Holistic Approach to Unravel Antibacterial Resistance in East Africa

(HATUA) MR/S004785/1
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A. Summary of major outcomes

HATUA has established an East African AMR Surveillance Network that is now operating across three countries, Uganda, Tanzania and Kenya. In this network HATUA has collected a wide range of data types, including quantitative biomedical and social data, and qualitative social data collected from urinary tract infection (UTI) patients, healthcare providers, antibiotic sellers and community members. The surveillance network has revealed a high level (>50%) of multi-drug resistance (MDR) in the study sample.

Findings from HATUA's AMR surveillance network have been disseminated to collaborators, stakeholders and the wider community. As such, it has provided a depth of understanding of the social, economic and behavioural drivers of AMR not currently available in East Africa. In the short-term, this will allow doctors to access information they can use to improve diagnosis and prescription patterns based on resistance profiles prevailing locally. Genomic data from the whole genome sequencing of UTI pathogens is being deposited in the public sequence database for the wider scientific community to use. Antimicrobial sensitivity data has been uploaded to WHONET for wider dissemination. To date, 9 papers have been published or submitted to peer-reviewed journals, 9 are in final stages of preparation prior to submission, and 20 papers have been presented at conferences. Local dissemination events and community dialogues resulted in action plans that will continue to improve understanding, knowledge and practice at the community level. A wide variety of training events have been held including training on bioinformatics, microbiology, ArcGIS, quantitative and qualitative research methods, data analysis, and participatory action research skills.

HATUA data has been cited in national treatment guidelines for UTI in Tanzania (Standard Treatment Guidelines and National Essential Medicines List (STG/NEMLIT), 5th edition 2021). HATUA strengthened capacity by equipping labs, introducing diagnostic testing, and training local healthcare professionals and researchers. Culture and susceptibility results are now used for routine patient care in the study clinics across East Africa. Many of these clinics did not have access to microbiology diagnostics prior to HATUA. Microbiological culture and antimicrobial susceptibility testing have been introduced for the first time at Sengerema District Hospital in NW Tanzania and in two health centres in Uganda: Nakasongola HC IV and Nakapiripirit HC IV. This work delivers immediate improvements in patient care in low-resource settings and communities.

B. Achievement against milestones

The project milestones described in the Case for Support have been achieved:

- Establishment and deployment of HATUA's East African AMR - Surveillance Network (EA-ASN).
  We built and deployed an EA-ASN that operates across Uganda, Tanzania and Kenya. We recruited 7,598 patients, of whom 2,563 (34%) were confirmed as UTI positive by culture.
- Description of the UTI patient pathways and antibacterial resistance (ABR) drivers
  We collated a rich mixed methods dataset which enabled us to: a) describe care-seeking pathways for UTI patients; b) understand why people make the care-seeking decisions that they do; and c) analyse the likelihood that these decisions are an important driver of ABR (see WS4 and WS6 below).
- Community action plans for making patient pathways more antibiotic friendly
  Country teams held community dialogues and dissemination events in 2020 and 2021. Key findings from in-depth interviews (n=360) with patients, healthcare workers, AB sellers and community focus groups were used to develop community action plans. The team also worked with community members in

Mbarara to co-design health messaging on AMR. Further work is ongoing in Mwanza to design and disseminate good practice guidelines on AMR to health clinics, AB sellers and community health teams.

C. Workstream updates

Workstream 1: HATUA Management

- A Project Executive Group (EG), led by the PI, supervised the scientific conduct and management of HATUA's work packages from 2018-2022. The EG met on a regular monthly basis with additional zoom meetings arranged as required. Agendas and minutes were produced for each meeting and action points circulated. In addition to meetings of the EG, workstream teams met on a regular basis to organise activity, plan analysis, and produce outputs. An experienced Project Manager, Dr Alison Sandeman, liaised with the project PI and Co-Is on a day to day basis on operational matters.
- HATUA consortium partners engaged collaboratively and contributed positively to project activities including research design, planning, development of protocols and research tools, training, piloting, fieldwork operations, reporting and dissemination.
- HATUA's Scientific Advisory Board (SAB) included two external appointments: Professor Iruka Okeke, University of Ibadan, Nigeria and Professor Helen Lambert, University of Bristol. The SAB provided support and guidance on research activities and findings.
- Copies of project documents were shared and stored on an online password-protected platform e.g. the Research Collaboration Agreement, ethical approvals and renewals, risk register, research tools, fieldwork and lab manuals, standard operating procedures, informed consent documents, and a publication and authorship strategy.
- Data managers were appointed in each country to oversee issues of data quality, security, storage and confidentiality. A Data Management Plan and standard operating protocols were produced.
- Financial and reporting tools were developed and training given to all consortium partners. Partners submitted quarterly statements of expenditure and funds were released in quarterly tranches.
- Annual consortium meetings were held in 2018 (Arusha, Tanzania), 2019 (Nairobi, Kenya), and 2022 (Arusha, Tanzania). The research tools for the study were co-designed at a planning workshop held in 2018 in Entebbe, Uganda. Residential training workshops were held in 2018 for microbiology and social science research skills, in Entebbe and Mwanza respectively. Additional online training sessions were delivered by St Andrews staff – see section F.
- Key stakeholders at local, regional and national levels, including those responsible for AMR National Action Plans, engaged with the consortium throughout the study and participated at annual consortium meetings.

Workstream 2: The disease and therapy landscape

Aims: WS2 had two main aims

- Map the antibiotic (AB) provision landscape by constructing geospatial maps of AB access and identifying areas of inappropriate provision, examine what are the provision practices and knowledge among different antibiotic providers, and what factors influence the AB offered.
- Capture the burden of disease and antibiotic resistance which includes measuring the burden of disease and AB resistance among patients presenting at hospitals. This is addressed under WS4 and WS5 below.

