Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Quantifying childhood TB burden to increase funding and access to treatment.

Period when the underpinning research was undertaken: 2012 - present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
James Seddon	Clinical Senior Lecturer in Paediatric Diseases	2013 - present

Period when the claimed impact occurred: 2014 - present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Tuberculosis (TB) is a major cause of global mortality but its burden in children was not known. Imperial researcher Dr Seddon undertook modelling studies to estimate the burden of tuberculosis (TB), drug-resistant TB, and TB mortality in children, as well as to evaluate the impact of household contact interventions. These studies have led to revised WHO burden estimates (from 490,000 to 1,200,000 cases per year) and have informed the market size for the development of new, child-friendly drug formulations, which have subsequently been rolled out to >90 countries.

2. Underpinning research (indicative maximum 500 words)

Dr Seddon, in collaboration with Dr Peter Dodd (University of Sheffield), sought to quantify the burden of childhood tuberculosis (TB).

The first study, published in 2014, provided estimates of the burden of TB in children (<15 years) in the 22 highest TB burden countries in the world. A mechanistic mathematical model was used, combining estimates of adult TB prevalence with aspects of the natural history of paediatric TB, including age, HIV status and BCG vaccination history. The researchers estimated that 7,500,000 million children become infected with TB each year in these 22 countries and that 650,000 children develop TB disease (1).

The second study modelled the global burden of drug-resistant TB in children. An analysis of drug resistance patterns for TB in each country in the world was conducted, which was then combined with a mathematical model of childhood TB incidence to produce drug-resistant TB estimates for children. The researchers estimated that 2,000,000 children are currently infected with multidrug-resistant (MDR) TB and that each year 25,000 children develop MDR-TB disease (2).

A systematic review and meta-analysis were carried out to better understand the impact of HIV on the risk of children developing TB. The review identified 64 studies and determined that HIV increased the risk of TB almost 8-fold. Children with more severe immunosuppression were at increased risk of TB yet antiretroviral therapy rapidly reduced this risk. One year after starting antiretroviral therapy, the risk had fallen by 90% (3).

The next project sought to estimate the global burden of TB mortality in children. The number of deaths in children was estimated for 217 countries using a case-fatality-based approach.

Paediatric TB notification data were used, and HIV rates and antiretroviral treatment coverage estimates for those children living with HIV were applied to disaggregate the World Health Organization (WHO) paediatric TB incidence estimates by age, HIV, and TB treatment status. The researchers estimated that 240,000 children died from TB in 2015, with 80% in children <5 years. More than 96% of all TB deaths occurred in children not receiving TB treatment (4).

The potential impact of household contact management on cases of childhood TB disease and deaths were estimated. The health system utilization required to prevent each case and each death was also calculated. Full implementation, on a global level, would prevent 160,000 cases of childhood TB and 110,000 deaths, representing 7,300,000 life-years. The model estimated that preventing one child death from TB would require 48 household visits (5).

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

(1) Dodd, P.J., Gardiner, E., Coghlan, R., Seddon, J.A. (2014). Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Global Health*; 2(8): e453-e459. DOI.

(2) Dodd, P.J., Sismanidis, C., Seddon, J.A. (2016). Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. *Lancet Infect Diseases*; 16(10): 1193-201. DOI.

(3) Dodd, P.J., Prendergast, A.J., Beecroft, C., Kampmann, B., Seddon, J.A. (2017). The impact of HIV and antiretroviral therapy on tuberculosis risk in children: a systematic review and meta-analysis. *Thorax*; 72: 559-575. DOI.

(4) Dodd, P.J., Yuen, C., Sismanidis, C., Seddon, J.A., Jenkins, H. (2017). The global burden of tuberculosis mortality in children: a mathematical modelling study. *Lancet Glob Health*; 5(9): e898-e906. DOI.

(5) Dodd, P.J., Yuen, C., Revill, P., Becerra, M.C., Jenkins, H., Seddon, J.A. (2018). The potential effect of household contact management on childhood tuberculosis: a mathematical modelling study. *Lancet Glob Health*; 6(12): e1329-e1338. DOI.

Key funding:
STEP-TB: Modelling childhood TB including mortality, drug resistance and preventive therapy (Co-PI; £86,000)

TB Alliance: Mathematical modelling estimates of the burden of childhood TB in the 22 high-burden countries (Co-PI; $15,000)

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

Dr Seddon and colleagues estimated that, globally each year, 1.2 million children develop TB of which 250,000 die. Until the described modelling work was undertaken, this burden was not recognised. These estimates have underpinned global and national estimates of burden. From 2015 onwards they have been directly incorporated into the annual World Health Organization (WHO) estimates of childhood TB disease and mortality [**A**]. As a result of this research, for the first time, childhood TB is now recognised as one of the top 10 causes of under 5 mortality [**B**] – it was previously unrecognised. As under 5 mortality is seen as a key metric in the funding agenda for research and operational investment globally, this is crucial for childhood TB funding [**B**].

