adopted in other overseas healthcare systems. For example, the Stop TB partnership recently published a press release which provides evidence for the impact of the Imperial led research on long-term efforts to tackle childhood TB in The Gambia, where Professor Kampmann has implemented a childhood TB research program. As a result of the Imperial research children identified through the contact tracing programme are now given prophylactic drugs [4].

The Imperial research has been formulated into expert review documents and educational reference chapters. These document impact the way clinicians and health practitioners are educated and results in the wide adoption of best practice. Professor Kampmann is the author of the chapter "How to use IGRA in children" [10]. The education and practice papers in Archives of Diseases of Childhood serve as a guide for general paediatricians. This journal has the full readership of the Royal College of Paediatrics and Child Health as it is published by the Royal College. It is the leading source of information for general paediatricians on this issue. The European Respiratory Society (ERS) is the leading professional organisation in its field in Europe. It is broad-based, with some 10,000 members and counting in over 100 countries. Its scope covers

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both basic science and clinical medicine. ERS seeks to alleviate suffering from respiratory disease and promote lung health through research, sharing of knowledge and through medical and public education. The Imperial College research has contributed to this mission through publications in the [ERS handbooks](#) and also on line teaching sessions.

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

- [1] [Nice clinical guidance on Tuberculosis](#) 117 (March 2011). [Archived](#) on 1st November 2013
- [2] Solovic, I., Sester, M., Gomez-Reino, J.J., Rieder, H.L., Ehlers, S., Milburn, H.J., Kampmann, B., Hellmich, B., Groves, R., Schreiber, S., Wallis, R.S., Sotgiu, G., Schölvinck, E.H., Goletti, D., Zellweger, J.P., Diel, R., Carmona, L., Bartalesi, F., Ravn, P., Bossink, A., Duarte, R., Erkens, C., Clark, J., Migliori, G.B., Lange, C. (2010). The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J.*, 36 (5), 1185-1206. [DOI](#).
- [3] Bumbacea, D., Arend, S.M., Eyuboglu, F., Fishman, J.A., Goletti, D., Ison, M.G., Jones, C.E., Kampmann, B., et al. (2012). The risk of tuberculosis in transplant candidates and recipients: A TBNET consensus statement. *Eur Respir J.*, 40 (4), 990-1013. [DOI](#).
- [4] Stop TB Partnership: http://stoptb.org/news/stories/2013/ns13_060.asp [Archived](#) on 1st November 2013.
- [5] [UK TB Register and the contact tracing module are now utilised by other international organisations and settings](#). [Archived](#) on 1st November 2013.
- [6] Use of interferon- γ release assays (IGRAs) in tuberculosis control in low and middle income settings: http://www.who.int/tb/features_archive/igra_egm_report_oct2011.pdf. [Archived](#) on 1st November 2013.
- [7] Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income Countries
http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf. [Archived](#) on 01/11/2013
- [8] Graham, S.M., Ahmed, T., Amanullah, F., Browning, R., Cardenas, V., Casenghi, M., Cuevas, L.E., Gale, M., Gie, R.P., Grzemska, M., Handelsman, E., Hatherill, M., Hesselning, A.C., Jean-Philippe, P., Kampmann, B., et al. (2012). Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis.*, 205 (Suppl 2), S199-208. [DOI](#).
- [9] ECDC guidance: http://www.ecdc.europa.eu/en/publications/publications/1103_gui_igra.pdf. [Archived](#) on 01/11/2013.
- [10] Educational texts:
- Education & Practice: Pollock, L., Basu Roy, R., Kampmann, B. (2013). How to use: interferon γ release assays for tuberculosis. *Arch Dis Child Educ Pract Ed*, 98 (3), 99-105. [DOI](#).
 - ERS book chapter: European Respiratory Monograph No 58, Dec 2012, Chapter 15; TB in children Published by the European Respiratory Society. <http://www.ers-education.org/publications/european-respiratory-monograph/archive/tuberculosis.aspx>
 - ERS Handbook: Paediatric Respiratory Medicine: Chapter 8; p 284 <http://www.ers-education.org/publications/handbook-series/ers-handbook-of-paediatric-respiratory-medicine.aspx>