Data collection: Table 1 presents a summary of drug access points mapped

Country	Study area	Estimated Population	Main economic activities	Number of Drug (Medicine) access points mapped
Tanzania	Mwanza	Based on the 2012 official census: 1.369.487 (Covering only Ilema, Nyamagana, Sengerema, districts)	Farming, fishing, and livestock keeping.	728

	Mbeya	Based on the 2012 official census: 690,598 (This covers Mbeya District and Mbeya City only)	Trade, Agriculture, livestock, bee keeping, and manufacturing	481
	Moshi	Based on the 2012 official census: 651.029 (covers Moshi Urban and Rural districts only)	Tourism, Trade & Farming	346
Uganda	Mbarara	Based on the 2014 official census: 472.629 (Includes Mbarara and Rwampara districts)	Trade & Agriculture	699
	Nakapiripirit	Based on the 2014 official census: 88,281	Animal husbandry, agriculture	43
	Nakasangola	Based on the 2014 official census: 181,795,	Agriculture	243
Kenya	Nairobi	Based on the 2019 official census: 4,397,073	Stock exchanges Business and tourism.	2328
	Nanyiki	Only includes the urban centre based on the 2019 census: 72,813	Economic trade, Tourism	213
	Makueni	For the entire district, based on the 2019 census: 987,653	Agriculture	159

Analysis and key findings: We found there were two main areas where people could access antibiotics: healthcare (hospital) associated pharmacies and freelance pharmacies or drug shops in communities/trading centres. A higher concentration of drug access points was found in central and more highly populated urban or trading centres. The more rural, the fewer the drug access points. Policies such as Tanzania's ADDO programme (first introduced in 2003) were intended to increase the public's accessibility to medicines (including prescription only antibiotics) in rural and peripheral urban areas but our results show that both Pharmacies and ADDOs (and small drug shops in Uganda) tend to be concentrated in central and more populated urban or trading centres. A 3-country manuscript describing the spatial distribution and dynamics of antibiotic access has been prepared.

Over 1780 mystery client surveys were conducted across the 3 East African countries to understand objectively how drug sellers supply ABs to the general population e.g. does practice conform to regulations, do sellers dispense ABs without prescription, do sellers offer appropriate advice, such as completing a full dose. Research assistants pretending to be patients were sent to the mapped drug access points. Two scenarios were used: 1. Asking directly for a named AB with no prescription, and 2. Describing symptoms of UTI and asking for advice. In both cases, the researcher asked to purchase a partial dose. Over 90% of the drug sellers sold antibiotics without asking for prescription and/or advising the client to complete a full course of the dispensed antibiotics. While there are discernible differences between types of outlets, with pharmacies performing slightly better than ADDOs or drugs shops in the various scenarios tested, the problems identified were sector wide. Two papers have been published on these findings from Tanzania while two 3-country papers are in preparation.

Workstream 3: Pathogen

Aims: WS3 had two main research questions:

- What are the pathogens responsible for UTIs, what is the burden of resistance and what are their origins?
- In patients, is there genomic evidence of long-term carriage of ABR pathogens linked to disease and treatment failure?

Data collection: Table 2 presents a summary of microbiology data collected by HATUA.

Type of samples collected	Tanzania	Uganda	Kenya	TOTAL

No. of patients recruited	3879	1824	1899	7598
No. of UTI positive patients	1124	506	1027	2563
Number of urine samples collected and cultures completed	3854	1782	1896	7532
No. of homestead visits	778	439	775	2011
No. of samples with AST data	1052	502	1012	2525
No of whole genome sequences	668	431	702	1801
No. of environmental samples	518	405		923

Key findings: We found that the predominant pathogens causing UTIs in the study sample are Gram-negative bacteria from the order *Enterobacterales*. The predominant Gram negative uropathogens were: *Escherichia coli* (n=985, 39.1%), *Klebsiella* spp. (n=247, 9.8%) and other *Enterobacterales* (n=154, 6.1%). HATUA data also reveal that antimicrobial resistance among common pathogens causing UTI is worryingly high. Overall, multi-drug resistance in the study sample exceeds 50%. For *Enterobacterales*, we observed that resistance to antibiotics (trimethoprim, ampicillin, tetracycline, amoxicillin/clavulanic acid, ciprofloxacin, ceftriaxone, ceftazidime, nitrofurantoin and gentamicin) ranged from 21.3% for gentamicin to 69.3% for trimethoprim. *Enterobacterales* that are carbapenem-resistant, 3rd generation cephalosporin-resistant, have been classified as critical priority pathogens by WHO; these pathogens require research and development strategies for new antibiotics in both hospital and community settings. A 3-country paper describing the microbiological and resistance characteristics of UTI pathogens has been prepared and is under review.

Whole genome sequencing was undertaken for 1800 samples to provide a more accurate identification of bacterial species populations. We used WGS to identify species diversity at the genetic level, the population structure, and AMR profiles (per species and per clone). The five most abundant species collections were found to be *E. coli* (n=764), *Klebsiella pneumoniae* (n=100), *Staphylococcus epidermidis* (n=92), *Staphylococcus haemolyticus* (n=63), *Enterococcus faecalis* (n=46). In terms of phenotypic AMR profiles, we found no distinct differences between the three East African countries. *In silico* analysis of the resistomes were undertaken on the genome sequences to identify the molecular basis of the resistance of the UTI isolates. We created and shared Microreact projects contain the genomic and phenotypic AST data for each country, and provided training in the use of Microreact to facilitate the exploration by country partners of the geographic spread of resistance and the genetic diversity in the population. Analysis of the genome data is ongoing and a manuscript describing the genomic epidemiology of UTI pathogens is being prepared.

Workstream 4: Patient

Aims: WS4 had two main research questions:

- What are the various patient pathways to treatment and how do they intersect with the ABR process?
- How is the ABR burden related to the risk burden at individual, household, and population level?

Data collection: 7,598 patients were recruited across 9 study sites in East Africa (2,563 patients were confirmed as UTI positive). All 7,589 patients were interviewed, detailed questionnaire survey data collected, and urine samples obtained for culture. Individual-level patient data and microbiology data were linked. In-depth qualitative interviews were conducted for a subset of patients (n=122).

Data cleaning and linkage: Intersecting with WS6, we linked individual patient level qualitative, quantitative, and microbiology data. An extensive data cleaning process was undertaken. Where necessary, this harmonised responses across countries and phases. We cleaned and recoded variables into a usable state for analysis and extracted data from free text responses and photographs. In doing so, we derived some variables so that they are in line with international standards (e.g., the Oxford multidimensional poverty index), and developed others using data reduction techniques (e.g. asset indices using Principal Components Analysis). We checked patterns of missing data. Finally, we created a comprehensive data codebook, and shared linked datasets across the analysis teams within the consortium.

