

Meeting report

Ongoing initiatives to improve the use of antibiotics in Botswana: University of Botswana symposium meeting report

Botswana, Gaborone 24 October, 2017

Celda Tiroyakgosi¹, Matshediso Matome², Emily Summers³, Yohana Mashalla⁴, Bene Anand Paramadhas^{5,6}, Sajini Souda⁷, Brigid Malone⁸, Fatima Sinkala⁹, Joyce Kgatlwane¹⁰, Brian Godman^{*11,12,13}, Keneilwe Mmopi⁴, Amos Masele⁴

¹Ministry of Health and Wellness, Nelson Mandela Drive, Gaborone, Botswana. Email: ctiroyakgosi@gov.bw

²Managed Care, AFA, Showgrounds Office Park, Gaborone, Botswana. Email: matshedisom@afa.co.bw

³British High Commission, Gaborone, Botswana. Email: Emily.Summers@fco.gov.uk

⁴Department of Biomedical Sciences, Faculty of Medicine, University of Botswana, Gaborone, Botswana. Emails: yohana.mashalla@mopipi.ub.bw; Keneilwe.Mmopi@mopipi.ub.bw; maselea@mopipi.ub.bw

⁵Department of Pharmacy, Nyangabgwe Hospital, Francistown, Botswana. Email: anandbene@yahoo.com

⁶University of South Africa, Pretoria, South Africa.

⁷Department of Pathology, Faculty of Medicine, University of Botswana, Gaborone, Botswana. Email: sajinisouda@gmail.com

⁸Bokamoso Private Hospital, Mmopane, Botswana. Emails: Brigid.Malone@bokamosohospital.org

⁹Letsholathebe II memorial hospital, Maun, Botswana. Email: gabsfats@gmail.com

¹⁰School of Pharmacy, University of Botswana, Gaborone, Botswana. Email: joyce.kgatlwane@mopipi.ub.bw

¹¹Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, Sweden. Email: Brian.Godman@ki.se

¹²Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK. Email: Brian.Godman@strath.ac.uk

¹³Health Economics Centre, Liverpool University Management School, Liverpool, UK. Email: Brian.Godman@liverpool.ac.uk

*Corresponding author:

Brian Godman, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: Brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562

Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se. Telephone + 46 8 58581068. Fax + 46 8 59581070

(Accepted for publication Expert Review Anti-Infective Therapy – Please keep Confidential)

Abstract

The objective of this meeting was to discuss ongoing initiatives in Botswana since February 2016 to improve antibiotic use. Subsequently, use the findings to refine national and local action plans. There was a high rate of antibiotic prescribing among ambulatory care patients in the public sector (42.7%) as well as for patients with URIs in the private sector (72.9%). Prophylactic antibiotics were given to 73.3% of surgical patients to reduce surgical site infections (SSIs) in a leading tertiary hospital in Botswana; however, SSIs at 9% of patients can be reduced further with better timing of antibiotic prophylaxis. To date, 773 patients have been enrolled into the national point prevalence study. Highlighted concerns included limited ordering and use of sensitivity tests despite functional laboratories, as well as concerns with missed doses of antibiotics across most hospitals. Activities are ongoing across sectors to address these concerns.

1. Introduction

There is a high burden of infectious diseases in Africa, especially sub-Saharan Africa, resulting in appreciable increases in antibiotic utilization in recent years, exacerbated by the ability of patients to

self-purchase antibiotics (1, 2). An appreciable proportion of antibiotic use is known to be irrational enhancing antimicrobial resistance (AMR); with AMR known to increase morbidity, mortality and costs (2-4). Irrational antibiotic prescribing includes the routine prescribing and dispensing of antibiotics for upper respiratory tract infections (URTIs), most of which are viral in origin (1, 4, 5). These concerns were drivers behind the first meeting held in Botswana in February 2016 to develop a deeper understanding of current antibiotic utilization, following the availability of antibiotic guidelines in Botswana, as well as plan for the future (3), whilst recognising that guidelines are not always followed, and there are concerns with the extent of empiric use of antibiotics and variable use of sensitivity analyses in Botswana (6, 7). The lack of adherence to guidelines is not helped by their variable availability (8). Activities recommended in February 2016 included the introduction of a national antibiotic point prevalence study (PPS), building on initiatives in Europe and globally (3).

