

Review

Efforts to identify and combat antimicrobial resistance in Uganda: A systematic review

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Abstract:

The global burden of antimicrobial resistance is on the rise, resulting in higher morbidity and mortality in our communities. The spread of antimicrobial resistance in the environment and development of resistant microbes is a challenge to the control of antimicrobial resistance. Approaches, such as antimicrobial stewardship programmes, and enhanced surveillance, have been devised to curb its spread. However, particularly in lower- and middle-income countries, the overall extent of antimicrobial resistance, and knowledge on on-going surveillance, stewardship or investigation efforts, are often poorly understood. This study aimed to look at the efforts that have been undertaken to combat antimicrobial resistance in Uganda as a means of establishing an overview of the situation, to help inform future decisions. We conducted a systematic literature review of the PubMed database to assess the efforts that have been done in Uganda to investigate and combat antimicrobial resistance. A search combining keywords associated with antimicrobial resistance were used to look up relevant studies between 1995 and 2020 on surveillance of antimicrobial resistance in Uganda, and susceptibility of microbes to different drugs. The search yielded 430 records, 163 of which met the inclusion criteria for analysis. The studies were categorized according to country and region, the type of antimicrobial resistance, context of the study, study design and outcome of the study. Antibacterial resistance and antimalarial resistance had the most published studies while antiviral and antifungal resistance each were represented by very few studies. Most studies were conducted in humans and hospital settings, with very few in veterinary and One Health contexts. The results from our work can inform public health policy on antimicrobial stewardship as it contributes to understanding the status of antimicrobial resistance surveillance in Uganda, and can also help to guide future research efforts. Notably, a One Health approach needs to be followed with respect to surveillance of antimicrobial resistance to better understand the mechanisms of resistance transfer across the human-animal –environment interface, including additional investigation in antiviral and antifungal resistance.

Keywords: antimicrobial resistance; antimicrobial stewardship; antiviral resistance; antibacterial resistance; antimalarial resistance; antifungal resistance; One Health; Uganda

1. Introduction

Antimicrobial resistance (AMR) is a phenomenon where bacteria, fungi, parasites and viruses that previously were responsive to medicines evolve to become less or unresponsive to these treatments, increasing the risk of disease spread, treatment failure, severe illness and sometimes death [1], [2]. The rapid evolution and spread of drug resistant microbes that acquire novel resistance mechanisms regularly is a threat to our ability of treating simple infections like urinary tract infections and also more severe infections like bacteremia, tuberculosis and pneumonia that are life threatening[3], [4]. There is also a rapid global spread of multi and pan-resistant microbes that are not responsive to most if not all available treatments[5]. AMR moreover can have a substantial

economic burden, and also significantly affect national health systems, due to its effect on productivity of patients and/or their care takers through prolonged stay in hospitals and more expensive drugs including the need for intensive care treatment. Redundancy in prevention and inadequate treatment strategies against superbugs, and insufficient access to existing and new antimicrobials can result in high rates of treatment failure and even death in some scenarios, which will disproportionately impact those countries with more limited resources. Delicate medical procedures like surgery, cancer therapy, organ transplants and others will become increasingly riskier and may result in death.

AMR is accelerated by clinical, biological, social, political, economic and environmental factors affecting both man, animals and the ecosystem [6]. The main drivers of AMR in developing countries, some of which also act as drivers in higher-income contexts, range from misuse and overuse of antimicrobials, self-medication, over prescription of antibiotics, high infection rates, use of antibiotics in livestock and fish farming, inadequate access to clean water facilities, sanitation and hygiene for man and animals, poor infection prevention and control strategies in the community, inadequate access to medical supplies like diagnostics, vaccines, and effective drugs, ignorance, lack of medicine regulatory policies, and poor enforcement of health regulation policies by relevant authorities[7]–[11], hunger and malnutrition, civil conflicts, and poverty[8]. As drivers for AMR span both human and animal health, with strong environmental components as well, it is increasingly being viewed as a “One Health” issue, requiring multisectoral collaboration to establish effective surveillance and stewardship initiatives[12].