Analysis: Clinicians and analysts from all locations across the consortium interacted at weekly WS4 meetings, to share and present work and solicit feedback from a larger cross-consortium and cross-disciplinary team. A number of methods were employed for analysing the quantitative data: Bayesian hierarchical modelling, Bayesian belief networks, process mining and sequence analysis. This was integrated with thematic qualitative coding of the patient interviews and supplemented with data from FGDs in order to understand whether patterns established in the patient recruits were also present in community samples. After conducting preliminary analysis, we developed several academic outputs (publication stage indicated in italics)

1. The Role of Multidimensional Poverty in Antibiotic Misuse: A Study of Self-Medication and Non-Adherence in Kenya, Tanzania, and Uganda. *Revise and resubmit with Lancet Global Health.* Preprint available. Presented at: ASTMH Annual Meeting Oct 2021; EAHRC Annual Conference Oct 2021; IUSSP International Population Conference Dec 2021.
2. Unravelling patient pathways in the context of antibacterial resistance in East Africa. *Manuscript submitted to BMC Infectious Diseases, August 2022*. Presented at: EAHRC Annual Conference Oct 2021; ASTMH Annual Meeting Oct 2021.
3. What drives preventative use of antibiotics in East African countries? A cross-sectional analysis of the role of knowledge, beliefs, and personal experience. *In preparation.*
4. Understanding treatment seeking for UTI symptoms in East Africa using process mining and sequence analysis. *In preparation.*

Key findings and future directions: Prior to attendance at HATUA study clinics, the range of treatment-seeking pathways used by study patients was diverse. Factors associated with antibiotic misuse (skipping antibiotic doses did not cluster with multi-dimensional poverty in a simple manner; in some settings, misuse was associated with patients with lower poverty ratings but it is clear that antibiotic misuse can be driven by different things at different ends of the socio-economic spectrum. It is therefore important for interventions not to neglect the wealthier sections of the population, whose behaviours may drive AMR no less than those with less income. Our findings have been presented to East African policymakers at face-to-face meetings. Future work based on specific results from WS4, and interactive analyses in WS6, will include examination of entry-points for antibiotic stewardship interventions within patient care-seeking pathways in order to reduce the burden of ABR in East Africa.

Workstream 5: Community

Aims: The key aim of WS5 was to understand the opinions and practices of community members (during focus group discussions and homestead follow-ups), health care professionals and AB sellers regarding AB use and ABR. WS5 sought to capture the social practices that intersect with biological drivers. Specific objectives were to:

- Ascertain knowledge, opinions and practices among health care providers, antibiotic sellers, patients and community members regarding AB use and ABR.
- Identify individual social and behavioral drivers of ABR in the community.
- Identify the extent of ineffective treatment and incomplete knowledge of proper use of antibiotics.
- Establish how AB knowledge is produced, how practices become embedded, and how these influence patient pathways.
- Suggest policy recommendations to improve AB provision, access and use.

Research questions:

1. How do household level factors including hygiene practices, health-related behaviours, social inter-relations and the household microbiological landscape influence the ABR process?
   This was addressed through homestead visits, questionnaire data but also through other workstream activities collecting biological (faecal and urine) samples from willing household members.
2. How do animal-human interactions including use of drugs on animals contribute to ABR and UTI?
   Links individual level clinical data with socio-demographic and socio-economic data.
3. What knowledge, opinions and practices exist among health care providers, antibiotic sellers, patients and community members regarding AB use and ABR.

Data collection: District and community members were engaged through inception workshops in all study sites. The participants included service users and practitioners from human and animal care sectors, and the political and administrative stakeholders. The following data were collected: In-depth follow-up interviews with patients at the household levels (n=122); In depth interviews with doctor (n=70); in-depth interviews with antibiotic sellers (n=111) and; focus group discussions with community members (n=57) (Table 3).

	Target per country	**Kenya**	**Uganda**	**Tanzania**	**EAST AFRICA TARGET**	**EAST AFRICA ACHIEVED**
Patient in-depth interviews	30	30	61	31	90	**122**
Doctor in-depth interviews	15	31	23	16	45	**70**
AB seller in-depth interviews	30	51	30	30	90	**111**
Focus group discussions	12-24	12	21	24	36-72	**57**

Table 3: HATUA WP5 data collection deliverables: target vs achieved

Key findings: Inappropriate use of antibiotics is common across all study areas. Normally, health workers conduct laboratory tests for UTI, but in some settings like at rural health centers they may not have reagents for some months, therefore health workers end up treating based on experience. Unnecessary prescription of antibiotics is quite common at the outpatient government health care facilities because of lack of testing kits and reagents, as there is a tendency to prescribe more than one type of antibiotic for effective cure among others. Data from the linked follow-up qualitative interviews, suggests that patient pathway decisions are influenced by factors including: a) finances, b) time, c) stigma, d) insurance (these findings as are based on patient's response when asked about their 'treatment constraints' and on examination of descriptions of patient's treatment seeking pathways. These factors also contributed to recurrent UTIs and increased AB consumption. Although most (UTI) patient respondents reported going to the recruitment hospital as their first pathway step, broader discussion of health seeking behavior, including focus group responses from community members and interview responses from drug sellers suggested that it was common for people to bypass government healthcare centres. Instead, people often favour self-medication with ABs obtained without a prescription from drug sellers or other sources closer at hand than health centres. This was driven by multiple factors, including: (i) insufficient funds to cover transport or drugs, (ii) long waiting times and frequent lack of drug availability at health centers: (iii) poor service and unhealthful staff (particularly in Uganda): (iv) the time penalty and inconvenience incurred by seeking a prescription (especially given patients are often instructed to source prescribed ABs from private sellers, and that most AB sellers will supply without a prescription).

Whereas patients would desire to follow advice given by health practitioners, both doctors and patients suggested that doctors do not always communicate many details to the patients about UTI prevention, drug course completion, drug safety or AMR. This resulted both from doctors' lack of time/capacity and their sense that patients did not want or could not handle detailed 'medical information'. Patients were able to recall some AB best practice advice (such as the need to finish a course) but did not seem to understand its import not did many know that ABs were by prescription only. This general lack of knowledge about ABs and illness was a barrier to following the best practice advice. Further, qualitative data shed light on attempts to measure AB 'knowledge' (in our own and other's studies); data collected often represent familiarity with a product rather than knowledge of its appropriate use. This is a complex phenomenon that deserves further unpacking.

