## Untangling interdependencies of antibiotic misuse and socioeconomic factors in Urinary Tract Infections in Tanzania: a case for Bayesian belief networks

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Introduction. The increase of antibiotic resistant pathogens is a concern for modern medical practices which rely on antibiotics to treat many common infections Shallcross 2014, Vedadhir et al. 2020. Exposure to these treatments at nonlethal levels (e.g., through the inappropriate use of drugs, poor drug quality, environmental contamination, etc.) is a known biological catalyst for this process Hughes and Andersson 2012, Andersson and Hughes 2014. Amongst the most common infections for which antibiotics are required and prescribed are Urinary Tract Infections (UTIs); these are estimated to account for one-sixth of all prescribed antibiotics in primary care Shallcross 2014, Wagenlehner et al. 2020. Countries wherein increasing access to antibiotics is paired with unevenly distributed infrastructure and healthcare, gross socioeconomic inequalities, and costly and underregulated healthcare systems, can contribute to a climate which incentivizes misuse of antibiotics (e.g., conserving treatment for future use, seeking alternative non-medical advice, limited education on the mechanisms of resistance).

Tanzania is an example of a country in socioeconomic transition (see Tanzania overview [The World Bank, 2022]), wherein previous assumptions around behaviour and disease are often unsupported (see Msisha et al. [2008]). An increasing trend of resistance amongst UTI isolates to commonly used antibiotics in the region is cause for concern [Mshana et al., 2013]. Understanding the sub-national complex social factors that modulate the risk of non-lethal exposure to antibiotics is essential for reducing the burden of disease, slowing the rate of resistance, and implementing policy and interventions in this region, which conserve these treatments for future generations. Bayesian Belief Networks (BBN) provide a useful tool for these type of complex interdependent data. Drawing on both BBN outcomes and BBN-derived Predictive Probabilities (PPs), we demonstrate the value of this method for untangling the relationships between socioeconomically and contextually complex factors, and antibiotic misuse behaviours in the socioeconomic heterogeneous and complex context of Tanzania.

Methods. Data for this analysis were obtained from the Holistic Approach to Unravel Antibacterial Resistance in East Africa (HATUA) consortium [Asiimwe et al., 2021]. Data was collected between February 2019-September 2020, with data on 3,348 UTI-symptomatic patients from Tanzania used here. After sub-setting the data by relevant variables and removing incomplete observations, 2,972 (11% loss) observations were available. The subset contained variables of misuse (skipping a dose, not completing a course, selfmedicating and self-administrating to prevent infection), socioeconomic measures of deprivation (education, electricity, assets, sanitation, employment, ability to pay medical costs and patient health-insurance status), demographic measures (age, gender and chronic health), area measures (site, rural location, attendance at a tertiary hospital) as well as variables related to stigma, medical advice, knowledge of the term "antibiotic" and familiarity with antibiotic types.

Banjo [Yu et al., 2004] was used to learn the BBN. Due to imbalanced discrete states, a pairwise chi-squared filtering (with a 0.25 p-value threshold) was used to to identify unsupported variable links [Milns et al., 2010]. These disallowed links were specified together with a maximum parent size of 4 (based on Yu [2005]) in Banjo. Based on outputs from the visualisation tool BayesPiles [Vogogias et al., 2018]), a simulated annealing (as opposed to greedy) search strategy was used. Results of a longer search suggested the top network had roughly the same equivalence class as short runs. The BBN top network structure was imported into RStudio where bnlearn and Rgrain packages were used to develop a table of predicted probabilities (PPs) for all misuse variables (state: 'yes'). These PPs were developed for each different directly-linked and socioeconomic measure node state.

**Results and Discussion.** All 20 variables were linked in the top network structure. All, except for two, of the nodes with a direct link to at least one misuse variable were related to area measures (i.e., site location, rural/urban classification, attendance at a tertiary hospital). The other variables with a direct link were medical advice and knowledge of the term "antibiotic". Across all node states, the PPs of all forms of misuse were less than 0.5, with the misuse variable skipping a dose having the three highest PPs ('Mbeya' site (PP= 0.45), 'attending a tertiary hospital' (PP=0.40) and being 'rural' (PP=0.36). No socioeconomic nodes are directly linked to any misuse node and, associated PPs are surprisingly consistent across the differing states of traditional indicators of structural poverty and deprivation (e.g. sanitation, education), although there is some variation according to health insurance and employment status. The PPs for not completing course are lower but follow a similar trend to skipping a dose. The other forms of misuse, using antibiotics prophylactically and self-medicating, have small PPs, which show, with the exception of three, little variation between node states. In relative terms, 'some' knowledge of antibiotics has a PP of using antibiotics prophylactically 2.6 times higher than none, having health insurance has a PP of using antibiotics prophylactically 1.4 time higher than having none and, the PP of self-medicating is 1.8 times higher if a patient had consulted a 'health worker' for advice than if they had not. Although some PPs of misuse vary more than others, this variation underlines the importance of changing contexts (even sub-nationally) for understanding misuse and are in-line with other evidence from low- and middle-income regions [Torres et al., 2019, Do et al., 2021].