2. Objectives and Rationale

The objective of this symposium on 'Enhancing the appropriate use of antibiotics in Botswana' held at the University of Botswana, 24 October 2017, was to present and discuss ongoing initiatives and findings since February 2016, and use these to further improve antimicrobial prescribing in Botswana as part of the ongoing National Action Plan (NAP) for antimicrobials. The latter involves Dr. Tiroyakgosi and her team at the Ministry of Health and Wellness in Botswana, together with the Ministry of Agriculture Development and Food Security and the Ministry of Land Management, Water and Sanitation Services, to develop the Botswana Antimicrobial NAP with input from across Botswana. The prepared draft is currently being circulated among the key stakeholder Ministries in Botswana, and will be updated in the future based on pertinent research findings.

The meeting was opened by the Dean of the Faculty of Medicine, University of Botswana, which was followed by Emily Summers, Deputy High Commissioner from the British High Commission (<http://muria.mandela.ac.za/Botswana-Symposium-October-2017>). Emily commented that the increase in AMR in recent years was a major concern to the British Government, resulting in publications to try and document its impact in terms of mortality, security and costs if not addressed (9). This builds on World Health Organisation (WHO) initiatives highlighting the impact of AMR, with the recognized need to develop global action plans (10). In addition, the UK Government is committing considerable funds (GB£165 million over 5 years) to help address this issue. This includes core funding to WHO and other multilateral organizations addressing resistance rates and the over use of antibiotics in Botswana. Initiatives such as this symposium were also welcome ways to cross sectors and seek to enhance the appropriate use of antibiotics in veterinary medicine, which is rapidly becoming a public health issue.

Brian Godman from the Karolinska Institute and Strathclyde University gave a brief summary of the activities of MURIA (Medicines Utilisation Research in Africa) group following the first meeting in South Africa in January 2015 to improve the rational use of medicines (RUM) in Africa (11). Since then, there have been three annual meetings in addition to the February 2016 meeting (3, 7, 12) (<http://muria.mandela.ac.za/>), as well as numerous publications in peer-reviewed journals (40 by October 2017). The July 2016 meeting included discussions to adapt the PPS forms following feedback of the pilot study (12). The adapted PPS forms are already being used across Africa, with the findings being part of NAPs (13-15). This Pan-African co-operation will continue benefiting all in Africa.

3. Plenary Session

Yohana Mashalla, Professor and Dean at the University of Botswana, discussed the findings of a study among public Primary Healthcare facilities (PHCs) in Botswana to assess the prescribing of medicines against WHO/ International Network for Rational Use of Drugs (INRUD) indicators and made suggestions for the future. There was an average of 2.8 medicines per prescription, with a high rate of INN prescribing and compliance with the Botswana Essential Drugs List (EDL) at 78.6% and 96.1% respectively (2). However, the rate of antibiotic prescribing was high at 42.7% with a number of patients having two and three antibiotics respectively. Amoxicillin accounted for 28.4% of systemic antibiotic use with Metronidazole second at 14.4%. Encouragingly, there was low use of co-amoxiclav (0.3%), third generation cephalosporins (9.8%) and no prescribing of fluoroquinolones. The majority of indications for antibiotic prescriptions were according to ICD classification; however, there is room for improvement. Future strategies could include developing pertinent quality indicators to more appropriately assess the quality of antibiotic prescribing among PHCs given the high burden of gynaecological and sexually transmitted infections in Botswana (2).

Matshediso Matome, head of Managed Care at the Associated Fund Administrators which administers two large medical aid funds in Botswana, discussed recent findings among the private sector in Botswana regarding antibiotic utilisation to treat patients with URIs (16). The data included 311,953 acute prescription encounters incorporating prescriptions dispensed by private GPs (49%), Community Pharmacists (30%), Hospital Pharmacists (16%) and Medical Specialists (3.9%). Only 12% of pharmacy claims had a specific ICD10 code. Overall, there were 216,256 encounters of which 17.4% were for URIs and 72.9% of these had at least one antibiotic dispensed. This is similar to the high rates of inappropriate prescribing for URIs in the private sector in other countries (17, 18). The prescribing of antibiotics for URIs is seen as inappropriate given that a high percentage of URIs are viral in origin (1, 5, 19) and there is limited effectiveness of antibiotics in this condition (20). The beta-lactams dominated the antibiotics prescribed and dispensed (J01C and J01D) at 81.4%, followed by the macrolides at 10.7% (J01F). Fluorquinolone use was low (J01M) at 0.5%. However, within the beta lactam penicillins, combination penicillins such as co-amoxiclav dominated at 84.9% of penicillin use despite concerns about their overuse. Given the considerable concerns regarding the high rate of inappropriate prescribing, future suggestions included strengthening current indicators to include new quality indicators, educational programmes among private medical practitioners and pharmacists, as well as utilising their help with designing future studies.