Uganda is a low-income country[13] situated in East Africa, and a member of the East African Community. Agriculture is a mainstay of the economy, with over 80% of the population estimated to engage in agricultural activities, although relatively little is intensive production. As a result of substantial health sector reforms initiated in the 1980s, more Ugandans now have access to basic healthcare services, including essential medicines, than ever before, although issues of quality and out of pocket expenses remain[14]. Antibiotics are reasonably widely available in local pharmacies, with rising concerns related to informal and unprescribed usage[15]. These factors are suspected to be leading towards a growing trend of AMR and a decrease in positive treatment outcomes with use of available medicines for both man and animals in Uganda over the past years[16]. In 2017, a World Health Organization-led Joint External Evaluation revealed weaknesses in Uganda’s efforts to address antimicrobial surveillance, highlighting that while detection of priority pathogens occurs, there is little coordination between sectors or operational guidance to support the country’s National Antimicrobial Resistance Action Plan[17], and also noted an absence of data on AMR activities within the veterinary sector[18]. The objective of this study was to determine the extent to which studies investigating AMR in Uganda, and to elicit information about trends in how these studies are undertaken that might help inform efforts to combat antimicrobial resistance in the country, including multisectoral coordination efforts, antimicrobial stewardship, policies and surveillance of resistance.

2. Materials and Methods

2.1 Systematic Literature Search

We carried out a systematic search in the PubMed database for publications on antimicrobial resistance, stewardship and antimicrobials in Uganda. The search query contained synonyms that included "Stewardship", "Resistance", "Resistant", "Antimicrobial", "antimicrobials", "antibacterial", "antibacterials", "antibiotic", "antibiotics", "antivirals", "antiviral", "antimalarial", "antimalarials" which were combined with Uganda to be able to return relevant studies. The references in the publications were also reviewed to see if they were relevant to the study, and subsequent snowball searches performed. The complete search syntax is available in a supplementary file (Supplementary File 1). Our last search was carried out towards the end of August 2020. We did not put any restrictions on language and affiliate institutions or multicountry studies to minimize bias.

2.2 Selection of Papers

Articles included in the research had to meet four predetermined criteria, notably: (i) discussion of antimicrobial stewardship and/or antimicrobial resistance surveillance, and antimicrobial agents; (ii) study location in

Uganda, or multicountry studies with sample and/or data collection sites in Uganda; (iii) published after 1994; and (iv) the outcome was on resistance genes, antimicrobial resistance surveillance, policy-making or susceptibility testing. Both authors independently screened titles and article abstracts. One author screened full texts. Discrepant articles were thoroughly screened, reviewed and discussed between the two authors until a unanimous decision on their inclusion was reached.

2.3 Data Analysis

We characterized the included articles based on Uganda as a geographic location (including the district, where this information was available; if the study included other countries it was classified as “multicountry”), the type of antimicrobial resistance described (antibacterial; antiviral; antifungal; or antimalarial), context of the study (human, veterinary or One Health, meaning considering of both human and animal populations), study design (field or laboratory study; note “field” study includes hospital and clinical settings) and outcome of the study (focus on resistance genes, antimicrobial resistance surveillance, policy, and/or susceptibility testing). Articles we reviewed for antimicrobial resistance testing, antimicrobial susceptibility, antimicrobial stewardship policies and antimicrobial resistance genes. We did not carry out meta-analysis of the data due to the diversity of the study types and identified data, and therefore instead present descriptive findings below.

3. Results

We identified a total of 427 titles published from 1995 to 2020 from the PubMed search. An additional three studies were identified through reference screening and snowball searches leading to a total of 430 records. They were screened for inclusion criteria and duplicates removed, leaving a total of 166 articles for full text screening. Of these, three were excluded for failing to meet the inclusion criteria, leaving a total of 163 articles included in our final analysis (Figure 1). A full list of the included articles and categorization is provided in Supplemental File 2.