**Conclusion.** Bayesian Belief Networks (BBNs) offer a novel approach for identifying the complex interdependencies within social science data. Here we have demonstrated the value of using PPs in conjunction with BBNs for exploring complex, interdependent–both indirectly and directly linked–contextual factors in social science data. Given our results suggest a direct link between area measures and antibiotic misuse, how socioeconomic states vary by area may be a way to further investigate the dynamics of this system.

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## References

- D.I. Andersson and D. Hughes. Microbiological effects of sublethal levels of antibiotics. *Nature Reviews Microbiol*ogy, 12(7):465–478, 2014.
- B.B. Asiimwe, J. Kiiru, S.E. Mshana, S. Neema, and K. Keenan *et al.* Protocol for an interdisciplinary cross-sectional study investigating the social, biological and community-level drivers of antimicrobial resistance (AMR): Holistic Approach to Unravel Antibacterial Resistance in East Africa (HATUA). *BMJ Open*, 11(3):1–12, 2021.
- N.T.T. Do, H.T.L. Vu, C.T.K. Nguyen, S. Punpuing, and W.

A. Khan *et al.* Community-based antibiotic access and use in six low-income and middle-income countries: a mixed-method approach. *The Lancet Global Health*, 9 (5):e610–e619, 2021.

- D. Hughes and D.I. Andersson. Selection of resistance at lethal and non-lethal antibiotic concentrations. *Current Opinion in Microbiology*, 15(5):555–560, 2012.
- I. Milns, C.M. Beale, and V.A. Smith. Revealing ecological networks using Bayesian network inference algorithms. *Ecology*, 91:1892–1899, 2010.
- S.E. Mshana, M. Matee, and M. Rweyemam. Antimicrobial resistance in human and animal pathogens in Zambia. *Annals of Clinical Microbiology and Antimicrobials*, 12 (28):1–10, 2013.
- W.M. Msisha, S.H. Kapiga, F. Earls, and S.V. Subramanian. Socioeconomic status and HIV seroprevalence in Tanzania: A counterintuitive relationship. *International Journal* of Epidemiology, 37(6):1297–1303, 2008.
- Laura J. Shallcross. Editorials: Antibiotic overuse: A key driver of antimicrobial resistance. *British Journal of General Practice*, 64(629):604–605, 2014.
- The World Bank. The World Bank in Tanzania Overview, 2022. URL https://www.worldbank.org/en/country/tanzania/overview#1.
- N.F. Torres, B. Chibi, L.E. Middleton, V.P. Solomon, and T.P. Mashamba-Thompson. Evidence of factors influencing self-medication with antibiotics in low and middleincome countries: a systematic scoping review. *Public Health*, 168:92–101, 2019.
- A.A. Vedadhir, C. Rodrigues, and H. Lambert. Social science research contributions to antimicrobial resistance: Protocol for a scoping review. *Systematic Reviews*, 9(1): 1–7, 2020.
- A. Vogogias, J. Kennedy, D. Archambault, B. Bach, V.A. Smith, and H. Currant. Bayespiles: Visualisation support for Bayesian network structure learning. ACM Transactions on Intelligent Systems and Technology, 10(1), 2018.
- F.M.E. Wagenlehner, B. Johansen, E. Truls, T. Cai, B. Koves, J. Kranz, A. Pilatz, and Z. Tandogdu. Epidemiology, definition and treatment of complicated urinary tract infections. *Nature Reviews Urology*, 17(10):586–600, 2020.
- J. Yu. Developing Bayesian network inference algorithms to predict causal functional pathways in biological systems. PhD, Duke University, 2005.
- J. Yu, V.A. Smith, P.P. Wang, A.J. Hartemink, and E.D. Jarvis. Advances to Bayesian network inference for generating causal networks from observational biological data. *Bioinformatics*, 20(18):3594–3603, 2004.