Institution: University of Strathclyde

Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Improved patient care through new antibiotic guidelines and resources

Period when the underpinning research was undertaken: 2007 - 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:
Alison Thomson	Senior Lecturer	1/10/2005 – present
Marion Bennie	Professor	1/10/2010 – present

Period when the claimed impact occurred: August 2013 – December 2020

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

1. Summary of the impact:

Thomson and Bennie's research led to the development of and revisions to dosing guidelines for a range of antibiotics to treat severe infections. These guidelines are available online and used throughout NHS Scotland, NHS England and internationally. Additional resources produced by the researchers have resulted in a substantial improvement in effective antibiotic use in NHS Scotland and research findings were incorporated into commercial software packages to optimise antibiotic therapy for individual patients in USA, New Zealand and Europe. Through these developments, the research has supported optimal dosing of vancomycin, amikacin and gentamicin, which is vital for patient recovery from severe infection and an important aspect of tackling antimicrobial resistance.

2. Underpinning research

The antibiotics vancomycin, gentamicin and amikacin are used to treat severe infections that may be resistant to other antibiotics, including bone and joint infections, endocarditis, pelvic inflammatory disease, meningitis, pneumonia, urinary tract infections, and sepsis. Vancomycin is one of the few antibiotics that is active against methicillin resistant *Staphylococcus aureus* (MRSA); amikacin is also used for the treatment of multidrug-resistant tuberculosis. Successful use of these particular antibiotics is challenging as therapeutic doses are similar to those that cause toxicity, and dose requirements can vary widely among patients. With vancomycin, amikacin and gentamicin, under-dosing can lead to treatment failure and development of antimicrobial resistance, whereas overdosing can cause kidney damage and permanent impairment of hearing and/or balance (ototoxicity).

Thomson and Bennie have carried out a sustained programme of research to inform, improve and implement guidelines on dosing of vancomycin, gentamicin and amikacin in hospital settings. Population pharmacokinetic (PopPK) data analysis methodology was used to identify factors that influence the antibiotic dose requirements of individual patients. Quality Improvement (QI) methodology was used to evaluate and improve implementation of guidelines in both adult and paediatric settings. Their key findings relate to:

Development and implementation of vancomycin and gentamicin dosing guidelines: The trough level or trough concentration is the lowest concentration reached by a drug before the next dose is administered and is often used as a guide to avoid under-dosing or overdosing the patient. Growing evidence that vancomycin trough concentrations of 5–10 mg/L were insufficient to achieve adequate tissue penetration and kill rates for more resistant species, prompted recommendations for a variety of higher target values, up to and exceeding 15 mg/L. In 2009, Thomson [**R1**] developed a PopPK model of vancomycin for adult patients from vancomycin dose and concentration data collected during routine therapeutic drug monitoring of 398 patients. New vancomycin dosage guidelines were developed that achieved trough concentrations of 10–15 mg/L earlier and more consistently than existing guidelines.

Following Thomson's recommendations, the Scottish Antimicrobial Prescribing Group (SAPG) introduced national guidance in 2009 to standardise dosage regimens for vancomycin and gentamicin (guidelines also developed by Thomson). These guidelines aimed to reduce calculation errors and improve the monitoring of these antibiotics. Further research in 2010 and 2011 identified limitations in guideline implementation, and a point prevalence study (PPS) in 2011

and a qualitative research study in 2014 led Thomson and Bennie to oversee the design and introduction of new QI resources for practitioners, to improve guideline implementation [R2]. A follow-up PPS in 2018 demonstrated statistically and clinically significant improvements in gentamicin and vancomycin prescription, administration and monitoring throughout Scotland [R2].

Intravenous vancomycin therapy typically starts with a loading dose followed by a maintenance dose 12 to 24 hours later. In the acute hospital setting, this often results in doses being administered late in the night. In 2016, Thomson sought to address this issue, which was challenging for staff and disrupted patient's sleep. Her research examined current practice and developed new guidelines to support greater flexibility in the timing of the first maintenance dose of vancomycin [R3].