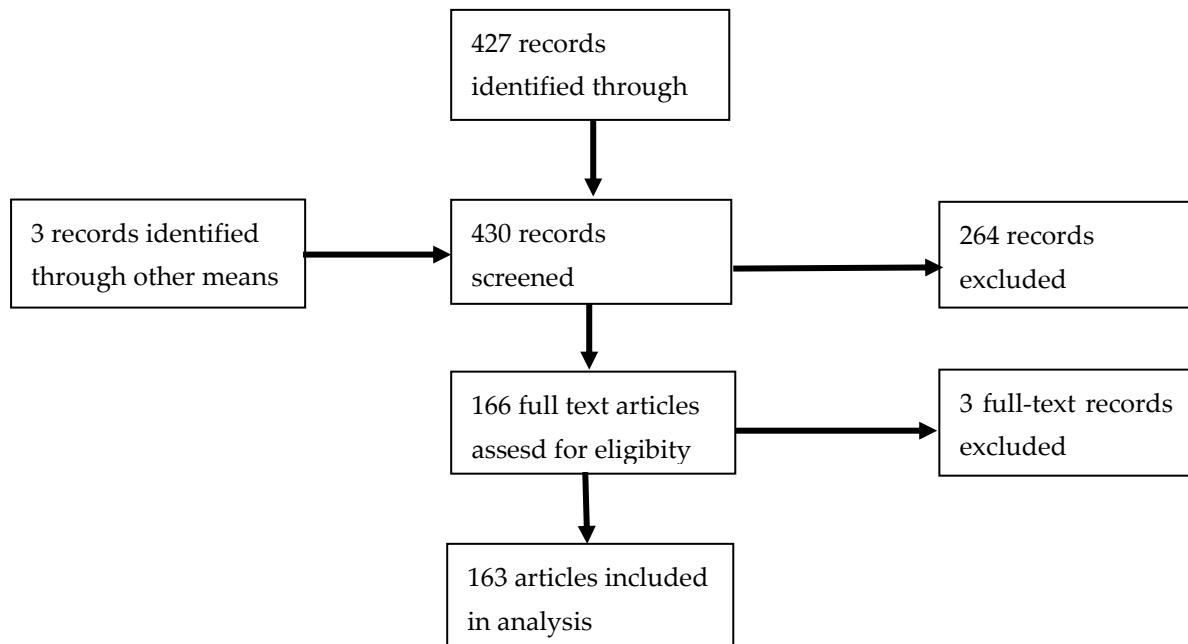


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flowchart for our identified articles

3.1 Study Characteristics

We identified articles on surveillance of AMR and resistance genes from research carried out across two dozen districts in Uganda (Figure 2). However, more than a third of the studies ($n = 60$) were carried out in Kampala, which is also the capital city and where the national referral hospital, Mulago Hospital, is located. The next three most frequently observed study sites were Tororo, Mbarara and Gulu districts ($n = 10$, $n = 10$ and $n = 7$ studies), each of which has a regional referral hospital, for western, eastern and northern Uganda respectively. Additional districts with multiple identified studies included Kasese in western Uganda and Iganga in eastern Uganda (both $n = 4$ studies), both of which have large district hospitals that serve large communities; Bwindi and Kabarole districts (both $n = 3$ studies), which are situated in the western cattle corridor bordering the Democratic Republic of Congo. Studies carried out in Uganda were 155 while 8 of the studies were multi-country studies; and Mayuge district ($n = 3$ studies) in eastern Uganda.

