

## Impact case study (REF3)

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| <b>Institution:</b> King's College London   |                                  |  |
| <b>Unit of Assessment:</b> 3  |                                  |  |
| <b>Title of case study:</b> Improving antibiotic stewardship: Changing the UK's oral penicillin dosing guidelines for children. |                                  |  |
| <b>Period when the underpinning research was undertaken:</b> 2010 - 2020  |                                  |  |
| <b>Details of staff conducting the underpinning research from the submitting unit:</b>  |                                  |  |
| <b>Name(s):</b>   | <b>Role(s) (e.g. job title):</b> | <b>Period(s) employed by submitting HEI:</b> |
| Paul Long   | Professor of Pharmacognosy       | 05/07/2010 - present                         |
| <b>Period when the claimed impact occurred:</b> 2014 – 2020   |                                  |  |
| <b>Is this case study continued from a case study submitted in 2014?</b> N  |                                  |  |

### 1. Summary of the impact

Given the challenges associated with increasing antibiotic resistance, optimal use of antibiotics for children is important for global antimicrobial stewardship. Oral penicillins contribute 5 of the 8 million prescriptions for oral antibiotics given to children in England each year. King's research (2011-2020) showed that age-band dosing guidelines had remained unchanged since 1963 and that there was a wide variation in prescribing practice, with the majority of children receiving sub-optimal doses. Following our recommendation that the UK dosing schedule be revised, new national prescribing guidelines were developed and introduced in 2014 by the UK Joint Formulary Committee (comprising the British Medical Association, the Royal Pharmaceutical Society and the Department of Health). This new dosing regime has dramatically changed prescribing practice, with 94% of children in the UK now receiving the correct dose (equivalent to over 4.7 million prescriptions per year). As of 2019, the new guidelines influenced by King's have also been adopted internationally as the primary dosing schedule in Brunei, Malta, Republic of Ireland, Seychelles and Sri Lanka; and have been incorporated alongside local prescribing guidelines in 40 countries, comprising of 28 Commonwealth countries and 12 G20 nations, including Australia, New Zealand, France, Germany, Nigeria, Pakistan, Saudi Arabia, and China.

### 2. Underpinning research

**Oral penicillins are the most commonly prescribed antibiotics for children worldwide.** They contribute to 5 of the 8 million prescriptions for oral antibiotics given to children in England each year. In the UK, most paediatric antibiotic prescribing occurs in primary healthcare, and an infection for which a penicillin is prescribed (typically an inner ear infection, symptoms of sore throat or cough) is the most common reason a child visits a General Practitioner (GP).

**Improving antibiotic stewardship requires accurate prescribing.** In recent years, antibiotic prescribing practices have come under scrutiny because of increased antimicrobial resistance (AMR) as a result of inappropriate prescribing. Promoting appropriate antibiotic prescribing is therefore an essential strategy to combat antibiotic resistance. In order to eliminate bacteria causing an infection, the antibiotic concentration in a patient's blood must be maintained above the minimum inhibitory concentration (MIC) for the bacteria. Penicillins work in a 'time-dependent' mechanism in order to kill bacteria: the longer the time the blood antibiotic concentration is above the MIC, the greater the killing effect of the antibiotic. In the event of antibiotic underdosing, the blood antibiotic concentration does not surpass the MIC or only attains the MIC for a short period of time. Therefore, the antibiotic activity is reduced. This leaves the bacteria exposed to non-lethal antibiotic doses, fuelling antibiotic resistance by allowing bacteria to mutate and evolve rather than being killed. There have also been extensive efforts to ration physicians' antibiotic prescribing practices in primary care to reduce the prevalence of inappropriate antimicrobial prescriptions for both children and adults.

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**The UK guidelines on prescribing antibiotics for children were not fit for purpose.** The British National Formulary (BNF) and BNF for Children (BNFc) are the gold standard publications in the UK to provide prescribers, pharmacists, and other healthcare professionals with evidence-based, up-to-date information about the selection, prescribing, dispensing and administration of medicines. The BNF/BNFc are so highly regarded that they are also used as reference formularies by national healthcare providers throughout the world. Nevertheless, before 2014, the BNF/BNFc recommended dosing of oral penicillins in children were complex and potentially confusing, using age-bands, weight-bands or weight-based calculations. Importantly, given that the weights of children do not change in a linear fashion with age, the UK's age-banding system was also more likely to result in suboptimal dosing. This situation was further complicated because the few original pharmacokinetic and pharmacodynamics studies underlying the guidelines predated the more recent rising trend of obesity in children.