Thomson collaborated in an international, pooled PopPK study (2018) which examined vancomycin handling in a large population of patients ranging from neonates to elderly adults [R4]. The results were used to evaluate current European and American guidelines and propose revisions. In 2020, this pooled PopPK model was used within a new genetic algorithm methodology to develop and evaluate revised guidelines [R5]. The study used a novel approach to define a dosing guideline and, due to the extensive patient database, covered a wide range of patient characteristics. This study aimed to optimise dosing during the first 3 days of therapy, to potentially avoid treatment failure.

A series of NHS research projects, led by Thomson (2013 - 2016), identified problems with vancomycin use in a large paediatric intensive care unit (PICU), and with gentamicin use in patients with endocarditis. Subsequent research by Thomson and Bennie led to the development and implementation of new vancomycin guidelines within the PICU in November 2016. QI methodology was used to support the process, which included logistic planning, the development of an in house computer decision support tool, a staff training package, disseminating the guidelines and resolving any problems in implementation. The implementation process was evaluated in 2018.

Development and evaluation of amikacin dosage guidelines: From 2018-20, Thomson supervised an analysis of data from patients within Greater Glasgow and Clyde Health Board (NHSGGC) who were treated with amikacin for multi-resistant mycobacterial infections. The aim was to develop a PopPK model for amikacin then use data simulations to compare the concentrations achieved by internationally recognised (WHO) amikacin dosage guidelines with recommended target ranges and identify whether modifications to guidelines or target ranges would be helpful for this patient group. A maximum daily dose of 1000 mg was recommended by the WHO, although higher doses may be used. Thomson's results showed that applying this limit would under-dose patients weighing more than 75 kg and that, for higher weights, the limit is inconsistent with the recommended dose of 15–20 mg/kg, for example 1000 mg represents only 12.5 mg/kg for a patient weighing 80 kg. The results of this analysis were used to evaluate the international guidelines and devise new guidelines to address local and national concerns around optimal dosing regimens and monitoring of amikacin. The modified guidelines included a wider range of doses to maximise the efficiency of amikacin treatment with a range of body weights [R6].

3. References to the research (Strathclyde affiliated authors in **bold**; FWCI at 02/02/2021)

R1 **Thomson AH**, **Staatz C**, Tobin C, Gall M, Lovering A. (2009). Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations. *Journal of Antimicrobial Chemotherapy* 63:1050-1057 https://doi.org/10.1093/jac/dkp085 [FWCI: 2.31; REF2 in 2014]

R2 **Semple Y**, **Bennie M**, Sneddon J, Cockburn A, Seaton RA, **Thomson AH**. (2020) Development and evaluation of a national gentamicin and vancomycin quality improvement programme. *Journal of Antimicrobial Chemotherapy* 75:1998-2003.

https://doi.org/10.1093/jac/dkaa096 [FWCI: 1.32; REF2]

R3 Carruthers A, **Thomson AH**, Semple Y, Rodger R. (2016). Timing of the first vancomycin maintenance dose in an acute hospital setting - room for improvement? *Journal of Medicines Optimisation* 2: 51-55. https://bit.ly/31fKI00

R4 Colin PJ, Allegaert K, **Thomson AH**, Touw DJ, Dolton M, de Hoog M, Roberts JA, Adane ED, Yamamoto M, García MJ, Simon N, Taccone FS, Lo Y-L, Barcia E, Eleveld DJ. (2019)

Vancomycin pharmacokinetics throughout life: implications for dosing recommendations. *Clinical Pharmacokinetics* 58:767-730. https://doi.org/10.1007/s40262-018-0727-5 [FWCI: 5.52]