In order to improve antibiotic stewardship health workers indicated the following: i) continuous sensitization of prescribers through workshops and other relevant avenues; ii) support supervision, iii) dispensing of drugs be done by trained personnel, iv) right/confirmatory tests of the disease to give right drugs. Health workers at the district health centres should be retrained to improve better antibiotic stewardship and follow the prescription guidelines.

Interviews with drug sellers tended to confirm the objective observations reported in WS2. Sellers were open about sellers' propensity to dispense drugs without prescription and in quantities below the minimum course, although often distanced themselves from these practices by ascribing them to others. For the most part sellers were aware of broad regulations relating to antibiotic stewardship but felt compelled to ignore them because: (i) competitors do: (ii) they felt compelled to serve the needs of their communities and further understood why customers eschewed formal healthcare services. Contrary to prevailing perceptions sellers were not simply self-interested but also driven by a duty of care. Policy makers need to mobilize these pro-social motivations, whilst simultaneously removing disincentives to stewardship by restructuring the drug sales market. This will require more than simply tightening regulation, and must involve work with sellers and their professional organization to ensure better AB stewardship becomes the rational choice for sellers as well as with citizens so that they better understand what constitutes good advice, service and dispensing among sellers.

After conducting preliminary analysis, several academic outputs emerged from this workstream:

1. See Mixed method papers (1&2) listed in WS4 above.
2. Exploring the situated rationality of antibiotic dispensing in East Africa and its implications for policy interventions: A qualitative study of drug sellers' perceptions. *In preparation*. Presented at: EAHRC Annual Conference Oct 2021.
3. The case of antibiotic sales in East Africa and the (imperfect) market provision of health. *In preparation*. Presented at: EGOS 2022 (Economy & Society and the management conference).
4. Labelling antibiotics *as* antibiotics is a missing link in the fight against AMR: evidence for East Africa. *In preparation.*
5. Expectations and (mis)communication in doctor-patient consultations: the impact of differing perspectives on AB use and AMR in East Africa. *In preparation*.

Workstream 6: Synthesis and Dissemination

Aims: WS6 had two main research questions:

- How do population and individual level behaviours and processes interact to contribute to the overall risk burden of ABR?
- What barriers currently prevent people from taking more clinically ideal pathways to treatment and how might these be addressed?

Data cleaning and linkage: Intersecting with WS2, WS3, WS4 and WS5, we linked individual patient data across qualitative, quantitative, and microbiology data, and linked household and environmental samples to these patients. Extensive thematic coding of individual patient, doctor and drug seller interviews and FGDs was conducted in NVivo, and where possible these were linked to quantitative data. Based on mapping and mystery client exercises in WS2, using geospatial processes we created variables indicating proximity and density of AB access points and attached these to data on recruitment clinics and households. WGS data was visualised and shared using Microreact. We created subsets of data to be used for various projects (e.g. a subset of UTI positive patients, then of those with household data). An extensive data cleaning and coding process was undertaken. We harmonised responses across countries and phases. We cleaned and recoded variables into a usable state for analysis, and extracted data from free text responses and photographs. In doing so, we derived some variables so that they are in line with international standards (e.g. the Oxford multidimensional poverty index), and developed others using data reduction techniques (e.g. asset indices using Principal Components Analysis). We checked patterns of missing data. Finally, we created a comprehensive data codebook, and shared linked datasets across the analysis teams within the consortium.

Analysis and key findings:
Regular consortium-wide meetings were held to bring together different expertise (statistical, genomic, clinical epidemiological and social scientists). At every meeting consortium analysts presented new explorations of the dataset and together we decided next steps. The process was iterative and collaborative. The main findings relating to the first research question on risk burden were:

- There are different factors associated with ABR in different patient populations (inpatients vs outpatients), suggesting different processes to investigate
- Contextual diversity – both country, site and even clinic was important to account for.

- Behavioural drivers (e.g. AB use and misuse) was less strongly associated with ABR than socioeconomic factors such as poverty and education
- Due to our cross-sectional dataset, it is quite difficult to disentangle patient pathway behaviours from ABR – a bi-directional association is rather likely

Based on this exploratory work, these outputs are being developed

- Understanding links between ABR, patient and household characteristics in East Africa using Bayesian profile regression. *Manuscript in preparation*
- Untangling interdependencies of antibiotic misuse and socioeconomic factors in Urinary Tract Infections in Tanzania: a case for Bayesian belief networks. *Working paper, published abstract for 16th Bayesian Modelling Applications Workshop (BMAW 2022) available*.

Our next steps are to further develop some analysis pieces:

- Understanding community and individual drivers of ABR using Bayesian Belief Networks.
- Multilevel socioeconomic drivers of ABR in East Africa, using a systems ecology approach
- Sociodemographic and socioeconomic factors associated with e coli resistance genes

The second research question (barriers to ideal treatment pathways) was addressed through a mixed-method approach which brought together quantitative data with qualitative interviews and FGDs. The main findings were:

- Following best practice advice on the part of patients is hindered by a number of factors: incomplete understanding of how to identify and use ABs, stock outs, time and resource constraints
- AB Stewardship for clinicians and medical staff is hindered by stock outs
- AB stewardship for drug sellers in hindered by a number of processes: economic incentive to sell drugs (even partial doses), incomplete knowledge, desire to help patients, and inadequate monitoring of AB seller practices
- Although much of our data were collected from individuals and whilst our tools tended to pursue information on individual knowledge, attitudes and behaviours, the project nevertheless highlighted the structural nature of many of the drivers that influence and shape these individual phenomena.

These findings are covered in a number of outputs, intersecting with other workstreams including these papers that are almost ready to submit for publication: i) *Unravelling patient pathways in the context of antibacterial resistance in East Africa*, ii) *Exploring the situated rationality of antibiotic dispensing in East Africa and its implications for policy interventions: A qualitative study of drug sellers' perceptions, and iii) Expectations and (mis)communication in doctor-patient consultations: the impact of differing perspectives on AB use and AMR in East Africa. In preparation*. In addition, we conducted Community Dialogues (as described in WS5 above) and worked with local community members at Rubaya Health Centre III, Mbarara to co-design AMR materials using local expertise and knowledge to ensure correct messaging. The participatory action research (PAR) explored the risks around AMR, reviewed existing WHO (and other) health information material, and developed new grassroots health information on AMR. PAR activities have been developed more fully in research projects that have spun off the HATUA award (see sections F and H).

