ANTIMICROBIAL STEWARDSHIP IN SUB-SAHARAN AFRICA

RESSOURCES AND BARRIERS OF ANTIMICROBIAL STEWARDSHIP INTERVENTIONS IN SUB-SAHARAN AFRICA: A MIXED METHODS RESEARCH PROTOCOL

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Descriptive Note

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Lay Abstract

Antimicrobial resistance (AMR) is present when drugs used to treat infections —like antibiotics— do not work. Infections might not be treatable anymore. AMR causes over a million deaths each year. The use and misuse of antimicrobial substances, such as antibiotics, are risks for the development of AMR. Antimicrobial stewardship programs are set up to reduce resistance. Using specific treatment guidelines should help hospitals to optimize treatment.

Infections and AMR are common in sub-Saharan Africa. Choosing the correct treatment is therefore important to provide the best care to patients but also reduce the risk of AMR.

The purpose of this thesis was to develop a study protocol to investigate availability of hospital guidelines and to include the experience of clinicians using them. A small pilot study showed that hospitals rarely have their own guidelines. The study protocol therefore needs to be changed, so that the view of clinicians can still be included.

Abstract

Antimicrobial resistance (AMR) is a major threat to global health. The annual number of deaths associated with AMR is estimated to increase to 1.9 million in 2050. The (mis)use of antimicrobials is a major driver for the development of AMR. Antimicrobial stewardship programs, aiming to optimize antimicrobial consumption, have demonstrated to be beneficial in certain settings, not only to reduce antimicrobial resistance, but also to shorten length of hospital stay and decrease economic costs. The core elements of these stewardship programs vary for different settings, but facility-specific treatment recommendations are a priority intervention for hospital programs.

Sub-Saharan Africa has a high burden of mortality associated with non-AMR and AMR infections. Therefore, the responsible consumption of antimicrobials is important to optimize patient outcomes and to prevent further development of AMR.

The thesis proposes a mixed-methods study protocol to assess information about the availability and agreement of facility-specific treatment guidelines with the WHO AWaRe book and to collect experiences of clinicians using these guidelines. A trial network across sub-Saharan Africa will be used to identify sites. This study will help to obtain comprehensive, in-depth insights into antimicrobial stewardship in sub-Saharan Africa.

The proposed study design, explanatory sequential, includes a quantitative strand (on the availability and agreement of guidelines), followed by a qualitative strand (semi-structured interviews).

A vanguard phase, assessing the feasibility of the proposed study, demonstrated that 78% of sites (7/9) provided a treatment guideline, but only one (11%; 1/9) was a facility-specific document. Items, representing important treatment elements, were extracted in over 50% in 4/7 facilities providing any document. Agreement of the guidelines with the WHO AWaRe book varied across facilities. The limited availability of facility-specific guidelines questions the feasibility of the proposed study as originally planned, and therefore, changes might be necessary to proceed.

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AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AWaRe	Access, Watch, Reserve
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
HAP	Healthcare-associated pneumonia
LMIC	Low- or Middle-income countries
NL	National Leader
PI	Principal Investigator
REVIVE	Reducing Mortality in Adults With Advanced HIV Disease
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia
WHO	World Health Organization

Declaration of Academic Achievement

I, Thomas C. Scheier, declare my thesis to be my own research work. I am the sole author of this thesis document and was involved in all stages of the research project under the supervision of Prof. Dominik Mertz. The following individuals contributed to the editing and refinement of my thesis work and acted as the members of my thesis committee: Prof. Jeffrey Pernica, Prof. Lawrence Mbuagbaw and Prof. Andrew Morris (external reader).

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1. Background

1.1. Antimicrobial Resistance (AMR)

1.1.1 Definition

According to the World Health Organization (WHO), antimicrobial resistance "*occurs when bacteria, viruses, fungi and parasites no longer respond to antimicrobial medicines*..."(1). AMR can be detected through phenotypic or genotypic approaches. For phenotypic methods the minimum inhibitory concentration can be determined, which is the lowest concentration of an antimicrobial preventing further growth of the microorganism. Based on this value and international standards, combinations between antimicrobial and microorganism can be classified as *resistant*, *susceptible* or *susceptible at increased exposure* (2, 3). Genotypic resistance detection can be performed using different techniques, such as polymerase chain reaction or whole-genome sequencing. These methods assess the presence of AMR genes in either a single or multiple microorganisms (4). Besides being intrinsically resistant to certain antimicrobials, bacteria can also develop de-novo resistance through several mechanisms (5, 6). Genetic material, harboring antimicrobial resistance, can be exchanged between microorganisms. Throughout several interactions between humans, resistant bacteria can subsequently spread (5). Moreover, resistant microorganisms can also be transferred between humans, animals and the environment (7).

The use or misuse of antimicrobials is considered as one of the better explored and impactful driver of antimicrobial resistance (5). Therefore, proper antibiotic consumption is warranted to prevent future increase of antimicrobial resistance rates.

1.1.2 Burden of Infectious Disease AMR

It is estimated that 1.27 million deaths worldwide were attributable to antimicrobial resistance in 2019, and this number will rise to 1.91 million annual deaths in 2050 (8, 9). The WHO lists antimicrobial resistance as one of the top ten global public health threats (10). Moreover, AMR does not only cause deaths but also threatens efficacy of infection prophylaxis in patients undergoing surgery or receiving chemotherapy which are critical aspects of health care (11, 12). The burden of deaths due to AMR is unequally distributed across the globe and is greatest in low- and middle-income countries (LMIC) (8, 9, 13).

Bacterial infection caused by non-AMR and AMR microorganism are a major driver of mortality in sub-Saharan Africa (14). The combination of the high prevalence and burden underscores the importance of appropriate treatment in this region to optimize patient outcomes and reduce mortality but also to minimize the development of resistance.