R5 Colin PJ, Elvend DJ, **Thomson AH**. (2020). Genetic algorithms as a tool for dosing guideline optimisation: application to intermittent infusion dosing for vancomycin in adults. *CPT-Pharmacometrics and Systems Pharmacology*. 9: 294-302 https://doi.org/10.1002/psp4.12512 [REF2]

R6 **Siebinga H**, Robb F, **Thomson AH** (2020). Population pharmacokinetic evaluation and optimisation of amikacin dosage regimens for the management of mycobacterial infections. *Journal of Antimicrobial Chemotherapy*. 75:2933-2940 75. *(Editor's choice)* DOI: https://doi.org/10.1093/jac/dkaa277

Notes on the quality of research: Key outputs are published in high quality peer reviewed journals. **R1** contributed to the award of three further grants to Dr Thomson and Professor Bennie from the Healthcare Associated Infection Task Force from 2010-12 to evaluate the implementation of national antibiotics guidelines. Other funding for a fellowship and further Quality Improvement research includes:

- Bennie M, Thomson AH (Fellow: Semple Y). SIRN/CSO Doctoral Training Fellowship in Healthcare Associated Infection - Quality Improvement of antibiotics with a narrow therapeutic index, Scottish Infection Research Network/Chief Scientist's Office, 01/10/2013-28/02/2019, GBP101,162.
- Bennie M, Thomson AH. Guidance on use of gentamicin and vancomycin Quality Improvement Program, NHS National Services, Scotland, 01/02/2010-31/03/2016, GBP165,741.

4. Details of the impact

Guidelines developed by Thomson in 2008-9 on vancomycin [**R1**] and gentamicin were implemented at that time across NHS Scotland by the Scottish Antimicrobial Prescribing Group (SAPG). Thomson and Bennie's research in 2010 - 2014 identified issues with this implementation and led them to produce new resources designed to improve implementation [**R2**] and update the existing guidance on these two antibiotics. Until December 2018, Thomson was a part-time NHS pharmacist in addition to her part-time academic position at the University of Strathclyde; she now holds an honorary NHS position as a Research Supervisor for pharmacists working towards higher degrees. Her advice is often sought by NHS colleagues, feeding into further research and new guidelines for antibiotic delivery with different patient groups [e.g. **R3, R6**]. Close integration of NHS and researcher roles has facilitated production of research which addresses important clinical need, and has resulted in the following impacts:

Updated guidance on antibiotic dosing for vancomycin, gentamicin and amikacin within NHS Scotland and internationally

Various factors affect the optimal dosage regimen for any drug, including the age, weight and kidney function of the patient. The timing of doses is also critical to maintain safe and effective drug concentrations, and to avoid under- or over-dosing the patient. With delivery of any antibiotic treatment, it is of utmost importance that 'under dosing' does not lead to bacterial resistance.

The national guidelines for gentamicin and vancomycin dosing, originally implemented in 2009, were updated in early 2013, in January 2015 and January 2017 [**S1**] with direct support from Thomson's research findings. The Project Lead for SAPG confirms Strathclyde's research to support the safe and effective use of gentamicin and vancomycin '*has informed national guidance, dosage calculators, prescription charts and education modules first launched in 2013 which are hosted by my organisation, (part of Healthcare Improvement Scotland) and utilised across the NHS in Scotland'* [**S2**]. The SAPG guidelines are frequently consulted by practitioners; they were viewed online 8,767 times between September 2016 and September 2017 alone. Between March 2018 and Jan 2020 there were typically between 100 – 400 page views every month [**S2**]. Since August 2013, the SAPG guidelines for gentamicin and vancomycin have informed the development of similar guidelines in the UK, including NHS bodies at York, Norfolk & Norwich and Salford. SAPG guidelines have also generated international interest and have been implemented in the Czech Republic [**S5**] and Malta [**S6**]. The SAPG Project Lead confirms '*these resources are also referred to outwith Scotland and you [Dr Thomson] have supported our group with expert*

advice to answer any queries about the methodologies used in their development which I receive on a regular basis' [S2].

