Institution: St George's, University of London

Unit of Assessment: 1 Clinical Medicine

Title of case study: Optimising antibiotic prescribing in children

Period when the underpinning research was undertaken: 2010 to 2020

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:
Michael Sharland	Professor of Paediatric Infectious Diseases	1989 – 2020 (present)
Bielicki Julia	Research Fellow, then Senior Lecturer	2011 – 2020 (present)
Hsia Yingfen	Senior Pharmaco-Epidemiologist	2014 – 2020 (present)

Period when the claimed impact occurred: 2014 to 2020

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

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

The inappropriate dosing and overuse use of antibiotics, particularly those with broad spectrum, is the most important driver of human antimicrobial resistance. The work of the St George's group has had a major national and global impact in terms of specific antibiotic dosing and duration recommendations and practice; and by providing indicators of appropriate prescribing at a country level that can be used as targets and monitoring tools to drive down inappropriate antibiotic use world-wide. The proportion of UK children receiving an optimal amoxicillin dose increased from 45.4% before 2014 to 93.7% after 2014, and evidence has been provided to reduce the duration of its use in pneumonia from 7 days to 3 days. Using the metrics developed by the St George's group, the WHO have set a target that 60% of all antibiotic prescribing globally should be narrow spectrum by 2023.

2. Underpinning research (indicative maximum 500 words)

Antimicrobial Resistance (AMR) has been identified as a huge and escalating threat to global health and prosperity, with drug resistant infections causing an estimated 700,000 deaths, and, in the USA alone, USD20,000,000,000 in excess costs each year, with deaths and costs rising rapidly (https://amr-review.org/). The inappropriate dosing and overuse use of antibiotics, particularly those with broad spectrum, is a critical driver of antimicrobial resistance; and childhood infections account for approximately 25% of all prescribing. In response to this threat, the St George's group have contributed a major body of work to optimise antibiotic use in children, taking an important global role in efforts to reduce the health and economic impacts of AMR.

Identifying evidence for antibiotic underdosing in children

The group's early work identified that the doses given by the British National Formulary (BNF) for Children for amoxicillin (the most commonly prescribed antibiotic for children in the UK), and used in practice, were very low in relation to increasing weights of children and had remained unchanged since 1976 [1]. Pharmacokinetic studies by the group in hospitalised children provided further evidence for a change in guidance [2] and the BNF changed the UK dose based on the evidence for underdosing.

Defining the optimal drug, dose and duration for Community Acquired Pneumonia (CAP)

As the optimal dosing and duration for CAP for younger children attending hospital was unclear, in collaboration with the MRC Clinical Trials Unit, the group were funded through NIHR to

conduct a double blind placebo controlled trial to assess dosing. The trial assessed higher (100mg/kg/day) and lower (50mg/kg/day) doses of amoxicillin at longer (7 days) and shorter (3 days) duration in 824 children with CAP, with clinical and antimicrobial resistance (AMR) outcomes. The study demonstrated that 3 days is as effective as 7 days, [3]. Major follow-up trials are underway (see impact).

Evaluating prescribing and defining a strategy to optimise treatment and prevent AMR
The group recognised the global threat of AMR in young children and the clear need to improve the quality of childhood antibiotic prescribing in both the community and hospital setting through improved stewardship programmes. To determine the variation in antimicrobial use for serious hospital infections, the group developed a novel methodology to conduct simple web-based point prevalence surveys (PPS) of neonatal and paediatric antimicrobial prescribing. The antibiotic resistance and prescribing in European children (ARPEC) PPS study demonstrated the feasibility of the method and led to the first ever paediatric quality indicators for hospital antibiotic prescribing [4].

Further work on quality indicators of optimal prescribing was undertaken in collaboration with the WHO Essential Medicines list (EML) and Healthcare directorate. The St George's group worked with the WHO to derive a novel classification of narrow, broad-spectrum and last resort antibiotics – the new Access, Watch and Reserve categories, respectively, which were then combined into the WHO AWaRe index. Access antibiotics (such as amoxicillin and penicillin) are cheaper, older off patent narrow spectrum antibiotics. The group used this methodology to extend the paediatric PPS method globally and developed new AWaRe based metrics for optimal prescribing in hospitalised children across both high-income and low- and middle-income Country (LMIC) settings, focussing on encouraging the use of narrow spectrum antibiotics.

The first global paediatric antibiotic PPS recruited over 25,000 children from 56 countries and successfully evaluated these novel indicators for optimal prescribing for children in the hospital setting [5]. The group then extended the use of the AWaRe index to the community setting. They determined the pattern and variation in global child antibiotic use across 70 countries, noting a high use of broad-spectrum antibiotics. The group derived a simple combination of metrics based on the AWaRe groups to assist countries to identify potential over use of broad-spectrum antibiotics [6].