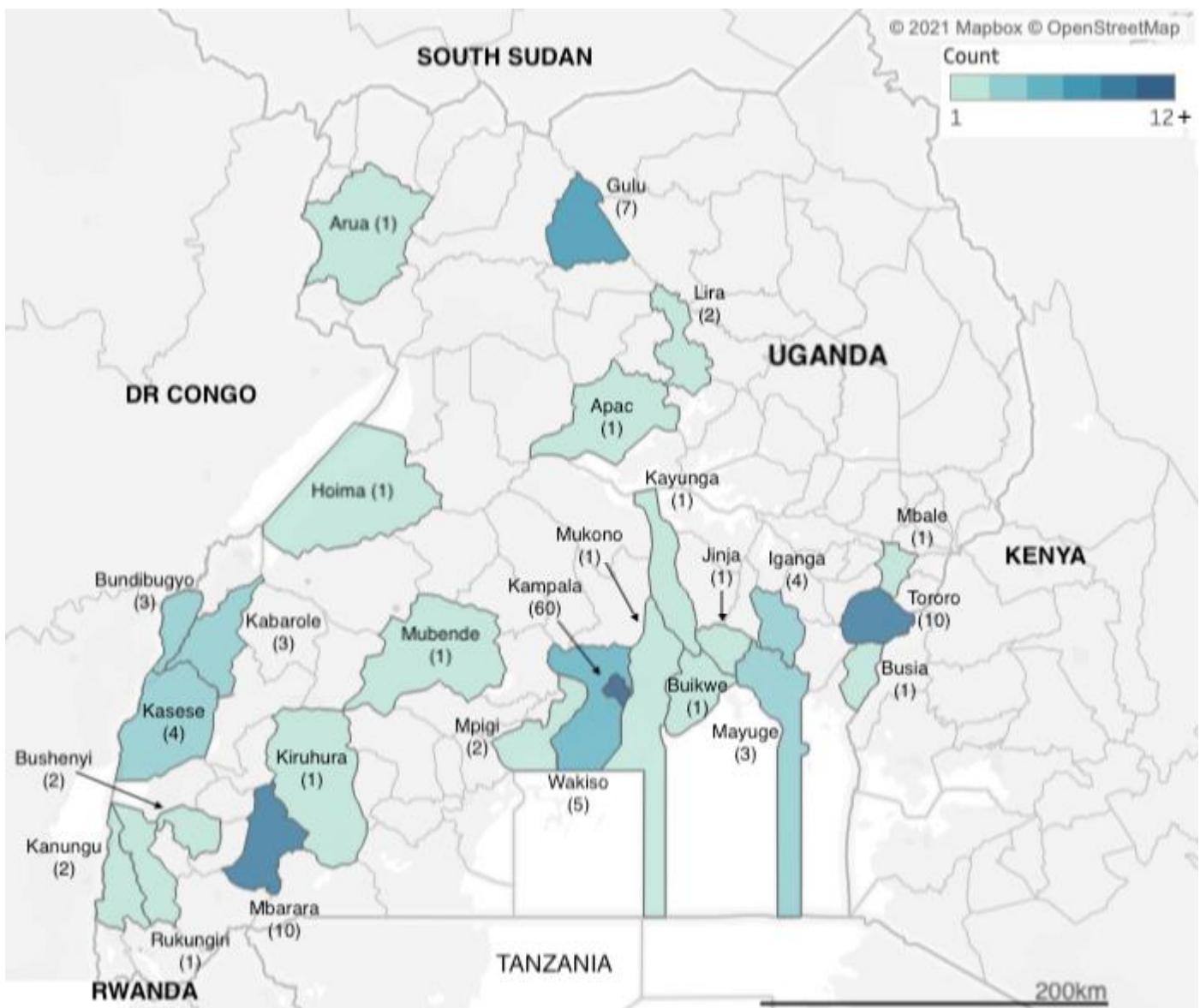
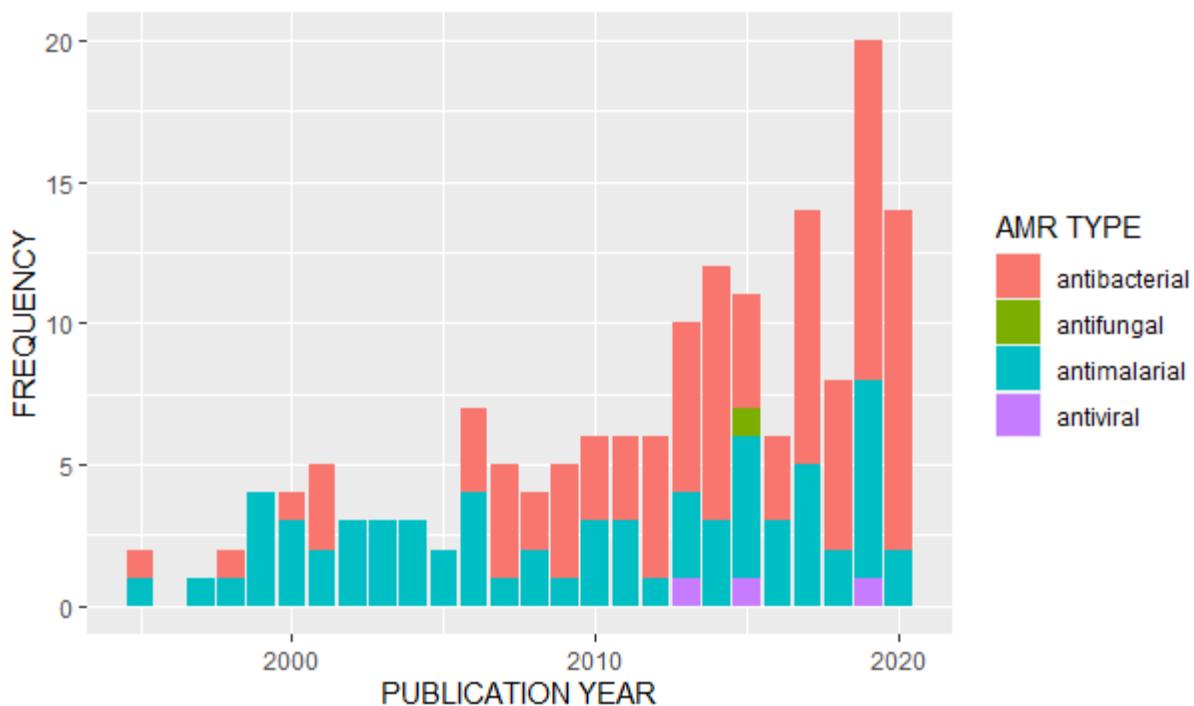