The underpinning research has also directly informed dosing guidelines for gentamicin, vancomycin and amikacin in the NHS Greater Glasgow and Clyde (NHSGGC) health board, which represents about 30% of all hospital beds in Scotland [S2]:

- **Guidelines for gentamicin dosing in patients with endocarditis** were developed from a pharmacokinetic study carried out by an NHS pharmacist, supervised by Thomson. These guidelines were introduced within NHSGGC in 2015 and nationally via the SAPG website in October 2016 [S1].
- Recommendations arising from Thomson's [R3] investigation into the **timing of vancomycin doses** were adopted by NHSGGC in February 2017 and implemented within the NHSGGC mobile app in 2020 [S3]. These revised guidelines removed the need to disturb patients in the middle of the night to administer vancomycin.
- New **paediatric intensive care guidelines on vancomycin dosage**, devised by Thomson, were implemented in the Paediatric Intensive Care Unit (PICU) of the Royal Hospital for Children, Glasgow in November 2016 [S4].
- The PopPK analysis of **amikacin for patients with mycobacterial infections** [R6] led to the development of new amikacin dosing guidelines for NHSGGC during 2018 - 2020. Hospitals in the Glasgow area are seeing more patients with non-tubercular mycobacterial infection and amikacin is increasingly used for these patients [S3]. The amikacin guidelines have been available for use in Scotland by specialised NHS staff since early 2020.
- Thomson presented draft recommendations for further guideline revision from the SAPG guidelines to NHSGGC antimicrobial pharmacists in July 2020 and submitted final recommendations in November 2020 [S3]. In addition, she updated the online dose calculator with new doses which were approved by the NHSGGC Antimicrobial Utilisation Committee in November 2020.

Improvement in resources available to medical practitioners

Thomson and Bennie's QI study led to the implementation of online calculators and training modules. Software packages that aid in the interpretation of measured antibiotic concentrations are increasingly being used to help modify doses for individual patients, based on models of drug handling in large patient populations. Online gentamicin and vancomycin dose calculators, originally devised by Thomson, were introduced across Scotland in August 2013. Usage has been continuous and sustained from this point. For example, between January 2018 - October 2019, the gentamicin calculator was viewed 13,178 times and the vancomycin calculator 4,984 times [S2]. These calculators were transferred by external developers to an NHSGGC phone app that was released in August 2014, and available to practitioners in the health board. The smartphone app was released across the UK in August 2016 [S9] commissioned by SAPG and registered as a medical device with the Medicines and Healthcare products Regulatory Agency. The SAPG app has been downloaded over 2,500 times in the UK and in other countries since launch. The Project Lead (SAPG) confirms that this app '*gives prescribers access to guidance and online calculators at the point of care to support best practice'*, with between 200 – 300 users per month (gentamicin calculator) and 400 - 600 users per month (vancomycin calculator) [S2]. Educational materials to support gentamicin and vancomycin prescribing and monitoring were also created and implemented on LearnPro®, an online training platform, and made available to NHS staff throughout Scotland in August 2013. This module was taken 1,299 times by NHS doctors, pharmacists and nurses between September 2013 and end 2016 [R2].

The two PopPK vancomycin models developed by Thomson [R1, R4] have been implemented since early 2017 by US based company *InsightRx,* in a commercial software package used to interpret vancomycin concentrations in clinical practice [S7]. The company has a user base of 80 hospitals in the USA and Europe, and the module for personalisation of vancomycin dosing is the most frequently used across their platform. The Chief Scientific Officer for *InsightRx* confirms that the Thomson 2009 model is '*often the best model in terms of its ability to predict future exposure to vancomycin within the patient… It is the model we recommend for new sites and it is included in all our training material. Over 2019 - 20 the model has been used in the dosing of 22,163 patients*

across 36 hospitals using our platform' [**S7**]. The 2009 vancomycin model was implemented in a similar package, *TCIWorks,* and since August 2013 this has been in continuous use in Christchurch Hospital, the largest tertiary, teaching and research hospital in the South Island of New Zealand, serving 510,000 residents [**S8**].