Sajini Souda Senior Lecturer, Department of Pathology, Faculty of Medicine, University of Botswana, discussed recent findings regarding the use of prophylactic antibiotics to prevent surgical site infections (SSIs) in PMH in Gaborone, the principal public hospital in Botswana. This prospective study involved 400 patients, with patients followed-up for 30 days post discharge to detect SSIs (21). The most common operations were exploratory laparotomy (25%), appendectomy (18.3%), excisions, and mastectomy (8%). Prophylactic antibiotics were given to 73.3% of patients; however, most were given post operatively (58.3%) with 15% commenced preoperatively, which is against current guidance. The most common antibiotics prescribed were cefotaxime (80.7%) and metronidazole (63.5%), with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* were the most common organisms identified. The incidence of SSI was 9%, and interventions have already been put in place to try and reduce this (21).

Tebogo Madidimalo from WHO Botswana (22) subsequently discussed ongoing global initiatives to help contain and reduce AMR, which is a growing concern with mortality estimated to increase to 10 million deaths per year and global GDP reduce by 1 to 3.5% by 2050 if not addressed (10). In addition, at the UN General Assembly in 2016, all countries committed to preparing antimicrobial NAPs. The guiding principles include: (i) one-health approach including human health, animal health, and agriculture; (ii) prevention first; (iii) access not excess; (iv) sustainability; and (v) incremental targets for implementation. This initiative also includes improving awareness and understanding of AMR through education and training as well as simple measures such as hand hygiene, vaccination and improved sanitation. The next steps include approving the Botswana NAP.

Celda Tiroyakgosi started by endorsing the WHO and UN initiatives followed by an update of current activities in Botswana to reduce AMR rates. Activities included attending a WHO AFRO workshop for the development of NAPs held in Zimbabwe 25th -27th January, 2017 which promoted the concept of 'one health'. Since then Botswana has embarked on developing its NAP with a governance structure now in place, and there is increased monitoring of antimicrobial use via the Technical Working Groups (TWG). The National Health Policy and National Drug Policy spearhead the health of the population to ensure access to safe, effective and quality medicines. Structures in place to implement the National Drug Policy include the Medicines Regulation Authority, responsible for registration of safe, effective quality medicines; BEDAP (Botswana Essential Drugs Action Programme) which selects and ensures rational use of medicines; Central Medical Stores, which is responsible for selection, forecasting, procurement, storage, and distribution of medicines and NDQCL (National Drug Quality Control Laboratory) which is responsible for testing and quality control. The antimicrobial NAP builds on this. In addition, the Botswana EML and guidelines are being updated and Drug and Therapeutic Committees promoted in hospitals by the the Ministry of Health. Infection control committees and Antimicrobial Stewardship Programmes (ASPs) are also being established, and future antimicrobial prescribing monitored.

Bene Paramadhas, Chief Pharmacist at Nyangabgwe Hospital, Botswana, together with Fatima Sinkala, Clinical Pharmacist Letsholathebe II memorial hospital, shared their experiences with

conducting PPS studies in Botswana. The data collection forms for the PPS study were adapted to include co-morbidities such as HIV, tuberculosis and malaria, which are appreciably more common in countries in sub-Saharan Africa than western countries (3, 7). They reported that 773 patients have been analysed to date with the majority being females (60.9%). Key co-morbidities included malaria (2.5%), malnourishment (5%), TB (25.4%) and HIV (40% of those tested were HIV positive with 85% on HAART). More than two thirds (70.6%) of admissions were for infectious diseases with a high proportion of HAs among children and the elderly. A total of 982 antibiotics were prescribed with a high frequency of missed doses (mean of 1.96 per patient, SD = 4.17). The highest proportion of antibiotics prescribed were in tertiary (1.76/ patient) and specialist hospitals (1.42/ patient). Cefotaxime (20.3%), metronidazole (12.8%) and the penicillins (27.4%) were the most prescribed antibiotics, with variations between hospital types. Surgical patients received more than 1 day of prophylaxis in 66.7%, 100% and 90.3% of specialist, tertiary and district hospitals respectively. Injectable use was higher in specialist and tertiary hospitals, with variable ordering of culture and sensitivities (CSTs) despite functional microbiology labs, and typically no antibiograms to guide prescribing. Only 20% of hospitals currently had ASPs, and there was an appreciable lack of antibiotic guidelines (50%) and essential medicine lists (40%) in the wards in a number of settings. These concerns are being addressed.