1.2. AMR Stewardship (AMS)

1.2.1 Overview

Tackling antimicrobial resistance is a difficult task. The challenge of optimizing antimicrobial treatments is to find the balance between short treatment duration and narrow antimicrobial drug, to reduce the burden of resistance but still provide efficient treatment to the patient. Studies have shown that antimicrobial prescription can be improved and that as many as 30% of treatment days might be unnecessary (15, 16). Antimicrobial stewardship programs have been shown to be beneficial for patients and healthcare systems, reducing length of stay, infection-related readmissions, antimicrobial use and costs and suggesting a decrease in AMR in specific settings (17-22). Therefore, these programs have been promoted by

several medical societies and organizations (23, 24). The WHO highlighted the importance of stewardship programs in the way forward and as an action item for member states, but also urged for further research to better support these programs (25).

Antimicrobial stewardship is a broadly defined term, which encompasses a number of different processes, programs or measures (26). Several descriptions exist; some of them focus on specific activities or goals AMS should have, and some describe it as a concept or program to promote evidence-based use of antimicrobials (24). Dyar and colleagues define antimicrobial stewardship as *'a coherent set of actions which promote using antimicrobials responsibly'* with a focus on how antimicrobials are used (26). Others reflect similar frameworks for antimicrobial stewardship programs but also include strategies which might not be considered directly linked to the responsible use of antimicrobials, such as vaccines to prevent infections (27).

To achieve a responsible use of antimicrobials, stewardship programs include several actors and stakeholders such as prescribers of antimicrobials, patients receiving antimicrobials, governments who provide financial support, and pharmaceutical companies that promote and provide antimicrobials (24).

Though antimicrobial stewardship programs have focused so far on human medicine, there is now also a shift towards veterinary medicine and the environment, especially in LMIC (7, 28), which is an important step to address the One Health approach aiming to "*balance and optimize the health of people, animals and ecosystems*". Besides human antimicrobial use, antimicrobial misuse or overuse in veterinary medicine is a substantial modifiable driver of

resistance (5). In addition, especially in certain LMIC settings, unregulated food production including missing biosecurity measures, the high proportion of people with agricultural employment, and lacking data about antimicrobial resistance in agri- and aquaculture, contribute to the development and transmission of antimicrobial resistance (29). The close interplay of resistance in humans and animals is demonstrated by the *mcr-1* gene, which was described in 2015 in food animals (30). This plasmid-mediated colistin resistance mechanism was traced back in chickens to the 1980s, a time when colistin was used in food-producing animals in China (31). Now, *mrc-1* is reported across the world in clinical isolates of humans and animals (32, 33).

Focusing on hospital antibiotic stewardship programs, studies and systematic reviews have shown that implementing these programs decreased antimicrobial consumption, infections caused by certain AMR pathogens, shorter hospital stay, and reduction of *Clostridioides difficile* infections; they have also been shown to have a positive economic impact (18, 34, 35).

Besides collecting quantitative data, researchers have emphasized and demonstrated how qualitative methodology can improve science, enhance the understanding of antimicrobial stewardship, and optimize programs (36-38). Using qualitative research methods might help to comprehensively investigate the inherently complex structure of AMS interventions, explore areas such as sociocultural inequalities or to understand and influence behaviours which are important for AMS, such as adhering to treatment guidelines (39, 40).

1.2.2 Elements of AMS

Given the complexity of antimicrobial consumption and its wide use, elements to promote responsible use are often tailored to specific settings. The Centers for Disease Control and Prevention in the United States (CDC) provide information about core elements in different scenarios, including health departments, hospitals, outpatients/telemedicine or resource-limited settings (41). Focusing on hospital antibiotic stewardship, core elements are (42):

- Hospital Leadership commitment: Dedication of necessary human, financial and information technology resources.
- Accountability: Appointment of leaders or co-leaders, such as a physicians and pharmacists, responsible for program management and outcomes.
- Pharmacy Expertise: Appointment of pharmacists, ideally as co-leaders of the stewardship program, to lead implementation efforts to improve antibiotic use.
- Action: Implementation of interventions, such as prospective audits and feedback or preauthorization, to improve antibiotic use.
- Tracking: Monitoring antibiotic prescribing, impact of interventions, and other important outcomes like *C. difficile* infections and resistance patterns.
- Reporting: Regularly reporting information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.
- Education: Educating prescribers, pharmacists, and nurses about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

1.3. Antibiotic Treatment Guidelines

The CDC lists facility-specific treatment guidelines as a priority within the core element 'Action' for antimicrobial stewardship in hospitals. Besides facilitating three other priorities (prospective audit, feedback, and preauthorization) the development of these guidelines helps to connect stakeholders and achieve consensus. Also, evidence-based guidelines are listed as an element for responsible antibiotic use (27) and up-to-date treatment guidelines are recommended in a practical toolkit by the WHO for health-care facilities in low- and middle-income countries (43).

The WHO has issued 'The WHO AWaRe (Access, Watch, Reserve) antibiotic book' to provide recommendations on the management of more than 30 infectious syndromes in adults and children. The evidence-based guidance includes choice, dose, and treatment duration of antibiotic therapies. The book was published in 2022 and can be downloaded free of charge. (44).

1.3.1 Impact of Guidelines on the Treatment of Infectious Diseases

Several studies investigated the impact of AMS on clinical outcomes, such as the prevalence of antimicrobial-resistant pathogens. However, this information is often limited by the specific setting in which a study was conducted (e.g., hospital, out-patient), but also by the investigated stewardship intervention. The resulting variation within and across studies is also reflected in systematic reviews pooling these data, showing wide confidence intervals for estimated outcomes and high heterogeneity (34, 35).

Even if the overall impact of antimicrobial stewardship programs is reported to be beneficial, not all studies are reporting positive findings. An overall judgment is even more complex, since settings might differ widely. The following two examples, focusing on treatment guidelines, are meant to highlight this.

In a pediatric hospital setting in Norway, adherence to antibiotic guidelines in inpatients was associated with favourable outcomes regarding lower mortality and shorter length of hospital stay (45). However, the dissemination of national guidelines in order to promote appropriate use of antibiotics did not show any impact on antibiotic use in outpatients with acute respiratory tract infection or gastroenteritis in Japan (46). In the latter study, using an interrupted time-series analysis, the authors demonstrated that there was no significant reduction in antibiotic use or specifically in board spectrum agents in the first year after the guidelines were issued. The authors discussed that in a recently conducted survey less than 50% of Japanese doctors were aware of the guidelines, and of those aware of the guideline, again less than 50% used it. This highlights the importance of using qualitative and quantitative data, to gain deeper insights into the effect (or lack thereof) after disseminating guidelines.