Figure 2 Geographic distribution of included studies

We observed an overall increase in the frequency of published studies on AMR in Uganda over time (Figure 3). Of the 163 articles analyzed, the majority ($n = 91$) reported data on antibacterials. Of these, the most frequently studied bacterial pathogens were *Escherichia coli* ($n=13$) and *Staphylococcus aureus* ($n=11$). A further eight studies looked at *Salmonella* species, *Streptococcus* pneumonia also was covered in eight studies, and seven studies were on tuberculosis (*Mycobacterium tuberculosis*). *Klebsiella pneumoniae* had four studies while *Enterococci* species, *H. influenza*, *V. cholera* and *H. pylori* were also covered by identified papers. Major antibiotics that were used for surveillance of antimicrobial resistance included: penicillin, tetracycline, ampicillin, chloramphenicol, ciprofloxacin, trimethoprim, sulfonamide, ceftriaxone, gentamicin, vancomycin, erythromycin, oxacillin, methicillin, clarithromycin, sulfamethoxazole/trimethoprim and other fluoroquinolones.



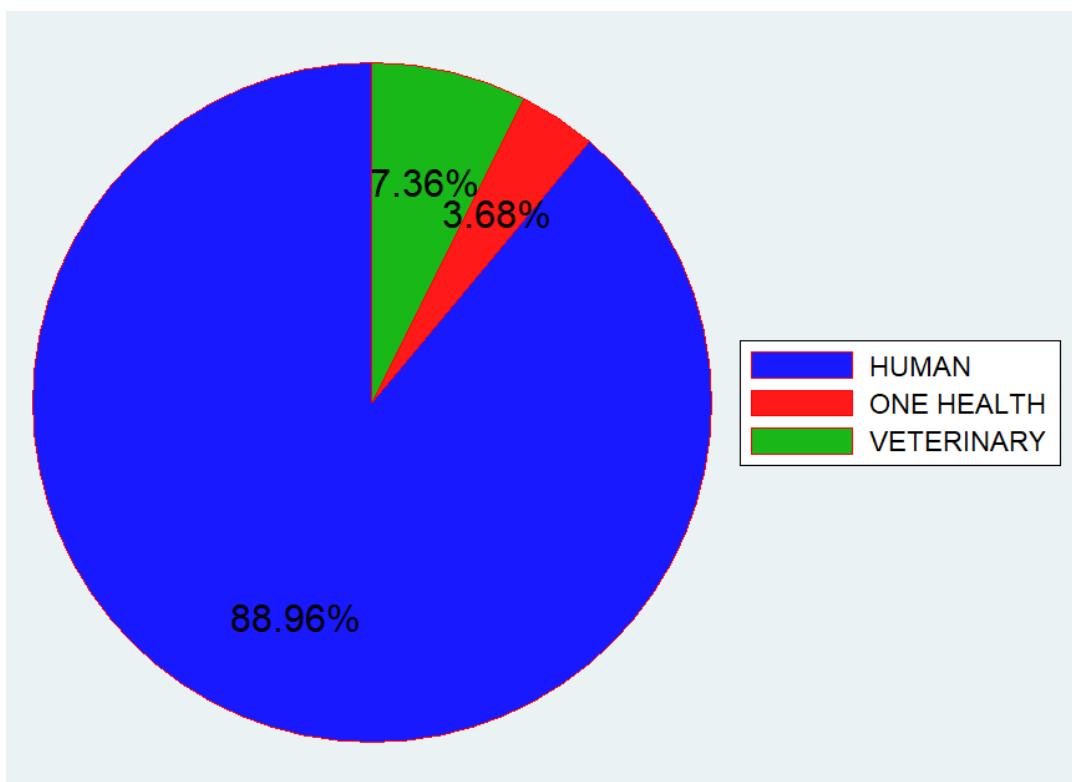


Figure 4 Showing the proportions of AMR Context.

Overall, only ten of the studies were laboratory-based, whereas the remaining 153 studies were done in the field, with recruitment specifically taking place in clinical/hospital settings. None of the human-focused studies appeared to include surveillance or recruitment at the community level, although all the veterinary and One Health studies were conducted in communities. Eighty-three of the studies produced results on resistance genotypes for instance TB resistance genes like *rpoB* gene, vancomycin resistance genes, tetracycline resistance genes, dihydrofolate reductase resistance genes, methicillin resistance genes, SCCmec genes, beta lactamase genes, *Salmonella* resistance genes and various polymorphisms associated with antimalarial resistance in *Plasmodium falciparum*, while 80 studies focused on simply looking at resistance profiles of the microbes for example methicillin-resistant *Staphylococcus*, riphampicin-resistant tuberculosis, vancomycin-resistant *Staphylococcus aureus*, beta lactamase-resistant *E. coli*, and carbapenem-resistant *Klebsiella pneumoniae*, etc. None of the articles we identified described the process or outcome of AMR stewardship initiatives, or focused on policy aspects of AMR prevention, mitigation or management, beyond noting policy changes with respect to anti-malarial use, for example, as a motivation for continuing to surveil for resistance phenotypes and genotypes.