D. Financial report on spending

A table of expenditure, by country, including amount and % of total spend is presented in Annex 1.

E. Stakeholder engagement

Throughout the study period, the consortium engaged with a wide network of policymakers and AMR stakeholders to ensure that findings were shared at the earliest opportunity. Engagement activities included:

- An end of project dissemination meeting held in March 2022 in Arusha Tanzania at which the consortium presented findings across the full breadth of the study. In-person and online delegates attended from across East Africa including national AMR chairpersons, Ministry of Health officials and technical advisors, regional and district medical officers, and public health specialists.
- The HATUA Consortium was awarded a dedicated scientific session to share findings at the 8th East African Health and Scientific Conference in November 2021. Nine members of the consortium presented

research and together provided a detailed overview of the holistic approach taken by HATUA. The talks were followed by a lively panel session with a large and engaged audience.

- The HATUA consortium, in partnership with Makerere University/UVRI Centre of Excellence in Infection and Immunity Research and Training (MUII-Plus) in Uganda, organised a symposium in October 2021 to showcase success stories and highlights of Infection and Immunity research in Uganda. The symposium was organised by Prof Alison Elliott, one of the HATUA Co-Is, based at UVRI and LSHTM. HATUA partners from St Andrews, Uganda, Tanzania and Kenya attended and presented findings from HATUA.
- Two outputs from HATUA were accepted for presentation at the American Society of Tropical Medicine and Hygiene (ASTMH) Conference in November 2021. Dr Dominique Green gave a talk on *The role of multidimensional poverty in antibiotic misuse in East Africa: A mixed-methods study*. Mary Abed Al Ahad presented on *Treatment seeking behaviours for symptoms of UTI in East Africa and irrational use of antibiotics: A mixed methods study*.
- In 2019, the consortium organised a breakout session at its Annual Meeting in Nairobi, and invited key AMR stakeholder and MoH officials to participate with the aim of aligning HATUA research activities to the strategic objectives of each country's National Action Plan. As a result of these discussions, HATUA was asked to contribute to national guidelines, including UTI treatment guidelines in Tanzania.
- Prior to commencing patient recruitment, HATUA's research teams in Uganda, Tanzania and Kenya organised district and community level inception meetings at each field site to engage local communities and seek support. The participants include service users and practitioners from both human and animal care sectors, and key political and administrative stakeholders. These meetings are used to raise awareness of AMR. Hospital-level inception meetings are also organised and help to increase knowledge of AMR e.g. inception meetings were held at three hospitals in Nairobi: Kiambu Hospital Level 5, Kenyatta National Referral hospital, Mbagathi Level 5 hospital.
- HATUA engaged with local community members at each study location to raise awareness of antibiotic use and AMR. In total, 57 community level group discussions were held with each group comprises 6-10 participants. HATUA also distributed information leaflets on UTI and AMR to patients recruited to the study.
- Examples of national-level engagement include: i) Prof Gibson Kibiki, HATUA Co-I and former Executive Secretary of East African Health Research Commission (EAHRC) represented HATUA at the 2020 G20 Health working group meeting in Jeddah, Saudi Arabia, and at a 2019 WHO Regional Africa meeting in Brazzaville, Republic of Congo; ii) Prof Stephen Mshana was invited to attend several meetings of Tanzania's National Antimicrobial Resistance Multi-Sectoral Coordination Committee in 2020-2022; iii) Prof Asiimwe was organiser, and PI Prof Holden an invited speaker, at Uganda’s National AMR conferences in 2018, 2019 and 2021; and iv) Dr Sabiiti presented at the 2019 East African Health and Scientific Conference under the theme of Technology for Health Systems Transformation.
- HATUA's research teams in Tanzania, Uganda and Kenya disseminated the findings from HATUA widely. For example, dissemination meetings were held in Mwanza, Mbeya, Kilimanjaro and Mbarara to share findings with stakeholders at the study sites. Participants included policy makers such as regional medical officers and council leaders, health professionals (clinicians, pharmacists, nurses, lab technologists) and journalists from radio, newspapers and TV. The country teams frequently engaged with national media to raise awareness of AMR to a wide audience. Dr Kiiru from KEMRI, was interviewed on Aljazeera English TV, Duetwelle Radio, and Kenyan national TV, and by Kenya's People Daily newspaper in an article entitled "Over the counter drugs fuel deadly antibiotics resistance: collaborative effort only way to curb resistance".

F. UK.HIC-LMIC Engagement

From 2018-2022 HATUA UK/HIC-LMIC consortium partners engaged collaboratively and contributed positively to project activities including research design, planning, development of protocols and research tools (lab and social science), training, piloting, fieldwork operations, analysis and dissemination.

The Project Executive Group (EG), met on a regular monthly basis with additional zoom meetings arranged as required. The EG was led by the consortium PI and consisted of the Country Leads and WP leads to ensure that each of the partners were represented.
In-person annual meetings and workshops were held in the UK, Kenya, Uganda and Tanzania.
As described in WS6, the team also held regular consortium-wide meetings to plan and draft outputs. These brought together multi-disciplinary expertise to interpret the data; the analysis process was iterative and collaborative. The consortium produced both 3-country and single country academic and policy papers. Policy papers often needed to be targeted at individual country level e.g. the Tanzania team released two policy papers in 2022 to address national polices on drug dispensing and UTI treatment: i) *Towards Improvement of Diagnosis and Patient Management of Urinary Tract Infection in Lower Health Facilities in Tanzania* and ii) *Urgent Need to Address Antimicrobial Dispensing Practices by Drug Outlets in Tanzania*.

A wide range of capacity strengthening measures was undertaken – these are described below in Section G.