1.3.2 Barriers of Implementation

Prescribing antibiotics is impacted by several factors. Common factors are i) prescriber characteristics, ii) complex risk perceptions, emotions, and judgments, iii) effects of the work environment on prescriber cognition, iv) features of the clinical setting, v) team structure and relationships, vi) hierarchy and power dynamics and vii) patient factors (47). An additional challenge for using antimicrobial responsibly is the correct indication to start

treatment, which is based on a reliably diagnosis. To achieve this, the inclusion of recommendations regarding the diagnostic approach should also be reflected in facility-specific guideline documents (41). This highlights the complexity and challenges the implementation of treatment guidelines into clinical care faces. Additional barriers for adherence to the guidelines include their accessibility, critical thinking skills, and training (48). Specific settings, such as patient characteristics, also influence adherence to antibiotic guidelines (49, 50). Identifying these barriers is important to develop targeted interventions. As an example, MacKinnon and colleagues optimized accessibility providing an app, which resulted in quality improvements of antimicrobial prescribing (51).

2. Study purpose and study aim

2.1. Study purpose

The intent of this study is to investigate resources regarding antimicrobial stewardship, explore lived experience of clinicians, and identify barriers of implementation into clinical routine in sub-Saharan Africa. To achieve this, a mixed-methods research design, combining quantitative and qualitative approaches, will be applied to assesses the availability of antibiotic guidelines and explores experiences of clinicians using these guidelines in a sequential way (explanatory sequential design) (52). The study will begin with a quantitative strand (survey of guidelines), followed and enhanced by a qualitative strand (interviews).

Availability of guidelines to treat bacterial infections will be collected from the study sites currently participating in a large, multinational trial in sub-Saharan Africa (Reducing

Mortality in Adults With Advanced HIV Disease (REVIVE)[1]; Clinicaltrials.gov ID: NCT05580666) and compared to international documents of the WHO. Clinicians at these sites utilizing facility-specific guidelines will be interviewed to obtain their viewpoint and experience on these documents in clinical routine. Combining both, quantitative and qualitative research in a mixed-methods research project will result in a comprehensive understanding of the antibiotic treatment guidelines across sub-Saharan Africa.

2.2. Research Question

What is the interplay of the availability and agreement of antimicrobial stewardship guidelines (quantitative) and barriers for implementation (qualitative) into routine clinical care in sub-Saharan Africa?

This research question can be further split into a quantitative and a qualitative strand. In addition, a mixed-methods research question will inform the integration of both strands (53).

2.2.1 Quantitative Research Question

Are facility-specific antibiotic guidelines available in sub-Saharan healthcare facilities and what is their agreement with the WHO AWaRe book?

[1] The REVIVE trial is a multicenter, placebo controlled, randomized trial, which evaluates the effectiveness of a four-week azithromycin prophylaxis to reduce mortality in adults with advanced HIV disease in sub-Saharan Africa. A total of 60 healthcare facilities across 14 countries are intended to participate in the trial. Local site oversight is provided by site principal investigators. Based on the setting most sites are also dealing with other, non-HIV associated infectious syndromes.

2.2.2 Qualitative Research Question

What are experiences of clinicians in sub-Saharan Africa using facility-specific antibiotic treatment guidelines regarding availability and agreement?

2.2.3 Mixed Methods Question

What are the barriers of implementation of local guidelines in health-care facilities across sub-Saharan Africa?

3. Objectives

To address the research questions, each research strand has its own objectives.

1) Objective of quantitative strand:
    - Assessment of availability and agreement of facility-specific guidelines
2) Objective of the qualitative strand:
    - Experience of clinicians using facility-specific guidelines for the treatment of infectious diseases
3) Objective of the mixed methods strand:
    - What are structural barriers to implement antibiotic guidelines despite the availability of facility-specific guidelines?

3.1. Quantitative Outcomes

3.1.1 Assessment of availability and agreement of facility-specific guidelines

3.1.1.1. Survey of Antibiotic Guidelines

i. Identifying availability of local guidelines

ii. Identifying availability of key elements of guidelines (diagnostic approach, choice of first line regimen, dosage, treatment duration)

iii. Agreement with international guidelines for selected bacterial infections

Sites participating in the REVIVE trial will provide their current guidelines for the empirical management of infectious diseases in adults. For each site, information about the availability of antibiotic guidelines will be assessed and baseline information (e.g., year of publishing, number of pages) will be extracted. The guidelines will be screened for the recommended diagnostic approach, choice and dosage of antibiotic substance and treatment duration for key bacterial infections. Agreement of the provided information with the WHO AWaRe guidelines will be assessed.

The three key bacterial infections considered in this study are community-acquired (CAP) and healthcare-acquired pneumonia (HAP), and urinary tract infections (UTI). These infections are included due to their relevance on antimicrobial resistance, antibiotic prescription, or associated mortality, especially in low- and middle-income countries (8, 54, 55)

3.2. Qualitative Outcomes

3.2.1 Experience of clinicians using facility-specific guidelines for the treatment of infectious diseases

3.2.1.1. Semi-structured interviews

Semi-structured interviews with people treating infections to explore:

- Use of guidelines in clinical care

- Appropriateness of guidelines for the facility and clinical setting
- Disagreement with guideline recommendations
- Challenges of implementation in clinical care

Sites which provide facility-specific antibiotic guidelines for the quantitative part of the proposed study will be utilised to assess the qualitative objective. Remote semi-structured, one-on-one interviews will be conducted with one infectious disease or, if not available, an internal medicine physician at each site, focusing on their views on and experience about agreement and quality, the use of facility-specific guidelines, and their limitations. The emphasis is on describing the lived experiences of the clinicians.