4. Discussion

Our systematic literature revealed that substantial work has been done in Uganda to investigate the emergence and spread of AMR over the 25 years. However, we observed large differences in terms of the type of AMR investigated, the settings in which those studies were conducted, and the locations of the studies, with the majority of studies performed in urban areas and large-scale health facilities. We observed very few studies that had been performed in rural settings, and many districts were not covered at all in the available literature. We also identified a handful of articles in which Uganda was included as part of a multi-country study, but in these cases, the specific district or location of the study or sample collection was rarely mentioned, limiting the application of the study's findings for the specific context within Uganda. The high frequency of studies in Uganda is in contrast to many other countries in Africa; a 2017 systematic review reported that about 42% of African countries do not have published studies on AMR [19].

Our systematic review demonstrated that a great number of infectious diseases have been shown to resist available and routine therapy in the Ugandan context, for example tuberculosis[27]–[29], pneumonia[30], [31], salmonellosis[32], [33], malaria[34], [35], gonorrhea[36]–[38] and other urinary tract infections and respiratory

infections, as well as important viral and fungal infections. There has been detection of wide spread beta lactam and non-beta lactam antibiotic resistance reported in district referral hospitals[39] as well as multidrug resistance amongst clinical isolates[40], [41]. Carbapenem resistance has also emerged and has been detected for *K. pneumonia* and *E. coli*. as well as other pathogens, together with methicillin-resistant *S. aureus* and extended-spectrum beta-lactamase producing bacteria. Collectively, these findings demonstrate the substantial threat posed, particularly by antibiotic resistance, in Uganda, with bacteria demonstrating resistance to even new and strong available antibiotics [42].