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

1. Saxena S, Ismael Z, Murray M, Barker C, Wong I, Sharland M, Long PF. Oral penicillin prescribing for children in the UK: a comparison with BNF for Children age-band recommendations. British Journal of General Practice. 2014; 64(621):e217-e222. DOI: 10.3399/bjgp14X677842. Journal article cited 9 times (WOS 08.02.2021)
2. Lonsdale D, Baker E, Kipper K, Barker C, Philips B, Rhodes A, Sharland M, Standing J. Scaling beta-lactam antimicrobial pharmacokinetics from early life to old age. British Journal of Clinical Pharmacology. 2018;85(2):316-346. DOI: 10.1111/bcp.13756. Journal article cited 4 times (WOS 08.02.2021).
3. Lyttle M, Bielicki J, Dunn D, Stohr W, Gibb D Sharland M on behalf of the CAP-IT study group. CAP-IT – a double blind randomised placebo controlled trial comparing higher and lower doses and shorter and longer durations of amoxicillin in children with Community Acquired Pneumonia. The Royal College of Emergency Medicine Conference, 1-3 October 2019. www.capitstudy.org.uk (*note; under review at Lancet*). URL: https://www.escmid.org/escmid_publications/eccmid_abstract_book/.
4. Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, ARPEC Project Group. The worldwide antibiotic resistance and prescribing in European children (ARPEC) point prevalence survey: Developing hospital- quality indicators of antibiotic prescribing for children. J Antimicrob Chemother. 2016;71(4):1106–17. DOI: 10.1093/jac/dkv418. Journal article cited 104 times (WOS 08.02.2021).
5. Hsia Y, Sharland M, Jackson C, Wong I, Magrini N, Bielicki J. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve

(AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. The Lancet Infectious Diseases. 2019;19(1):67-75. DOI: 10.1016/S1473-3099(18)30547-4. Journal article cited 38 times (WOS 08.02.2021).
6. Hsia Y, B R Lee, Versporten A, Y Yang, J Bielicki, C Jackson, J Newland, H Goossens, N Magrini, M Sharland. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRE): an analysis of paediatric survey data from 56 countries. 2019;7(7), E861-871. Lancet Global Health. DOI: 10.1016/S2214-109X(19)30071-3. Journal article cited 27 times (WOS 08.02.2021).

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

The work of the St George's group has had major national and global impact in terms of specific dosing and duration recommendations and practice, and by providing simple indicators that can be used as targets and monitoring tools to drive down inappropriate antibiotic use on a world-wide basis.

Improvements in antibiotic dosing for children in the UK
Prolonged use of inappropriately low, less effective doses is a particularly strong driver of antimicrobial resistance. The recognition of the low doses of amoxicillin used in UK children led to the 2014 changes in the BNF for Children doses [A]. Approximately 3,000,000 children receive amoxicillin each year in primary care in the UK and data from our group [B] demonstrated that the proportion of children being under dosed decreased from 54.6% before 2014 to 5.8% after 2014. As a result, the proportion of children receiving an optimal dose was found to be 93.7% after 2014. Since 2014, approximately 9,000,000 more children are now being given appropriate amoxicillin doses for common community infections in the UK.

Furthermore, the CAP-IT trial has shown very similar outcomes with 3 days as opposed to 7 days of amoxicillin therapy in children with pneumonia. In the UK there are around 4,000,000 children aged under 5, with a pneumonia incidence rate of 0.5%[C], so that an altered recommendation for duration moving from 7 days to 3 days would enable 100,000 young children in the UK to safely receive significantly shorter durations of antibiotic from 2021 to 2026. This will reduce the burden of families giving medicines to young children, and significantly reduce antibiotic use and the pressure for the further development of penicillin resistance.

Development of a WHO-co-ordinated global programme to optimise childhood antibiotic prescribing.
CAPIT and the group's other studies led directly to funding for a WHO co-ordinated global programme of major trials now underway to define optimal antibiotic regimens for childhood pneumonia in low- and middle-income settings, and in neonatal sepsis [D, Neovanc, Pedicap, Neomero Trials, NeoAMR Study in neonatal sepsis]. In addition, the group were asked by WHO to review the evidence for the WHO antibiotic guidelines for childhood pneumonia and neonatal sepsis [E], and to be clinical leads in the Global Antibiotic Research and Development Partnership (GARDP), a collaboration between WHO and Drugs for Neglected Diseases initiative (DNDi) to combat AMR that is co-ordinating a number of these studies.

Setting global targets for appropriate antibiotic use
The analyses discussed above demonstrated the feasibility of deriving simple ratios of narrow vs broad spectrum antibiotic use at an individual country level. Specifically, the proportion of Access antibiotics for systemic use as a proportion of broad spectrum Watch antibiotic consumption (the Access/Watch ratio) provides a simple indicator for the appropriateness of prescribing practice and has now been included in the WHO Monitoring and Outcome Framework [Fa (WHO AMR MEF – Outcome 4.1b p25)], and implemented in the NHS England Quality Improvement Program [Fb].