3.1. Mixed-methods outcomes

3.1.1 Linkage of facility-specific guidelines and experiences

3.1.1.1. Identifying barriers of implementation of facility-specific guidelines

Experience of sites with facility-specific antibiotic guidelines will be assessed to investigate any barriers to their implementation and obtain a more comprehensive insight into the agreement with the WHO AWaRe book and limitations of these documents in sub-Saharan Africa.

4. Methods

4.1. Study overview

4.1.1 Set up

The proposed study will be conducted as a mixed-methods research project. An outline of the design and set up is delineated in this section. An overview on mixed-methods research, justification for the proposed study design and key dimensions of this methodology is discussed in the following sections.

This study employs a sequential explanatory mixed-methods research designs (52, 56). This approach comprises a quantitative first part, followed by a qualitative second part. Data obtained and analyzed in the first part will inform participant selection for the second part. This approach is referred to as *follow-up explanation variant*, or as *participant selection model* (57). The emphasis of the overall design is on the quantitative part, whereby the qualitative part will help to get a better understanding of the findings of the quantitative part (52).

After conducting the qualitative strand of the study, the information will be analyzed to address the mixed-methods question. The design is displayed in figure 1. Before launching the quantitative part, a vanguard phase was conducted to investigate the feasibility of the overall study design. Details of the vanguard phase are presented at the end of the thesis.

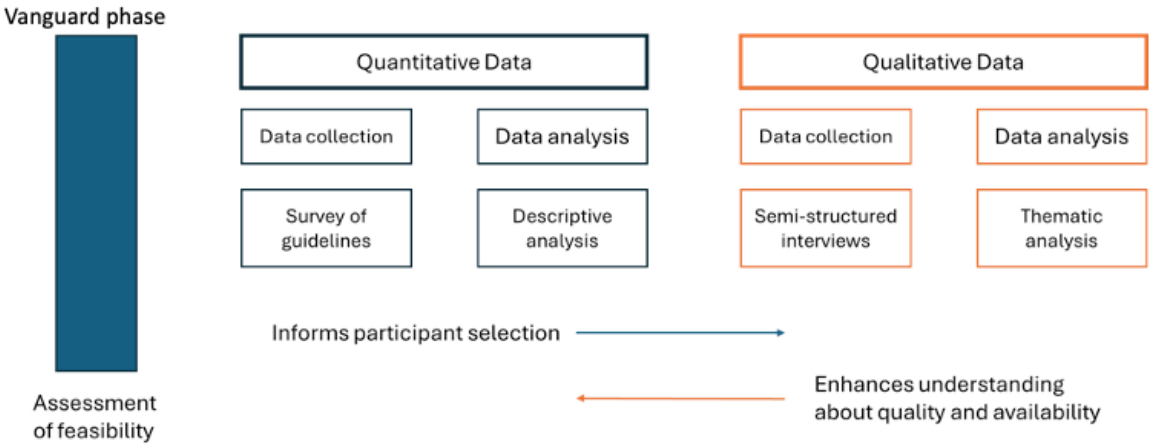

***Figure 1**: Overview of the study scheme of the mixed-methods research study*

4.1.1.1. Vanguard phase

A vanguard study of the quantitative data was conducted to investigate the feasibility of the proposed trial design. Assessing the availability and agreement of guidelines in a smaller set provided preliminary information about the quantitative findings but also informed the feasibility of the qualitative strand. Based on the vanguard findings modification of the sampling strategy or assessment of agreement are needed to conduct the complete mixed-methods study. This is discussed in more detail in section 6.

4.2. Justification of Design

4.2.1 Overview of Mixed-Methods

Mixed-methods research combines the qualitative and quantitative research paradigms, bridging the differences between both (58). It is worth noting that mixed-methods research is not uniformly defined but includes the mix of qualitative and quantitative research elements, which can occur at different points of the conduct of a study including philosophical and theoretical viewpoints, data collection, and analysis (52). In some

publications, especially in the earlier literature, mixed methods research is also referred to as ‘multi-method’, ‘combining methods’ or ‘multiple methods’ (59, 60). However, these terms refer often to the use of more than one qualitative or quantitative research method in a single project (61, 62).

Qualitative and quantitative research paradigms vary in several aspects, including different methodological and philosophical concepts to address a research question (63).

Quantitative research strives to establish cause-effect relationships, using limited number of variables and a large number of participants, and generalizes the findings to a larger population (64-66). However, the complexity of information gets either not completely represented or ignored (63).

Qualitative research uses information to understand beliefs, experiences, or real-life situations of a small number of participants (65, 67). This method is prone to the introduction of bias because the researchers act themselves as a research instrument, including personal experiences influencing interpretations while collecting and analyzing data. In addition, qualitative research lacks generalizability (68, 69).

The overarching idea of mixed-methods research is not only to overcome the shortcomings of one methodology with strengths of the other methodology and vice-versa (70). In the end, mixing quantitative and qualitative methodology should provide a more comprehensive exploration of the research phenomena and provide results which closely reflect reality (71, 72).

In 1989, Greene and colleagues summarized five main purposes for mixed-methods evaluation designs: Triangulation, Complementarity, Development, Initiation, Expansion (Table 1). Over the years, items were added, or their description modified. However, more recent data demonstrates that these purposes are still widely mentioned in contemporary mixed-methods research (56, 57, 68, 73).

***Table 1**: Purposes of mixed-methods evaluation designs. From: Greene, 1989 (73)*

Purpose	Aim	Rationale
Triangulation	Convergence, corroboration, correspondence of results from the different methods	Increase validity of constructs and inquiry results by counteracting or maximizing the heterogeneity of irrelevant sources of variance attributable to inherent method bias, inquirer bias, bias of substantive theory, biases of inquiry context
Complementarity	Elaboration, enhancement, illustration, clarification of the results from one method with the results from the other method	Increase the interpretability, meaningfulness, and validity of constructs and inquiry results by both capitalizing on inherent method strengths and counteracting inherent biases in methods and other sources
Development	Use the results from one method to help develop or inform the other method, where development is broadly construed to include sampling and implementation, as well as measurement decisions	Increase the validity of constructs and inquiry results by capitalizing on inherent methods strengths
Initiation	Discovery of paradox and contradiction, new perspectives of frameworks, the recasting of questions or results from one method with questions or results from the other method	Increase the breadth and depth of inquiry results and interpretations by analyzing them from the different perspectives of different methods and paradigms

Expansion	Extend the breadth and range of inquiry by using different methods for different inquiry components	Increase the scope of inquiry by selecting the methods most appropriate for multiple inquiry components

Besides assessing information on facility-specific guidelines, capturing the experience and perception of clinicians using these guidelines is key to get a comprehensive understanding of this stewardship intervention. By conducting a mixed-methods research study, the meaningfulness of the study is increased, and the qualitative part will complement the quantitative part ('Complementary'). Also, including results of the quantitative part in the qualitative part will help to increase the validity and impact of the study ('Development').