Most of the studies from other countries in sub-Saharan Africa overall focused on antibacterial resistance, with very few or no studies in areas of antivirals and antifungals, and moderate numbers of studies on antimalarials, which aligns with our observations from Uganda [27][28]. Countries with high prevalence of HIV tended to have higher numbers of studies on HIV viral resistance[21]; Uganda's HIV prevalence was estimated in 2017 at just over 6%, with higher levels in urban versus rural areas, and women disproportionately impacted[22]. While not as high as HIV prevalence levels in other countries in Africa, this represents a substantial burden of disease, and it is was surprising to identify just a single study focused on antiretroviral resistance in Uganda[23], particularly given concerns around emerging and spreading resistance to antiretroviral therapies in the African region[24]. We similarly identified only one article examining antifungal resistance in Uganda[25]. Globally, an estimated 1.7 million die each year from fungal infections[26] – a similar number as for tuberculosis and malaria combined – and yet antifungal resistance has only recently been integrated into global AMR initiatives. Antifungals are similarly not mentioned in Uganda's AMR National Action Plan[17].

We also observed that most studies on AMR in Uganda focused on resistance in human beings, neglecting animals and the environment, despite the known importance that all three sectors play in preventing and mitigating the spread of AMR. In Uganda, the launch of the National One Health Platform in November 2016 presaged a strong emphasis on multisectoral coordination across a number of areas of infectious disease control, and with a particular emphasis on emerging zoonotic diseases[43]. While AMR is highlighted as a key priority area of the National One Health Platform, which moreover is the designated responsible body for implementation of the AMR National Action Plan, the lack of published One Health studies on AMR in Uganda suggests additional efforts will be required to encourage greater integration and coordination in this area. As noted previously, Uganda's Joint External Evaluation in 2016 specifically noted the absence of available data on AMR in the environmental and veterinary sectors as a limitation for providing specific recommendations to strengthen AMR control; these deficits must be addressed.

In Uganda, the majority of the studies we identified focused on specimens collected from patients at different clinical health facilities, and especially in larger district or regional hospitals, while a much smaller number used archived laboratory specimens. Similarly, analysis of the studies revealed that the outputs largely focused resistance profiles or detection of resistance genes. While this information is very important in surveillance of AMR, particularly for guiding decisions on appropriate treatment protocols for patients, without analyses of the broader drivers of AMR, or studies conducted outside of acute clinical settings, the results may have limited broader applicability for the development of policies and practices to mitigate further AMR emergence. We noted few studies that integrated multiple forms of data, or attempted mixed-methods approaches for understanding drivers of AMR, or that focused on the implications or impacts of policy initiatives related to AMR. However, this may be changing, with studies planned that will explicitly look across social, biological, and community-level drivers of AMR in Uganda and neighboring countries[44].

Based on our findings, we recommend that efforts be taken to conduct surveillance for AMR more broadly across different regions in Uganda, and across a more diverse array of rural and urban settings, to include community cross-sectional studies, and incorporating investigations into attitudes and practices as well as resistance profiles and genetics. We encourage that more attention be paid to antiviral and antifungal resistance; a key step in this regard would be to include antifungal resistance as a topic area under the AMR National Action Plan and related policy documents. Similarly, where possible, researchers should be encouraged to collaborate across sectors to approach AMR from a One Health perspective. The National One Health Platform should encourage researchers to consider One Health methodologies that explicitly look at outcomes across human, animal and environmental health indicators; frameworks such as the Checklist for One Health Epidemiological Reporting of Evidence can be particularly helpful in assisting researchers in guiding the design,

analysis and dissemination of multisectoral studies, for AMR as well as other One Health issues[45]. Finally, the wealth of research on AMR in Uganda must not be sequestered in the scientific literature, but rather utilized to inform policy and practice. To this end, initiatives such as the National Antimicrobial Resistance Conferences, each hosted by different Ugandan universities or public health-affiliated agencies, and supported by the Africa One Health University Network (formerly the One Health Central and East Africa University Network), present an ideal mechanism for broader sharing of knowledge and novel research related to AMR, particularly in a One Health context, provided policy- and decision-makers are included as participants. In this way, research data, across human, animal and environmental contexts, can be more directly utilized for the development and implementation of policies and laws to control the spread of AMR in Uganda and in neighbouring countries.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Full search syntax for the systematic review, Table S2: Table of 163 included articles and analysis findings.

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