Brigid Malone, Family Physician at Bokamoso hospital, described some of the experiences in Bokamoso hospital (23). The PPS was undertaken on an atypical day where most patients admitted were either elective surgery or non-infectious medical patients. The study involved 57 patients (6 others did not give their consent). There was no infectious diagnosis recorded for 73% of patients. Among those recorded, community acquired infection predominated (93%), with HIV status recorded in only 26% of patients despite the majority of patients in Botswana knowing their HIV status. Nearly all the antibiotics prescribed were on the Botswana EML, with 40% prescribed for prophylaxis and 60% for treatment. 66% of antibiotics prescribed for prophylaxis were prescribed for longer than 24 hours. There were concerns with missed doses (27%) as well as low rates of CST requests. These areas are being addressed.

4. Conclusion and next steps

Agreed next steps following this interactive symposium included submitting a number of the studies for potential publication including the PPS, SSI and private sector URTI studies. In addition, there is a proposal to study on SSIs as well as hang-time in Bokamoso and other interested hospitals; undertaking the PPS study in PMH and other interested hospitals; and documenting the findings as part of Botswana NAP and IRB research activities. Additional activities proposed include instigating interventions to address areas of concern, instigating protected time to undertake ASPs, revising the current antibiotic guidelines, and monitoring subsequent antibiotic use against agreed guidance. In addition, the PPS data collection tools are being revised to improve collection of relevant data, potentially incorporating APPs (13).

Funding

There was no funding for this study.