4.2.1.1. Benefits of Mixed-Methods Studies

As outlined above, not all research questions can be fully addressed using either quantitative or qualitative research methods alone. Authors argue that mixed methods research provides a more comprehensive answer to the research questions and goes beyond adding up two separate parts (62).

Moreover, research teams are not limited to a specific set of skills and elements which allow for a more flexible and holistic application of methodological approaches (52). Also, based on the purpose of the mixed-methods research project and the chosen design, specific aims can be achieved, such as the development and application of research instruments. This would not be possible without mixing qualitative and quantitative research.

However, a clear justification for the need for a mixed-methods study is essential, since this approach is generally resource intensive and time consuming (52, 62).

4.2.1 Rationale for using Mixed-Methods in this Study

Adherence to antibiotic guidelines has been shown to improve patient outcomes in certain settings (45). Providing information on indication, choice, and duration of antibiotic administration might optimize antimicrobial consumption. Infectious disease societies suggest the development of facility-specific guidelines for the treatment of common infectious diseases to standardize prescribing practices in view of local epidemiology (74). The availability of diagnostic tools, local antibiograms describing the microbiology of commonly-encountered isolates, and antibiotic supplies are existing challenges in low- and middle-income countries, and interfere with the development and adherence to treatment recommendations (75). This also might be addressed in facility-specific guidelines and highlights their importance.

Previous research focused on the comparison of national antimicrobial treatment guidelines in the African Union (many of which did not meet international standards) and concluded that member states need to include locally derived evidence (76). Data about availability of guidelines on a healthcare facility level was limited.

Using a quantitative paradigm to assess the availability and agreement of the guidelines with the WHO AWaRe book and a qualitative paradigm to enhance the quantitative findings with experiences of clinicians using facility-specific guidelines will provide in-depth information about antibiotic treatment guidelines in sub-Saharan Africa. If both research questions are addressed separately, conclusions will either lack insights in the experience using these guidelines or lack information about availability and agreement of the guidelines.

Using a mixed-methods research design does not only answer both research questions but provides a more comprehensive picture of the studied phenomena.

4.2.2 Dimensions of Mixed-Methods Studies

4.2.2.1. Worldviews

Philosophical and theoretical foundations of a study are important and shape the research process (52). The nomenclature is not consistently defined, and terms such as 'paradigm', 'theoretical lens', and 'worldview' are often used interchangeably to describe beliefs and assumptions that inform researchers (52, 57). In this work 'worldview' will be used to refer to the first level of philosophical assumptions, the broadest level in the process of developing a research study. Further levels include the theoretical lens (stances), methodological approach (design), and methods of data collection (techniques) (52).

Four major worldviews exist in the field of mixed methods research, namely postpositivist, constructivist, transformative, and pragmatist. All these worldviews differ in philosophical elements, including their underlying ontology, epistemology, axiology, methodology and rhetoric. Therefore they are often linked with specific research paradigms (52). Table 2 provides an overview on the worldviews.

Table 2: *Overview about worldviews. From: Creswell and Clark, 2017 (52)*

Philosophical Question	**Postpositivism**	**Constructivism**	**Transformative**	**Pragmatism**
Ontology (What is the nature of reality?)	Singular reality (e.g., researchers reject or fail to reject hypotheses)	Multiple realities (e.g., researchers provide quotes to illustrate different perspectives)	Multifaceted and based on different social and cultural positions (e.g., researchers recognize different power	Singular and multiple realities (e.g., researchers test hypotheses and provide multiple perspectives)

			positionalities in our society)	
Epistemology (What is the relationship between the researcher and that being researched?)	Distance and impartiality (e.g., researchers objectively collect data on instruments)	Closeness and subjectivity (e.g., researchers visit with participants at their sites to collect data)	Collaboration (e.g., researchers actively involve participants as collaborators, build trust, and honor participant standpoints)	Practicality (e.g., researchers collect data by "what works" to address research question)
Axiology (What is the role of values?)	Unbiased (e.g., researchers use checks to eliminate bias)	Biased (e.g., researchers actively talk about and use their personal biases and interpretations)	Based on human rights and social justice for all (e.g., researchers begin with and advocate for this premise)	Multiple stances (e.g., researchers include both biased and unbiased perspectives)
Methodology (What is the process of research?)	Deductive (e.g., researchers test an a priori theory)	Inductive (e.g., researchers start with participants' views and build "up" to patterns, theories, and interpretations)	Participatory (e.g., researchers involve participants in all stages of the research and engage in cyclical reviews of results)	Combining (e.g., researchers collect both quantitative and qualitative data and mix them)
Rhetoric (What is the language of research?)	Formal style (e.g., researchers use agreed-upon definitions of variables)	Informal style (e.g., researchers write in a literary, informal style)	Advocacy, activist-oriented (e.g., researchers use language that will help bring about change and advocate for human rights and social justice)	Formal or informal (e.g., researchers may employ both formal and informal styles of writing)

Based on the chosen study design, a mixed-methods research study can include and mix various worldviews across the different strands (71). However, some argue that the beliefs of both research strands cannot be combined and are mutually exclusive (77). Authors also state that worldviews are belief systems and therefore a researcher might not be able to hold

more than one worldview (77). Despite this debate, recent research supports the integration of multiple worldviews (78). Using different worldviews in one study is also referred to as pluralistic position (79).

Given the proposed study design, different and distinctive worldviews can be applied to address the research questions in the most appropriate way for each strand.