The burden estimates in children from this modelling work and reported by WHO have been used by Ministries of Health and National TB Programmes to carry out national and regional service evaluations. A recent example is the FIKIA Project in Kenya, which seeks to increase case-finding in children. It uses as its justification the fact that the WHO estimates suggest

that 10-15% of the overall TB burden is in children, while in Kenya, only 8.7% is in children. This has led to the use of enhanced case-finding to look for these missing children [**C**]. A similar justification for case-finding is seen in national TB guidelines, for example [**D**] which cites reference (1) above. The burden estimates have also led to childhood TB being prioritised in global and national TB planning due to increased perception of burden of disease and death. In the 232-page WHO Global TB Report in 2010 the terms "child" or "children" were used 5 times. In the same report in 2020 they were used 163 times [**A**]. The WHO carries out reviews of country TB Programmes and it is now mandatory to include a reviewer with paediatric TB expertise on these panels. These reviewers use the modelled estimates to evaluate the discrepancies between expected and diagnosed cases of childhood TB.

The estimates from Dr Seddon's work have been cited in multiple advocacy materials, especially in the run up to the first UN high level meeting on TB in September 2018 [**E**]. When competing for scarce resources for both child TB service implementation and research, burden estimates have proved crucial. For example, Dr Seddon's work has been included in WHO advocacy material ('*At least 1 million children fall ill with tuberculosis (TB) each year. Children represent about 11% of all TB cases*') [**F**] and the 2018 revised Roadmap for childhood TB ('*We now know that 10% of all TB affects and manifests in children – over half of that among children under five years of age.*') [**B**], as well as the 2018 Union advocacy document, the silent epidemic [**G**]. The estimates have resulted in changes to attitudes and awareness around childhood TB for the public as well as for policymakers – this body of work has influenced the development of strategic research priorities [**H**] and best practices [**I**] for childhood TB at a WHO level.

Dr Seddon has also worked with industry to develop new drugs for children. The TB Alliance is a product development partnership that works to develop new TB drugs. They received a grant of USD16,700,000 from Unitaid in 2013 to develop child-friendly drug formulations. A key first step was to develop market estimates for TB in children to strengthen negotiations with drug companies [**J**]. Dr Seddon and Dr Dodd worked with Unitaid and TB Alliance to ensure that their estimates could be used for these negotiations (acknowledged in [**J**]). The first ever fixed-dose, fully dispersible, palatable TB drug formulation was subsequently developed by Macleods and these formulations have now been rolled out to >90 countries, making it much easier to treat children with TB [**J**].

Finally, children with TB ultimately benefit from the increased funding and prioritisation of diagnosis and treatment. This has benefits for families and communities in high TB burden countries. The number of children diagnosed with TB and notified to WHO increased from 327,000 in 2011 to 523,000 in 2019 [**A**]. In 2015, 87,242 children <5 years were given preventive therapy following household exposure to TB. In 2019, this figure was 433,196 [**A**].

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

Page numbers refer to pages in report not the PDF.

[**A**] WHO Global Tuberculosis Report: 2015 (page 11, page 32); 2016 (page 19); 2017 (page 55); 2018 (page 57); 2019 (references 12 and 14 from page 69 referring to text on pages 34 and 45); 2020 (references 13 and 16 on page 69 referring to text on pages 31 and 42). These reports are all archived here: 2015, 2016, 2017, 2018, 2019, 2020.

[**B**] WHO. Roadmap towards ending TB in children and adolescents (pages 6-7, 9). Archived here.

[**C**] FIKIA Project in Kenya https://www.chskenya.org/what-we-do/fikia/. Archived here.

[**D**] National Tuberculosis Control Programme, Bangladesh. National Guidelines for the Management of Tuberculosis in Children (reference 2 on page 65 referenced from text on page 1). Guidelines archived here.

[**E**] Political Declaration of the UN General Assembly High-Level Meeting on the Fight Against Tuberculosis. https://www.who.int/tb/unhlmonTBDeclaration.pdf (children mentioned 17 times in 20 page document). Archived here.

[**F**] WHO: Ending Tuberculosis in Children (page 1). Archived here.

[**G**] The International Union Against Tuberculosis and Lung Disease: Silent Epidemic (references 11, 12 and 28 on page 37 referring to text on pages 6, 8, 9, 11, 12 and 13). Archived here.

[**H**] Research Priorities for Paediatric Tuberculosis. World Health Organization (reference 1 referring to text on page1). Archived here.

[**I**] Best Practices in Child and Adolescent TB Care. World Health Organization (references 6, 7 and 8 on page 124 referring to text on pages 10, 11 and 12). Archived here.

[**J**] TB Alliance: New Pathways for Childhood TB Treatment (page 14). Archived here.