A further global analysis using the St George's metrics, covering antibiotic sales between 2000 and 2015 identified an increase of 90% in Watch antibiotics, with higher resistance potential, particularly in LMIC countries, emphasizing the urgent need for specific targets to enhance the

use of Access antibiotics [G]. This increase in Watch antibiotic use, alongside demonstration of the variation in the proportions of Access and Watch antibiotics used globally, and the potential for monitoring trends in use over time, led to the development of specific targets of optimal antibiotic use globally.

In 2019, the WHO Director General announced the first global target to reduce inappropriate broad-spectrum antibiotic use, setting a target for individual countries that 60% of their total prescribing should be of the Access group of antibiotics by 2023 [H]. Thus, the AWaRe metric developed by the group has now become an important global antibiotic stewardship tool and a vital initial component of WHO efforts to combat AMR [I, J]. A new WHO Antibiotic Guidance Handbook, incorporating AWaRe principles, and covering over 90% of global antibiotic prescribing for adults and children has been developed in 2020 [K].

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

A. BNF-C Amoxicillin recommendations.
https://bnfc.nice.org.uk/drug/amoxicillin.html#indicationsAndDoses

B. Rann O, Sharland M, Long P, Wong ICK, Laverty AA, Bottle A, Barker CI, Bielicki J, Saxena S. Did the accuracy of oral amoxicillin dosing of children improve after the British National Formulary dose revisions in 2014? National cross-sectional survey in England. BMJ Open 2017;7 e016363. DOI: 10.1136/bmjopen-2017-016363.

C. British Lung Foundation Pneumonia statistics (Respiratory Health of the Nation project supported by teams at St George's University of London, Nottingham University and Imperial College London.)
https://statistics.blf.org.uk/pneumonia#:~:text=How%20many%20people%20in%20the,diagnosis%20of%20pneumonia%20each%20year.

D. NeoVanc: https://www.neovanc.org/en/; Pedicap: https://projectpedicap.org/; Neomero: PLoS One 2020 Mar 4;15:e0229380; NeoAMR Observational Study in Neonatal Sepsis. https://clinicaltrials.gov/ct2/show/NCT03721302

Ea. Mathur S, Fuchs A, Bielicki J, Van Den Anker J, Sharland M. Antibiotic use for community-acquired pneumonia in neonates and children: WHO evidence review. Paediatrics and International Child Health. 2018;38(sup1):S66-S75.
b. Fuchs A, Bielicki J, Mathur S, Sharland M, Van Den Anker J. Reviewing the WHO guidelines for antibiotic use for sepsis in neonates and children. Paediatrics and International Child Health. 2018;38(sup1):S3-S15.

Fa. WHO September 2019. MONITORING AND EVALUATION OF THE GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE. Framework and recommended indicators. ANNEX 3. Methodology sheets for recommended indicators [see Outcome 4.1b p25]
https://www.who.int/antimicrobial-resistance/global-action-plan/monitoring-evaluation/AMR-M-E-indicator-reference-sheets-web-high-December-2019.pdf?ua=1
b. HM Government. Tackling Antimicrobial Resistance 2019-2024: The UK's Five-Year National Action Plan. 2019. www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024. [see p21, and p53, 3.1 measuring success]
and Adaptation of the WHO Essential Medicines List for national antibiotic stewardship policy in England: being AWaRe. J Antimicrob Chemother 2019; 74: 3384–3389 doi:10.1093/jac/dkz321

G. Klein E, Milkowska-Shibata M, Tseng K, Sharland M, Gandra S, Pulcini C, Laxminarayan R. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000-2015: an analysis of pharmaceutical sales data. Lancet Infectious Diseases Jul 2020. S 1473-3099. DOI: 10.1016/S1473-3099(20)30332-7.

H. WHO News release 18 June 2019. In the face of slow progress, WHO offers a new tool and sets a target to accelerate action against antimicrobial resistance https://www.who.int/news-room/detail/18-06-2019-in-the-face-of-slow-progress-who-offers-a-new-tool-and-sets-a-target-to-accelerate-action-against-antimicrobial-resistance

Ia. Sharland M, Pulcini C, Harbarth S, Zeng M, Gandra S, Mathur S, Magrini N, on behalf the 21st WHO Expert Committee on Selection and Use of Essential Medicines. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. Lancet Infect Dis. 2018;18(1):18–20. DOI: 10.1016/S1473-3099(17)30724-7.
b. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, Mendelson M, Cappello B, Cooke G, Magrini N; EML Expert Committee and Antibiotic Working Group. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use—the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. Lancet Infect Dis. 2019 Dec;19(12):1278-1280. DOI: 10.1016/S1473-3099(19)30532-8.

J. Testimonial Letter from secretary of WHO EML

K. WHO EML NEW ANTIBIOTIC USER GUIDE. Selecting the right drug, dose and duration for community and hospital infections – being AWaRe! WHO webinar 23/11/2020. https://penta-id.org/event/who-eml-new-antibiotic-user-guide-selecting-the-right-drug-dose-and-duration-for-community-and-hospital-infections-being-aware/