Postpositivism assumes that there is only one singular reality, researchers collect data objectively, try to reduce bias to a minimum and test an a priori theory using a formal style of rhetoric. In contrast, constructivism beliefs that multiple realities exist, researchers are biased and are involved in data collection. The findings are inductive and start with participants view and build up patterns and are reported in an informal style (52, 57).

For the quantitative part, a postpositivism worldview will be applied to provide detailed, unbiased, observations and measures of variables about the guidelines. In the second part, the qualitative strand, a constructivism worldview will be applied, offering inclusion of multiple realities and using an inductive process to include the viewpoints of the participating clinicians in its completeness.

In theory, a pragmatic worldview could serve as an alternative overarching approach for the research question of this study, which allows to assess what works best and combines philosophical elements of postpositivism and constructivism. However, this approach is more appropriate for convergent designs when both strands get conducted and analysed at the same time and data are mixed (52). The fourth above-mentioned worldview is transformative, which is commonly used for studies addressing social justice and human

rights. As this focus does not align with the objectives of this study, it is not considered an appropriate approach (52, 57).

4.2.2.2. Mixed-Methods Study Designs

Several mixed-methods research designs, which refer to the set-up of the qualitative and quantitative strands, have been described in the last years. However, their definitions changed over time. Based on this, multiple approaches for typology of mixed-methods research designs have been proposed and in recently published literature the following examples have been listed as core designs (56, 57): convergent parallel (sometimes also referred to as triangulation), exploratory sequential, explanatory sequential and embedded/nested designs (65, 80). Others such as the sequential transformative design were described earlier but this typology was dropped over time (52).

Besides the differences in how the study gets conducted, these designs also have differences regarding the research purpose, interaction of both strands, timing, and their weight (71). The decision to choose a design should be led by the underlying research question (52).

The purpose of the mixed-method approach in this study is to complement the quantitative data with the qualitative data. Therefore, an explanatory sequential mixed-methods research design seems to be the most appropriate choice. Moreover, data about availability and agreement with international standards of antibiotic guidelines in healthcare settings in sub-Saharan Africa on a facility level are limited and therefore the quantitative part also enables us to create the needed sampling frame to identify participants for the qualitative

strand. This is referred to – besides other typology - as explanatory participant selection design in the literature (52).

The other two commonly described designs, exploratory sequential design and convergent design vary widely from our approach and do not fit our research question.

The exploratory sequential design has the inverse sequence of research paradigm strands compared to the explanatory sequential design. It starts with the qualitative strand first, followed by a quantitative one. This design focuses in most cases on the qualitative strand, which serves to design the quantitative part of the study. This approach does not fit our research question and does not provide any information about the possible sampling frame. In this thesis, availability of facility-based guidelines and their agreement will only be identified after the data collection of the quantitative strand (52).

The convergent design, which is also described as triangulation, concurrent or parallel design, does not fit the needs of our research question. As a concept, both strands are conducted at the same time and the collected data will be compared or combined to provide a more complete understanding of the problem. Even if it would be a suitable design theoretically and enhance the knowledge about the quantitative data, we would lack the availability of the quantitative data to further explore it in the qualitative part. Also, we are not intending to combine or compare the two data sets.

4.2.2.3. Theoretical drive and weight of strands

Quantitative and qualitative strands in mixed-methods research can have either the same weight, or one is deemed to be more important than the other strand.

This unequally distributed weight of strand is also highlighted by the fact that some authors consider that one strand leads the theoretical drive of the study, based on its either inductive or deductive approach (81). In this scenario, the driver is referred to as '*core',* the other strand is called '*supplement'* (82). The *'core'* component addresses the research question and is conducted as rigorously and complete as possible, so that this strand can stand alone. In contrast to this, the supplement component is conducted less rigorously and cannot stand alone. The *'supplement'* serves to enhance the *'core'* strand. Being unaware of the theoretical drive, and not having identified *'core'* and *'supplement' a priori*, might ultimately threaten validity of the mixed-methods research design (81).

The approach of the theoretical drive has been a subject of discussion. Information on the extent and approach of how the *'supplement'* strand can be conducted in a less complete and rigorous manner is limited. Furthermore, the 'core' component is impacted by the research question, challenging the application of this concept if several research questions exist (56). Also, it interferes with the idea that the additional benefits of mixed-methods research are based on mixing different methodological paradigms, which are conducted as rigorously as if they were done in a non-mixed-methods study (52, 56).

For the proposed research the quantitative part has slightly more weight (71). Even if the weight might distributed quite evenly, the qualitative strand in this study focuses on a small, highly selected population, to enhance the quantitative findings (83). However, we aim to conduct both strands as rigorously as possible.

4.2.2.4. Notation

A notation system exists to indicate the differences of research paradigm, timing and weighting of the strands (84). By using the abbreviation 'QUAN/quan' and 'QUAL/qual' for the quantitative and qualitative strand respectively, the sequence of the strands is represented by a plus sign (+) if conducted parallel and an arrow (→) if conducted sequentially. Capital letters refer to the strand with more weight. Therefore, the notation of the proposed study is QUAN → qual.

4.2.2.5. Integration

Integration of data derived from both research strands in mixed methods studies has many potential gains and is considered the central defining characteristic of mixed-methods studies (85). Incomplete or missing integration jeopardizes the merit of conducting a mixed-method research project and might result in inappropriate conclusions (86, 87). Several levels exist where the integration can occur, including at the study design, methods, reporting or interpretation of the results (88).

Approaches for data integration at the design level are based on the core mixed-methods research designs, and their complex applications. Connecting, building, merging, or embedding are different approaches to link both methodological paradigms and achieve integration at the method level. Integration at the interpretation and reporting level can occur through different approaches: narrative, data transformation, or a joint display (87, 88).

For the proposed study, integration will occur at the design, method, and data interpretation levels using different approaches. The concept of a sequential design provides the opportunity to build one strand on the other for integration at the design level. The study will

sample participants for the qualitative part within the healthcare facilities who provided guidelines in the quantitative part (connecting approach). Also, the interview question will be adjusted based on the findings in the quantitative part. This process can be considered as part of the building approach on the method level of integration (88). In addition, a contiguous narrative approach will be used to report and interpret findings in one single report, but in different sections (89).