Improvement in patient care

Patients being treated with vancomycin, amikacin and gentamicin are usually seriously ill with infections which may be resistant to other antibiotics. The Lead Antimicrobial Pharmacist for NHSGGC states that '*work done by Thomson has allowed us … to update our therapeutic vancomycin and amikacin monitoring guidelines ... for patients with serious infections who also have penicillin allergy*.' [**S3**] NHS Scotland funded QI work by Bennie and Thomson between 2013 and 2014, which led to major improvements in clinical practice for patients treated with gentamicin and vancomycin. Following the QI programme, the percentage of patients who received the recommended gentamicin dose doubled from 44% (baseline in 2011) to 89% in 2018. Appropriate blood sample times increased from 63% to 75% between 2011 and 2018. For vancomycin, the correct loading dose increased from 50% to 85% and the correct maintenance dose from 55% to 90% by 2018 [**R2**].

Implementation of the vancomycin guidelines in a large Czech hospital in 2015 improved the achievement of target trough concentrations from 45.4% prior to introduction of guidelines to 63.1% after introduction. A publication [**S5**] on the implementation states that '*the adopted Scottish model of vancomycin therapeutic dose monitoring (TDM) resulted in very significantly higher achievement of recommended trough concentrations during first measurements and significantly more effective maintenance of subsequent concentrations, without increased nephrotoxicity*.'

New paediatric intensive care guidelines, devised by Thomson, were implemented in the PICU of the Royal Hospital for Children, Glasgow in November 2016 . A consultant paediatrician confirms that '*achieving therapeutic target range is challenging in the diverse range of patients seen within the PICU due to multiple pathologies and large variations in patient size and renal function… A follow-up evaluation of this implementation found that the percentage of satisfactory concentrations increased from 45% to 55% and the risk of under-dosing fell from 41% to 29%. These guidelines are still used (Dec 2020) within PICU and have significantly improved patient management of this highly complex patient group*' [**S4**].

Improved guidance, with related online tools to assist practitioners has led to better delivery and monitoring of the dosage regimens of an important group of antibiotics, notably in Scotland, and used in the treatment of severe infection in hospitals across the UK, Europe and the US. This ultimately has led to benefits for patients, avoidance of over-dosing which can cause toxicity, and reduction of under-dosing which can lead to treatment failure and antimicrobial resistance.

5. Sources to corroborate the impact:

S1 Scottish Antimicrobial Prescribing Group. Gentamicin and vancomycin. https://bit.ly/3b4FiuB
S2 Corroborating statement from Project Lead, SAPG, NHS Healthcare Improvement Scotland, dated 4 November 2020, with appended SAPG website data.
S3 Corroborating statement from Lead Antimicrobial Pharmacist NHSGGC, dated 12 November 2020.
S4 Corroborating statement from Consultant Paediatric Intensivist, Paediatric Intensive Care Unit, Royal Hospital for Children, Glasgow, dated 19 February 2021.
S5 Zahalkova K et al, (2018). The Scottish model of vancomycin dosing and therapeutic drug monitoring improves both efficacy and safety of vancomycin therapy Vnitr Lek, 64; 717-724 https://pubmed.ncbi.nlm.nih.gov/30441978/
S6 Dimech A et al (2016). The practice of gentamicin prescription at Mater Dei Hospital (Malta) DOI: 10.13140/RG.2.2.23213.18402
S7 Corroborating statement from CSO of *Insight RX*, date 12 November 2020.
S8 Corroborating statement from Senior Lecturer of Clinical Pharmacology, University of Otago.
S9 SAPG smartphone app for mobile devices and online at http://www.antimicrobialcompanion.scot