New UK/HIC-LMIC engagement activities, which developed out of HATUA, are responding to global health priorities:

- HATUA partners from the UK, Tanzania and Uganda were awarded funding to examine the impact of COVID-19 on AMR. The project entitled *CARE: COVID-19 and Antimicrobial Resistance in East Africa - impact and response* was funded by the Medical Research Council (MRC), 2020-2022.
- In May 2022, St Andrews (Dr Mike Kesby, PI, £69,849) was awarded an MRC-funded Impact Acceleration Award to work in Tanzania and Uganda: *Impacting antibiotic dispensing in Tanzania: going beyond stricter enforcement of regulations to improved antibiotic stewardship through participatory citizen science"*
- PhD funding was secured from the Scottish Graduate School for Social Sciences for a thesis entitled *Development of a Bayesian network approach for analysing interdisciplinary social science and biological data: the case of antimicrobial resistance* (supervisors Keenan, Smith, Holden) (£ 79000; 2020 - 2024)
- The team was also awarded a University of St Andrews World-Leading PhD Scholarship: - *Integrating Interdisciplinary Big Data: A Network-Based Approach* (PI: Keenan K, Smith VA) (£ 116000; 2020 - 2024)
- HATUA is a partner in a GCRF Challenge Cluster consortium (comprising DRUM, HATUA, SNAP, AMIS consortium partners and lead by LSTM) that received funding for *An Essential Information Package for Optimising Community Antibiotic Use in East Africa*. The project is designing an information package that considers both the materials used to convey information and the implementation processes necessary to support the optimal use of antibiotics in communities across East Africa.
- Global Challenges Research Fund awarded for - *Enabling optimal antimicrobial use in East Africa, GCRF Challenge Clusters Call* (£ 149,950; 2020 - 2021)
- In 2019, Scottish Funding Council awarded funding to St Andrews, *Maximising analytical and translational capability for social science data on antimicrobial resistance (AMR) in East Africa*.
- In 2018, St Andrews (Kesby) was awarded £18,540 from Global Challenges Research Fund, *Grassroots 'hatua' to promote better Antibiotic stewardship in East Africa.*

G. Summarise outputs, publications, presentations, workshops etc.

Publications and conference papers

Publications	Number	%
LMIC lead author	15	47
Female lead author	14	41
LMIC and female lead author	7	22

Published or submitted papers

Ndaki, P.M.; Mwanga, J.R.; Mushi, M.F.; Konje, E.T.; Sandeman, A.; Mugassa, S.; Kesby, M.; Manyiri, M.W.; Loza, O.; Keenan, K.; Mwita, S.M.; Fredricks, K.J.; Holden, M.T.G.; Mshana, S.E.; HATUA Consortium. Is this Dispensing or Selling? Motives behind Antibiotics Provision Practices in Human Drug Outlets in Tanzania: A qualitative study (*manuscript submitted to Journal of Pharmaceutical Policy and Practice, May 2022)*

Katherine Keenan, Kathryn J. Fredricks, Mary Abed Al Ahad, Stella Neema, Joseph R. Mwanga, Mike Kesby, Martha F. Mushi, Annette Aduda, Dominique L. Green, Andy G. Lynch, Sarah I. Huque, Blandina T. Mmbaga, Hannah Worthington, Catherine Kansiime, , Emmanuel Olamijuwon, Nyanda E. Ntinginya, Olga Loza, Joel Bazira, Antonio Maldonado-Barragán, V Anne Smith, Arun Gonzales Decano, John Njeru Mwaniki, Alison Sandeman, John Stelling, Alison Elliott, David Aanensen, Stephen H. Gillespie, Gibson Kibiki, Wilber Sabiiti, Derek J. Sloan, Benon B. Asiimwe, John Kiiru, Stephen E. Mshana, Matthew T. G. Holden, and HATUA Consortium Unravelling patient pathways in the context of antibacterial resistance in East Africa (*manuscript submitted to BMC Infectious Diseases, August 2022*).

Green, Dominique L.; Keenan, Katherine; Huque, Sarah I.; Kesby, Mike; Mushi, Martha F.; Kansiime, Catherine; Asiimwe, Benon; Kiiru, John; Mshana, Stephen E.; Neema, Stella; Mwanga, Joseph R.; Fredricks, Kathryn J.; Lynch,;y G.; Worthington, Hannah; Olamijuwon, Emmanuel; Ahad, Mary Abed Al; Aduda, Annette; Mmbaga, Blandina T.; Bazira, Joel; Sandeman, Alison; Stelling, John; Gillespie, Stephen Henry; Kibiki, Gibson; Sabiti, Wilber; Sloan, Derek J.; Holden, Matthew T. G.; Consortium, HATUA, The Role of Multidimensional Poverty in Antibiotic Misuse: A Study of Self-Medication and Non-Adherence in Kenya, Tanzania, and Uganda. *Submitted to Lancet Global Health July 2022. Preprint available at* http://dx.doi.org/10.2139/ssrn.3938836

Ndaki, P.M.; Mushi, M.F.; Mwanga, J.R.; Konje, E.T.; Ntinginya, N.E.; Mmbaga, B.T.; Keenan, K.; Sabiiti, W.; Kesby, M.; Benitez-Paez, F.; Sandeman, A.; Holden, M.T.G.; Mshana, S.E.; HATUA Consortium. Dispensing Antibiotics without Prescription at Community Pharmacies and Accredited Drug Dispensing Outlets in Tanzania: A Cross-Sectional Study. *Antibiotics* 2021, 10(8), 1025; https://doi.org/10.3390/antibiotics10081025

Asiimwe BB, Kiiru J, Mshana SE HATUA Consortium, *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* 2021;**11:** e041418. doi:10.1136/bmjopen-2020-041418

Untangling interdependencies of antibiotic misuse and socioeconomic factors in Urinary Tract Infections in Tanzania: a case for Bayesian belief networks. *Working paper, published abstract for 16th Bayesian Modelling Applications Workshop (BMAW 2022) available*.