4.2.3 Examples of Studies investigating Antimicrobial Stewardship using a Mixed-Methods Design

Many researchers have been investigating various antimicrobial stewardship interventions using a mixed-methods research design. A PubMed search using the terms '(antimicrobial stewardship) AND (mixed methods)' provided a total of 297 results, with an increase from 2 in 2011 to 61 in 2024.

To provide an overview on the most recently published studies, this section of the thesis summarizes all mixed-methods studies listed for 2024 in PubMed. Table 2 shows the extracted data.

All 61 studies listed in 2024 were screened and 30 studies could be identified applying a mixed-methods research design. Two of these 30 publications were study protocols, one study was a pilot study, one was labeled a feasibility study, one was a systematic review using a mixed-methods approach and combined quantitative and qualitative findings.

Studies were conducted in at least 19 different countries. One study, investigating pharmaceutical development goals, indicated that it was conducted across 21 countries in

five WHO regions, but did not specify the countries. The mixed-methods systematic review was not allocated to any country. The United Kingdom represented the country with most studies conducted (n=4). Previous research stated that mixed methods research is a common methodology in the UK, which might also be reflected by this finding (59). Five out of the 30 studies were conducted in Africa (17%) and a total of 12 studies (40%) report findings from low- or middle-income countries as defined by the Organisation for Economic Co-operation and Development (90).

Study designs were often poorly described and a clear statement about the design was only provided by nine articles. The majority of these studies used an 'explanatory sequential' approach (n=6, 66%), followed by 'convergent design' (n=2, 22%) and 'embedded design' (n=1, 11%). This reflects the importance of these so called 'core' mixed-methods design. The embedded design is considered as core design by some authors, especially in evaluation studies and social science studies, but is not considered any longer as a core design by other research groups (52, 91). One study is a mixed-methods systematic review. Of the remaining 20 primary studies without clearly indicated design, nine, seven, and four studies were judged to be most likely 'convergent', 'complex applications of a core design' and 'sequential explanatory' studies, respectively. Overall, only one study used a notation to represent the sequence and weight of the used strands.

Several quantitative methods were used to collect data, whereby 47% (n=14) used surveys, either as a single tool or combined with other data collection methods. Other data collection methods included questionnaires, review of medical charts and prescription data, or focus groups. Qualitative data was mainly collected through semi-structured interviews or focus

groups (18/30 studies: 60%). In addition, six studies used interviews, but did not state exactly what kind of interviews. Other listed qualitative data collection tools included reflection, structured interviews, observations, group conversations and surveys.

Participants approached in the qualitative strand included veterinarians, patients, healthcare workers, pharmacists, farmers, veterinary drug store owners, students, member of stewardship teams and stakeholders of national professional bodies regarding pharmacy and members of medicine and therapeutic committees. This also reflects the broad range within the One-Health approach, which can be tackled by mixed-methods studies.

This focused literature review highlights the increasing interest in mixed methods research in antimicrobial stewardship research at several levels of antimicrobial stewardship, including veterinary medicine and different key stakeholders. Mixed-methods design is often applied using the explanatory sequential design, which aims to explain quantitative data with qualitative findings to enhance understanding. Quantitative data regarding antimicrobial resistance are collected for several reasons, including surveillance or to inform on the impact of stewardship intervention. The increasing number of mixed-methods studies, and the most frequently chosen design, might reflect the need to get a deeper understanding of experiences of individuals involved in antimicrobial stewardship. Moreover, this need seems to exist globally and is independent of the economic status. Nevertheless, the quality of reporting the methodological approach and mixed-method designs in this set of studies was limited, and key features such as used design are only clearly stated for a minority of papers.

Pilot or vanguard phases seem to be a rare methodological approach in mixed-methods studies, since only one of the identified studies is labeled as pilot, another one as feasibility trial. However, this thesis includes a vanguard phase, which is important to assess the overall feasibility of the proposed main study and provide information about the collected outcome measures.

None of these studies analyzed the availability of guidelines, nor included more than four countries in sub-Saharan Africa to provide a comprehensive overview, as suggested by the proposed study.

***Table 3**: Characteristics of mixed-methods studies investigating antimicrobial stewardship intervention listed in PubMed in 2024*

Author	**Country**	**Design**	**Quantitative**	**Qualitative**	**Population for qualitative strand**
Abbs (92)	UK	Complex application of core design (Pr)	Randomised controlled trial	Interviews	Trial participants and treating clinicians
Aqqad (93)	21 countries	Sequential explanatory	Survey	Structured interviews	Stakeholder national professional bodies
Baudet (94)	France	Most likely convergent	Questionnaire	Interviews	Stewardship teams
Bedford (95)	Argentina	Sequential explanatory	Survey	Focus group	Veterinarians and farmers
Beynon (96)	Tanzania, India, Kenya, Senegal	Complex application of core design	Trial	Interviews, observations	Healthcare workers
Cassel (97)	USA	Most likely convergent	Surveys	Group conversations	Veterinarians
Chukwu (98)	Nigeria	Most likely convergent	Questionnaire	Focus group	Healthcare workers
Constantinescu (99)	Canada	Sequential explanatory	Audit cards	Semi-structured interviews	Healthcare workers

Debnath (100)	India	Convergent	Prescription and biological samples	interviews	Healthcare workers
Flett (101)	UK	Complex application of core design (Pr)	Randomised controlled trial	interviews	Patients and Healthcare worker
Hamilton (102)	UK	Convergent	Survey	Survey	Antimicrobial stewardship nurses
Hassan (103)	Qatar	Convergent	Survey	Semi-structured	Clinical nurses in ASP
Jokanovic (104)	Australia	Most likely sequential explanatory (P)	Questionnaire	Semi-structured interviews	Stewardship teams
Kimbowa (105)	Uganda	Sequential explanatory	Questionnaire	Interview	Members of the medicines and therapeutic committees
Kovacevic (106)	Serbia	Most likely complex application of core design	Surveys	Focus groups	Veterinarians
Lim (107)	Australia	Sequential explanatory	Survey	Reflection	Pharmacists
Misailovski (108)	Germany	Exploratory sequential	Survey, systematic review	Semi-structured interviews	Healthcare workers