**King's researchers identified inaccuracies in the evidence base for current prescribing guidelines.** We undertook an extensive search of the literature and historical formularies (lists of approved medicines, their chemical formulae and associated clinical data) dating back to the 1930s. Using the Freedom of Information Acts both in the UK and USA to request and search clinical trial data held in the UK by The Medicines and Healthcare products Regulatory Agency (MHRA), and in the USA by the Food & Drug Administration (FDA), we uncovered the evidence-based origins of the age band regime **(1)**. Specifically, our research uncovered that the current UK dosing schedule was based upon a relatively arbitrary principle of (i) halving adult oral penicillin doses for older children; and (ii) halving again for younger children and infants. We showed that this principle had remained unchallenged in the literature and hence, dosing was unchanged in clinical practice since its introduction into the UK prescribing guidance in 1963 **(1)**. Astonishingly, we subsequently demonstrated that this age band dosing principle was based solely on a 1955 publication, drawing on the clinical observations of a single UK GP which, in effect, meant the guidelines had no evidence base at all **(2)**. This opened the question as to whether children today are receiving a clinically effective dose. A 10 year old child weighing 30 kg and receiving 250 mg three times a day will, under this schedule, receive 25 mg/kg/day – a very low dose, compared to the Summary of Product Characteristics (SPC; the description of a medicinal product's properties and the conditions attached to its use, explaining how to prescribe) recommendation for Amoxil Paediatric Suspension for all indications in children weighing <40 kg, of 40-90 mg/kg/day.

**Comparing prescribing practice and accuracy of antibiotic exposure with age-weight data for children prescribed amoxicillin.** In collaboration with researchers at UCL, Imperial, Basel and Hong Kong University, King's used data from the Antibiotic Resistance and Prescribing in European Children (ARPEC) survey of antimicrobial prescribing on the age and body weights of children in hospital, to compare the three main dose selection methods used globally: US/EU exact weight based dosing; UK age banded dosing; and WHO weight banded dosing **(3)**. We calculated the accuracy of amoxicillin exposure (the most common penicillin) and found that because of the rising prevalence of childhood obesity, age-band-based prescribing (such as the UK's system) could lead to sub-therapeutic dosing **(3)**. This is because fat tissue can affect the distribution, metabolism and clearance of antibiotics differently in obese compared to lean children. Body size affects liver and kidney function, with antibiotics being removed faster from the blood of obese children than lean children.

**King's demonstrated the discrepancy in antibiotic prescribing due to weight variation and strongly advocated new guidance was urgently required.** To find out the extent to which childhood weights might influence the starting dose of oral penicillins, in 2014 we undertook a review of data collected by GP practices from across the UK. By comparing actual dosing in prescriptions issued by GPs with the 2011–12 BNFc age-band dosing recommendations, we made some worrying findings: First, that there was a wide variation in the dosing of penicillins for children in UK primary care, and second, that 55% of children receiving oral penicillin in the UK in 2014 were underdosed **(2, 4)**.

### 3. References to the research

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1. Ahmed U, Spyridis N, Wong IC, Sharland M, Long PF; improving Children's Antibiotic Prescribing UK Research Network. (2011). *Dosing of oral penicillins in children: is big child=half an adult, small child=half a big child, baby=half a small child still the best we can do?* BMJ. Dec 15;343:d7803.
2. Sharland E, Long P, Sharland M, Bielicki, J, Saxena, S, Wong ICK, Barker C. (2019). *Early origins of oral penicillin dosing for children.* Arch Dis Child. doi: 10.1136/archdischild-2018-316531. [Epub ahead of print]
3. Bielicki JA, Barker CI, Saxena S, Wong IC, Long PF, Sharland M. (2015). *Not too little, not too much: problems of selecting oral antibiotic dose for children.* BMJ. Nov 3;351:h5447.
4. Saxena S, Ismael Z, Murray ML, Barker C, Wong IC, Sharland M, Long PF. (2014). *Oral penicillin prescribing for children in the UK: a comparison with BNF for Children age-band recommendations.* Br J Gen Pract. Apr;64(621):e217-22.

### 4. Details of the impact

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**Changing the UK's national prescribing guidelines.** Following the King's led review of UK paediatric antibiotic dosing guidelines, in relation to the weights of children today **(1-4)**, our research was part of the evidence used by the Joint Formulary Committee to support changes to the UK prescribing guidelines in 2014 **[A]**. The Joint Formulary Committee is comprised of representatives from the British Medical Association, the Royal Pharmaceutical Society and the Department of Health, and is the group responsible for making decisions on behalf of the National Institute for Clinical Excellence (NICE) about national prescribing guidelines, which are followed by all health professionals in the NHS.