Declaration of interest

Tiroyakgosi C is employed by the Ministry of Health and Wellness in Botswana. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Godman B, Fadare J, Kibuule D, Irawati L, Mubita M, Ogunleye et al. Initiatives across countries to reduce antibiotic utilization and resistance patterns; impact and implications. Drug Resistance in Bacteria, Fungi, Malaria, and Cancer - Arora, Sajid, & Kalia Eds Publisher Springer Nature ISBN 978-3-319-48682-6 Available at URL: [https://purestrathacuk/portal/en/publications/initiatives-across-countries-to-reduce-antibiotic-utilization-and-resistance-patterns\(bb445446-fd1d-47b3-8f91-def5d9e5e3db\)/exporthtml](https://purestrathacuk/portal/en/publications/initiatives-across-countries-to-reduce-antibiotic-utilization-and-resistance-patterns(bb445446-fd1d-47b3-8f91-def5d9e5e3db)/exporthtml).
2. Mashalla Y, Setlhare V, Massele A, Sepako E, Tiroyakgosi C, Kgatlwane J, et al. Assessment of prescribing practices at the primary healthcare facilities in Botswana with an emphasis on antibiotics: Findings and implications. *International journal of clinical practice*. 2017;71(12).
3. Massele A, Tiroyakgosi C, Matome M, Desta A, Muller A, Paramadhas BD, et al. Research activities to improve the utilization of antibiotics in Africa. *Expert review of pharmacoeconomics & outcomes research*. 2017;17(1):1-4.
4. Dyar OJ, Beovic B, Vlahovic-Palcevski V, Verheij T, Pulcini C. How can we improve antibiotic prescribing in primary care? *Expert review of anti-infective therapy*. 2016;14(4):403-13.
5. Kibuule D, Kagoya HR, Godman B. Antibiotic use in acute respiratory infections in under-fives in Uganda: findings and implications. *Expert review of anti-infective therapy*. 2016;14(9):863-72.
6. Tafuma TA, Burnett RJ, Huis In 't Veld D. National guidelines not always followed when diagnosing smear-negative pulmonary tuberculosis in patients with HIV in Botswana. *PLoS one*. 2014;9(2):e88654.
7. Massele A, Burger J, Katende-Kyenda NL, Kalemeera F, Kenaope T, Kibuule D, et al. Outcome of the first Medicines Utilization Research in Africa group meeting to promote sustainable and rational medicine use in Africa. *Expert review of pharmacoeconomics & outcomes research*. 2015;15(6):885-8.
8. Mashalla YJ, Sepako E, Setlhare V, Chuma M, Bulang M, Massele AY. Availability of guidelines and policy documents for enhancing performance of practitioners at the Primary Health Care (PHC) facilities in Gaborone, Tlokweng and Mogoditshane, Republic of Botswana. *J Public Health Epidemiol*. 2016;8(8):127-35.
9. O'Neill J. Securing new drugs for future generations: the pipeline of antibiotics. The review of antimicrobial resistance. Available at URL: https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf.
10. WHO. Global action plan on antimicrobial resistance. Available at URL: <http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/>
11. Massele A, Godman B, Adorka M, Fadare J, Gray A, Lubbe M, et al. Initiative to progress research on medicine utilization in Africa: formation of the Medicines Utilization Research in Africa group. *Expert review of pharmacoeconomics & outcomes research*. 2015;15(4):607-10.
12. Massele A, Burger J, Kalemeera F, Jande M, Didimalang T, Kalungia AC, et al. Outcome of the second Medicines Utilisation Research in Africa Group meeting to promote sustainable and appropriate medicine use in Africa. *Expert review of pharmacoeconomics & outcomes research*. 2017;17(2):149-52.
13. Schellack N DN, Meyer JC, Godman B. Point prevalence survey of antimicrobial utilisation in an academic hospital in the Gauteng province, South Africa. *MURIA 3 2017*; 7. Available at URL: <http://muria.mandela.ac.za/muria/media/Store/documents/Abstract%20book%20-%20MURAI%203/MURIA3-AbstractBook-July-2017.pdf>.
14. The first point-prevalence survey in different hospital settings in Zimbabwe. *MURIA 3 2017*; 8. MTAPURI-ZINYOWERA S, MADZIKWA N, NDHLOVU M, CHAIBVA B, HOVE R, ROBERTSON V. Available at URL: <http://muria.mandela.ac.za/muria/media/Store/documents/Abstract%20book%20-%20MURAI%203/MURIA3-AbstractBook-July-2017.pdf>.
15. PARAMADHAS BDA, KGATLWANE J, TIROYAKGOSI C, MATOME M, MASSELE A, GODMAN B, ERIKSEN J, GUSTAFSSON LL. Antibiotic Utilization Studies Using Point Prevalence Survey in Botswana. *MURIA 3 2017*; 8. Available at URL: <http://muria.mandela.ac.za/muria/media/Store/documents/Abstract%20book%20-%20MURAI%203/MURIA3-AbstractBook-July-2017.pdf>
16. Matome M, Kgatlwane J. Outpatient Antibiotic Utilisation Review for members of AFA administered schemes. October 2017. Available at URL: <http://muria.mandela.ac.za/Botswana-Symposium-October-2017>.

17. Butt AA, Navasero CS, Thomas B, Marri SA, Katheeri HA, Thani AA, et al. Antibiotic prescription patterns for upper respiratory tract infections in the outpatient Qatari population in the private sector. *International journal of infectious diseases*. 2017;55:20-3.
18. Hassali MA, Kamil TK, Md Yusof FA, Alrasheedy AA, Yusoff ZM, Saleem F, et al. General practitioners' knowledge, attitude and prescribing of antibiotics for upper respiratory tract infections in Selangor, Malaysia: findings and implications. *Expert review of anti-infective therapy*. 2015;13(4):511-20.
19. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ open*. 2016;6(10):e012244.
20. van der Velden AW, Kuyvenhoven MM, Verheij TJ. Improving antibiotic prescribing quality by an intervention embedded in the primary care practice accreditation: the ARTI4 randomized trial. *The Journal of antimicrobial chemotherapy*. 2016;71(1):257-63.
21. Mwita JC, Souda S, Magafu M, Masele A, Godman B, Mwandri M. Prophylactic antibiotics to prevent surgical site infections in Botswana: findings and implications. *Hospital practice (1995)*. 2018:1-6.
22. Madidimalo TP. Anti-Microbial Resistance Response and Containment – A Global Approach. October 2017. Available at <http://muria.mandela.ac.za/Botswana-Symposium-October-2017>.
23. Malone B. Antibiotic Point Prevalence Study Bokamoso Private Hospital June 2017. October 2017. Available at URL: <http://muria.mandela.ac.za/Botswana-Symposium-October-2017>