Shukrani Phillip, Martha Mushi*, Arun Gonzales Decano, Jeremiah Seni, Blandina T Mmbaga, Happiness Kumburu, Eveline T Konje, Joseph R Mwanga, Benson R. Kidenya, Betrand Msemwa, Stephen Gillespie, Antonio Maldonado-Barragan, Alison Sandeman, Wilber Sabiti, Mathew T. G Holden and Stephen E. Mshana. Molecular characterizations of the coagulase-negative staphylococci species causing urinary tract infection in Tanzania: A laboratory based cross-sectional study", (*manuscript submitted to Pathogens, Special issue Virulence Mechanisms of Uropathogenic Bacteria, July 2022).*

Betrand Msemwa; Martha F Mushi; Benson Kidenya; Bernard Okamo; Katherine Keenan; Wilber Sabiiti; Donald N. Miyaye; Eveline T. Konje; Vitus Silago; Mariam M. Mirambo; Joseph R. Mwanga; Stephen Gillespie; Antonio Maldonado-Barragan; Alison Sandeman; Mathew Holden; Stephen E. Mshana. Urogenital pathogens in urine samples of clinically diagnosed urinary tract infected patients in Tanzania: A laboratory based cross- sectional study. *Submitted BMC Microbiology, August 2022*

Adam A. Mwakyoma, Benson R. Kidenya, Caroline A. Minja, Martha F. Mushi, Alison Sandeman, Wilber Sabiiti, Mathew T. G. Holden and Stephen E Mshana. Comparison of Horizontal blaCTX-M gene Transfer via

Conjugation among Extended Spectrum β-Lactamases Producing Escherichia coli Isolates from Patients with Urinary Tract Infection, their Animals and Environment. *Manuscript ID: 996507 Submitted on: 17 Jul 2022: Frontiers in Antibiotics.*

Decano, A.G.; Pettigrew, K.; Sabiiti, W.; Sloan, D.J.; Neema, S.; Bazira, J.; Kiiru, J.; Onyango, H.; Asiimwe, B.; Holden, M.T.G. Pan-Resistome Characterization of Uropathogenic Escherichia coli and Klebsiella pneumoniae Strains Circulating in Uganda and Kenya, Isolated from 2017–2018. Antibiotics 2021, 10, 1547. https://doi.org/10.3390/antibiotics10121547

Papers currently in preparation – aim to submit before end of 2022.

- Predominance of multidrug-resistant (MDR) bacteria causing UTI among symptomatic patients in East Africa: A call for action.
- Understanding links between ABR, patient and household characteristics in East Africa using Bayesian profile regression.
- Geospatial distribution of drug access points, drivers and possible implications for antibiotic use or misuse.
- What drives preventative use of antibiotics in East African countries? A cross-sectional analysis of the role of knowledge, beliefs, and personal experience.
- Understanding treatment seeking for UTI symptoms in East Africa using process mining and sequence analysis.
- Exploring the situated rationality of antibiotic dispensing in East Africa and its implications for policy interventions: A qualitative study of drug sellers' perceptions.
- The case of antibiotic sales in East Africa and the (imperfect) market provision of health.
- Labelling antibiotics *as* antibiotics is a missing link in the fight against AMR: evidence for East Africa.
- Expectations and (mis)communication in doctor-patient consultations: the impact of differing perspectives on AB use and AMR in East Africa.

Conference presentations

- The case of antibiotic sales in East Africa and the (imperfect) market provision of health. *In preparation*. Presented at: EGOS 2022 (Economy & Society and the management conference).
- The Role of Multidimensional Poverty in Antibiotic Misuse: A Study of Self-Medication and Non-Adherence in Kenya, Tanzania, and Uganda. Presented at: ASTMH Annual Meeting Oct 2021; EAHRC Annual Conference Oct 2021; IUSSP International Population Conference Dec 2021.
- Unravelling patient pathways in the context of antibacterial resistance in East Africa. Presented at: EAHRC Annual Conference Oct 2021; ASTMH Annual Meeting Oct 2021.

Eight papers were presented at the EAHRC Annual Conference, 2021

- Treatment-seeking behaviours for symptoms of urinary tract infection in East Africa and links to antibiotic misuse: A mixed-methods study
- Geospatial distribution of drug access points, drivers and implications on antibiotic use or misuse in East Africa
- Exploring the situated rationalities of antibiotic dispensing practices among drug sellers in East Africa
- Predominance of MDR enterobacteriaceae causing UTI among symptomatic patients in East Africa: a call for action.
- Poor antibiotic dispensing practices for COVID like symptoms and lack of adherence to preventive measures at community ADDOs and pharmacies in Mwanza, Tanzania
- Pan-resistome characterization of uropathogenic Escherichia coli and Klebsiella pneumoniae strains circulating in Uganda and Kenya isolated from 2017-2018
- Urogenital pathogens causing pyuria in clinically diagnosed UTI-patients in Tanzania: The need of increasing clinical suspicious index in urine culture negative patients

- Molecular characterization of Coagulase-negative Staphylococci spp. causing urinary tract infections in Tanzania.

Four papers were presented at the World One Health Congress. Edinburgh June 2020.

- Mshana SE, Multidrug resistant bacteria in the households of patients with significant bacteriuria in Mwanza community, Tanzania.
- Neema S, Asiimwe B, Antibiotic stewardship among health workers at district health centers in Mbarara district, south western Uganda: a qualitative study.
- Kansiime, C, Neema S, Asiimwe B, Availability and access to antibiotics in pharmacies and drug shops in three districts in Uganda.
- Kesby M , Neema S, Asiimwe B, HATUA Consortium, Talking back to the WHO: How grassroots communities in Uganda used Participatory Action Research (PAR) to produce 'glocally' meaningful health information on AMR.

Seven papers were presented at the 11th Scientific Graduation Conference, CUHAS, Tanzania.

- Kajinga H, Mushi M, Msemwa B, Mshana SE, 2019, Gastrointestinal Carriage of Multidrug Resistant Bacteria among Clinically Diagnosed Urinary Tract Infections Patients at Sengerema Designated District Hospital, Tanzania.
- Malindisa K, Peter P, Mushi M, Mshana SE, Utility of Urine Dipstick in the Diagnosis of Urinary Tract Infections (UTIs) Using Culture as Gold Standard among Symptomatic Patients.
- Temu L, Mushi M, Mwanga J, Mshana SE, Antibiotic Provision Practices at Community Pharmacies and Accredited Drug Dispensing Outlets Shops in Mwanza Region, Tanzania.
- Mnyamosi K, Mushi M, Mwanga J, Mshana SE, Information Given to Client by Dispensers on Provision of Antibiotics Without Prescription in Pharmacies and ADDO Shops Mbeya, Tanzania.
- Yusufu S, Mushi M, Silago V, Mshana SE, Prevalence of Multi-Drugs Resistant Gram-Negative Bacteria Colonizing Gastro-Intestinal Tract of Patients with Urinary Tract Infection in Mwanza, Tanzania.
- Satima A, Mushi M, Msemwa B, Mshana SE, Patterns of Bacteria Causing Symptomatic Bacteriuria among Patients in Sengerema, Mwanza.
- Zawadi A, Mushi M, Hamasaki K, Mshana SE, Geographical distribution of pharmacies and drug shops, and antibiotics dispensing in Mwanza.
- Kesby M, Keenan K, Neema S, Asiimwe B, 2018, Seeking UTI care 'that works' in Uganda, *Fresh perspective: social research on Antimicrobial Resistance Symposium, British Academy*, *https://www.antimicrobialsinsociety.org/commentary/amr-symposium-presentation-videos/* .