As a result of the Joint Formulary Committee recommendations, the UK's prescribing guidelines were updated and adopted by the BNF/BNFc in 2014 **[B]**. These changes introduced into the BNF/BNFc by the Joint Formulary Committee meant that most children prescribed amoxicillin would now receive the SPC recommended dose of at least 45mg/kg/day for children weighing <40 kg, which for ease of use would be expressed in age bands. For example, a 10-year-old child weighing 30 kg and receiving the revised dose of 500 mg three times a day will now receive 50 mg/kg/day compared to the previous old dose of 25 mg/kg/day.

**New prescribing guidelines have been adopted by NHS Primary Care across the UK.** These new prescribing doses have been introduced into the computer prescription software used by over 9,000 GP surgeries across the UK. This is significant because it ensures that the new dosing is widely adopted: the software generates prescriptions with specific dosing levels, thus making it highly likely that GPs will adhere to the new, correct dosing level **[C, D]**.

**The resulting changes in prescribing practice ensure most children now receive the correct dose of antibiotics in the UK.** Having demonstrated that, before 2014, 55% of children receiving oral penicillin were underdosed **(3)**, King's led a cross-sectional survey of oral penicillin dosing across the UK following the introduction of new guidelines in 2014: After the guidance changed in 2014, the number of children estimated as being underdosed dropped to 5.8% **[E]**. In other words, ~94% of children in the UK now receive an optimal dose of penicillin appropriate for their age and weight **[E]**.

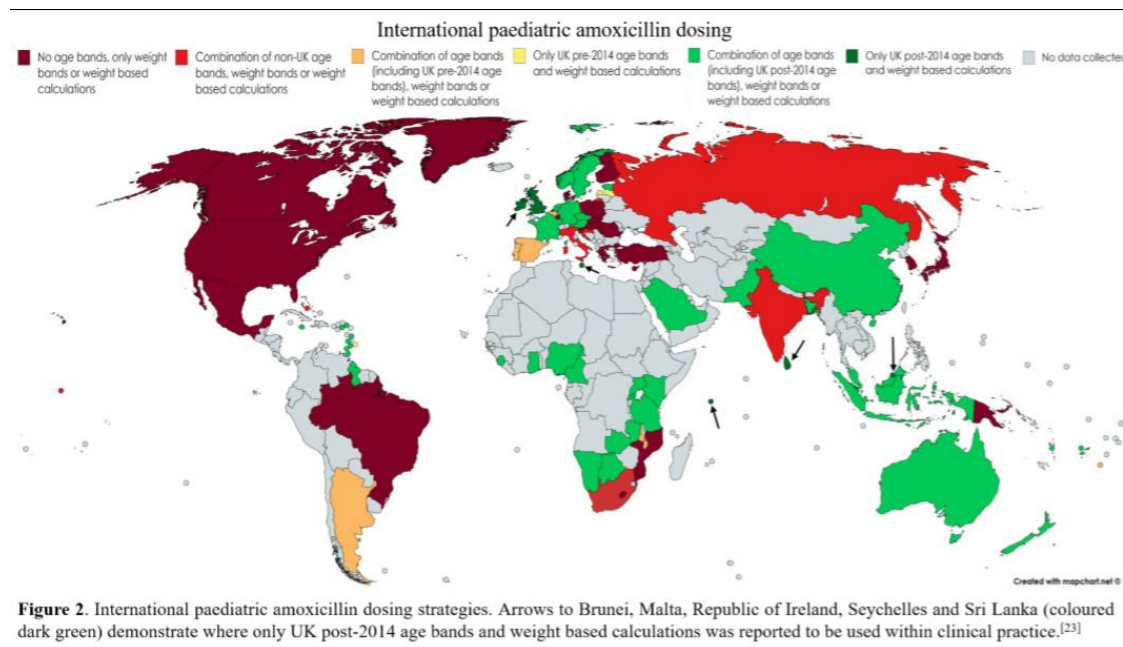
**The UK's new prescribing guidelines have also been integrated into prescribing guidelines internationally.** In 2019 we undertook a review of prescribing guidelines globally by auditing individual prescribing formularies of pharmaceutical societies and government health departments in different countries, and by contacting (clinically) practicing academics in schools of pharmacy. Our review showed that **[F]**:

- (i) **the new 2014 guidelines have been adopted in their entirety by Brunei, Malta, Republic of Ireland, Seychelles and Sri Lanka.** This represents a combined population of approximately 6,000,000 children under the age of 14.

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(ii) and have been **incorporated alongside existing prescribing guidelines in 28 Commonwealth countries and 12 G20 countries**, including China, which alone has a childhood population of 255,000,000 under the age of 14.

The countries that use the new prescribing guidelines recommended by the UK Joint Formulary Committee are shown in the map below [F]. We estimate that globally, around 500,000 GPs and other healthcare providers (e.g. nurses, pharmacists, dentists) across these countries have access to these guidelines through print and digital versions of the BNF/BNFc.



**The significance of this work has been recognised by an RCGP research impact award.** In 2014, the King’s study uncovering the historical evidence base for dosing guidelines and discrepancies in UK prescribing practices (1, 4) was awarded the Research of the Year Award in ‘Paediatrics, Obstetrics and Reproductive Health’ by the Royal College of General Practitioners, in recognition of the impact of the research [G]. Moreover, endorsement for the impact of this research by the NHS, learned societies, the global medical and scientific community, and World press and TV has been persistent and consistent since 2011 [H] [I].

**Careful antibiotic stewardship is now considered critical in the fight against AMR.** A growing awareness of the urgency for action to tackle AMR has put the problem high on the global political agenda, and the need to address prescribing practice has been widely recognised. The UK Special Envoy on Antimicrobial Resistance, Professor Dame Sally Davies, former Chief Medical Officer for England explains: “As Chief Medical Officer, I advised the UK government on the development and delivery of the 5-year National Action Plan (2019 to 2024) and 20-year vision for AMR. The Action Plan specifically highlights the necessity for sound antibiotic stewardship through prescribing.”

Importantly, specific action on prescribing in children is needed: “While hard to measure specific, direct impacts on the larger problem of AMR from any individual study, we now have compelling evidence that reducing inappropriate prescribing will make an important contribution. Across the world, infectious diseases are the leading cause of death and disability in children under the age of five years; this is exacerbated by drug-resistant infections. AMR disproportionately impacts low- and middle-income countries, and children. Both of these demographics suffer a delay in access to the treatments they need, which puts the Sustainable Development Goals at risk – especially that of ensuring healthy lives for all at all ages. Addressing prescribing in children is therefore a vital step – both for improving an individual patient’s prospects, and for preserving treatments for future patients who need it.”



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*“In my role as a representative to the United Nations’ Global Leaders Group on AMR, I am most keen to find and support work that is scalable and that can be tailored to communities and countries across the world. Professor Long’s work has now been adopted by 40 countries from across both the Global South and the Global North. Raising awareness is one thing – but changing behaviour and practice, as Professor Long’s research has done, paves the way for better patient outcomes across the world.”*

**5. Sources to corroborate the impact**

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**[A] Evidence used by the Joint Formulary Committee to support changes to the UK prescribing guidelines:** Paediatric penicillin dosing “needs urgent review” The Pharmaceutical Journal, 5 April 2014, Vol 292, No 7804, p361 | DOI: 10.1211/PJ.2014.11136576

**[B] 2014 update to the BNF guidelines on antibiotic prescribing for children:** Pharmaceutical Press newsletter (April 2014)

**[C] Evidence of NHS Primary Care rollout of new prescribing guidelines:** NHS Forth Valley Prescriber file from the Primary Care Prescribing Group - Volume 23 No. 1 (January/February 2015)

**[D] Evidence of prescribing software changes adopted across NHS Trusts:** NHS Dorset Clinical Commissioning Group - REMINDER ABOUT PAEDIATRIC AMOXICILLIN DOSES

**[E] Evidence that prescribing practice (of antibiotics for children) changed in the UK following 2014 revision of guidelines:** Rann O, Sharland M, Long P, et al. Did the accuracy of oral amoxicillin dosing of children improve after British National Formulary dose revisions in 2014? National cross-sectional survey in England. *BMJ Open* 2017;7:e016363. doi:10.1136/bmjopen-2017-016363

**[F] Map showing all countries where new BNF guidelines have been integrated:** Audit of Paediatric Amoxicillin Dosing in the Commonwealth and in the ‘Group of Twenty’ (G20) Countries - Eren Halil in partial fulfilment of the requirements for the MPharm degree, King’s College London, Paul F Long (January/2020)

**[G] Evidence of the Royal College of General Practitioners 2014 Research of the Year Award in ‘Paediatrics, Obstetrics and Reproductive Health’:** Out of Hours RCGP Research Paper of the Year 2014 partnership with patients is an important theme in primary care research - *British Journal of General Practice*, November 2015, page 595

**[H] Five media articles illustrating endorsement by the NHS and independent commentaries by experts representing professional societies:** [Pulse Today](#), [Australian Prescriber](#), [Irish Medical Journal](#), [The Pharmaceutical Journal](#) and [Bulletin of the World Health Organization](#) (2011 – 2020)

**[I] Twelve examples of the impact and implications for this research disseminated to the public, wider scientific and medical communities by the World’s press:** BBC, Daily Mail, Telegraph, Medical Express... (2011 – 2014)

**[J] Testimonial from Professor Dame Sally Davies, the UK Special Envoy on Antimicrobial Resistance and former Chief Medical Officer for England**