Workshops and training courses

- A bioinformatics training course was delivered by HATUA's Genome Data Analyst, Dr Arun Decano, to 20+ consortium staff. Participants gained skills and techniques on handling, QCing and investigating Whole Genome Sequence data. The workshop ran over a 4-week period in 2021 and provided hands-on training examining whole genomes of UTI-causing bacteria using Galaxy Europe interface and other bioinformatics platforms.
- Training in ArcGIS Online was delivered to partners across East Africa in 3 separate workshops. This was an online introductory course on mapping and GIS techniques to support in-country analysis of HATUA geospatial data. 10 participants attended for Uganda, Tanzania and Kenya and a CPD certificate was issued upon completion. Participants were taught GIS concepts, trained in ArcGIS online software, symbology and spatial analysis. Participants were then taught how to create, customise and share web maps suitable for publication.
- A workshop on participatory digital methods was held in St Andrews in March 2019. Attendees included HATUA social science colleagues from East Africa, colleagues from Glasgow's SNAP AMR GCRF project, and postgraduate students. Participants subsequently engaged with local communities in East Africa to disseminate training and ideas.
- Online training in qualitative research methods. The focus of these workshops was on qualitative data analysis. Three, 3-hour workshops were held. The first dealt with the principles of qualitative analysis and the following two sessions focused on systematic analysis using Nvivo software. The aim was to equip

colleagues in partner countries with the skills to analyse the qualitative data collected by HATUA from focus group discussion and in-depth interviews.

- Training in quantitative data analysis skills for partners in East Africa (training delivered online due to COVID travel restrictions). This was an introductory level course that covered: Introduction to R: how to upload and open data - Basics on how to manage data: how to recode a variable, for example - Basic descriptive statistics, creating univariate and bivariate tables, including chi-squared test for difference - Creating basic graphs (histograms, bar charts) The aim of the training course was to equip colleagues in partner countries with the skills required to analyse HATUA data and collaborate on research outputs.
- HATUA Co-Is Keenan and Kesby secured additional funding (£31,117) from the Scottish Funding Council Overseas Development Assistance Global Challenges Research Fund to run a two-week workshop in Tanzania in 2020 to *Maximise analytical and translational capability for social science data on antimicrobial resistance (AMR) in East Africa*.
- A one-week Microbiology Training Course was held at UVRI Campus, Entebbe, Uganda in 2018 for 20 team members from Uganda, Tanzania, Kenya, USA and the UK. The aim of the course was to build capacity in lab skills and deliver training in the use of EpiCollect5
- Training in WHONET was delivered in 2018 to the East African partners. Dr John Stelling has provided ongoing ad hoc WHONET training throughout the project.
- A second training course in 2018 was held in Mwanza, TZ, to build capacity in social science research on AMR across all partners.
- Prof Gibson Kibiki (EAHRC) facilitated research skills training to young East African health researchers in 2019, Nairobi, Kenya. The programme, which included both theoretical and practical training, focused on Research Skills: ICT Apps and Tools for Research. 26 PhD students, and 26 MSc students from East Africa participated, with mentors from across East Africa were invited.

Capacity strengthening

In addition to the formal training events described above, research capacity was strengthened via the co-production of research outputs and training of research interns. PhD students and research assistants joined the workstream analysis teams, developed new skills and made significant contributions to the consortium. The Kenyan team recruited 17 students from 8 universities to support HATUA as research interns. They received training in microbiology techniques and worked alongside the KEMRI HATUA lab team on culture and susceptibility testing.

HATUA equipped labs, introducing diagnostic testing, and trained local healthcare professionals in Kenya, Uganda and Tanzania. Culture and susceptibility results are now used for routine patient care in study clinics. Many of these clinics did not have access to microbiology diagnostics prior to HATUA. For example, microbiological testing has been introduced for the first time at Sengerema District Hospital in NW Tanzania and in level 3 clinics in Nakasongola and Nakapiripirit Uganda. This work delivers immediate improvements in patient care in remote communities. Equipment purchased for labs included incubators for bacterial growth, desktop computers for data analysis, fridges for sample storage, microscope for microbiological training, ultra-cold freezer for biobanking.

H. Outcomes

There have been a number of additional outcomes:

- HATUA has been invited by the Tanzanian Ministry of Health to participate in a review of the National Action Plan on AMR for 2023 to 2028.
- HATUA data has been cited in national treatment guidelines for UTI in Tanzania (Standard Treatment Guidelines and National Essential Medicines List (STG/NEMLIT), 5th edition 2021).
- HATUA contributed to the development of a new MSc in Clinical Microbiology and Diagnostic Molecular Biology at CUHAS, Tanzania led by Prof Stephen Mshana. Three HATUA research staff were enrolled on the course: Mr. Betrand Msemwa (CUHAS), Mr. Adam Mwakyoma (CUHAS) and Mr. Fredrick Njeleka (Makerere University). In addition, three Bachelor of Pharmacy students at CUHAS used HATUA data for their Bachelor projects. In St Andrews: 2 BSc Medical Sciences undergraduates are using HATUA data for their dissertations. 5 students received partial tuition support towards their MSc

degree at Makerere University. Several students who worked as research interns on HATUA in Kenya have been successful in applying to PhD and MSc courses in European universities. There have been promotions of HATUA team members across all partners, in which HATUA engagement was seen as an important marker of achievement.

I. Update on intellectual property arrangements

Not applicable.