Morang'a (109)	Kenya	Most likely convergent	Focus group	Focus group, interviews	Veterinarians, farmers, veterinary drug store workers
Qureshi (110)	USA	Most likely convergent	Survey	Semi-structured interviews	Neonatal intensive care unit site leaders
Ross (14)	Uganda	Not described, most likely complex application of core design	Point prevalence	Semi-structured interviews	Key stakeholder of hospitals
Rutten (111)	Netherlands	Most likely complex application of core design	Data of a RCT, questionnaires	Semi-structured interviews	Health-care workers
Schaad (112)	Switzerland	Convergent	Survey	Survey	Primary care physicians
Sinto (113)	Indonesia	Sequential explanatory	Surveys	Focus group	Stewardship teams
Surendran (114)	India	Most likely convergent	Chart reviews	Observations and Semi-structured interviews, Case study	Healthcare workers
Taisne (115)	France	Most likely sequential explanatory	Questionnaire	Focus group	Students (Pharmacology)

Vaughn (116)	USA	Sequential explanatory	Surveys	Semi-structured interviews	Stewardship teams
Vinh Nguyen (117)	Vietnam	Explanatory sequential	Surveys	Focus groups and interviews	Pharmacists
Wang (118)	Online	Mixed-methods systematic review			
Watson (119)	Australia	Most likely convergent	Survey	Semi-structured interviews	Healthcare workers
Weir (120)	UK	Most likely complex application of core design (F)	Chart review	Semi-structured interviews and non-participant observations	ePAMS+[a] users

[a] ePrescribing-based Anti-Microbial Stewardship complex intervention; Pr = Protocol, P=Pilot, RCT= Randomized controlled trial, (F) Feasibility

4.3. Projected Timeline

The projected timeline of the proposed mixed-methods study will be as following (Figure 2):

- Vanguard study: December 2024 - February 2025
- Mixed-method study: September 2025 – April 2027
    - Quantitative strand: September 2025 – March 2026
        - Data collection: August 2025 – February 2026
        - Analysis: January 2026 – March 2026
    - Qualitative strand: June 2026 – February 2027
        - Data collection June 2026 – November 2026
        - Analysis: August 2026 – February 2027
    - Interpretation and reporting of results: February 2027 – April 2027

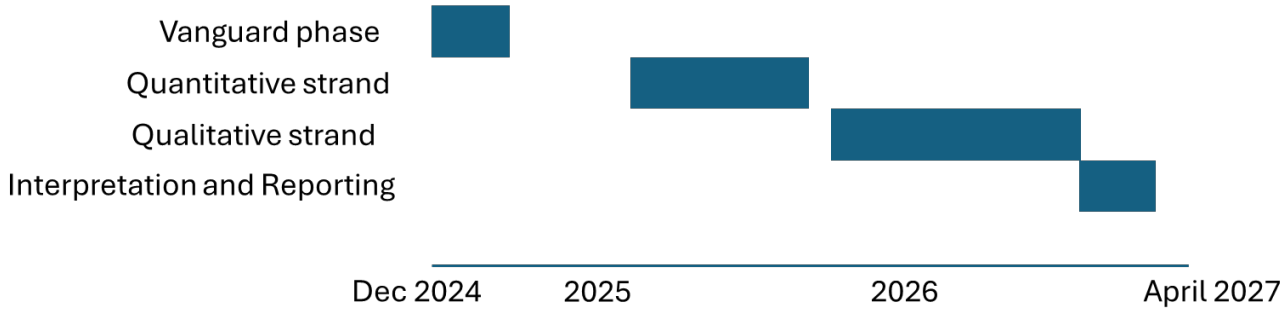

***Figure 2**: Timeline of the proposed mixed-methods research study*

4.4. Inclusion/Exclusion criteria

4.4.1 Quantitative strand

All sites participating in the REVIVE trial will be included in the survey. The REVIVE trial includes clinical sites across sub-Saharan Africa (target: 60 trial sites), which are involved in the treatment of patients with advanced HIV disease. Sites can be outpatient clinics, but

most are affiliated with a hospital. There are no exclusion criteria for sites to participate in the mixed-methods study.

4.4.2 Qualitative strand

All PIs of sites providing facility-based guidelines in the quantitative strand will be invited to participate in the qualitative strand. If the PI is not an infectious disease or internal medicine physician, they will be asked to provide a representative fulfilling this inclusion criteria. Individuals who refuse to participate or do not provide written consent for the participation in the semi-structured interviews will be excluded.

4.5. Recruitment and Sampling Strategy

Different sampling strategies can be used for mixed-methods research without being restricted to either quantitative or qualitative research methodology. Therefore, especially in the setting of a sequential design, both strands might have different sampling strategies (52, 121). Both here suggested sampling strategies – convenience and purposeful/purposive – are non-probability (also called non-random) sampling strategies, meaning that participants are not selected randomly (122).

4.5.1 Quantitative strand

A convenience sampling approach will be used for the quantitative strand and include all sites participating in the REVIVE trial.

Convenience sampling is one of several non-probability sampling strategies. Authors often describe it as a process where participants are selected based on their accessibility (123, 124). However, other mention that convenience sampling refers to a strategy where the study

gets announced and potential participants might self-select to participate (125). By including participants which meet inclusion criteria and are easily accessible by the research team, there are limited feasibility concerns, and the strategy is cost effective. The strategy has an increased risk to introduce selection bias, and the sample might not be representative of the complete population potentially limiting the generalisability of the findings (122, 126).

Based on the research question and the trial setting, convenience sampling is the most suitable approach for the quantitative strand. Using the REVIVE trial as sampling frame offers the unique opportunity to access healthcare facilities dealing with infectious diseases across sub-Saharan Africa and to include clinicians in the process, which can be beneficial for the participant selection for the qualitative part. Moreover, the REVIVE trial has selected its study sites with the goal of a broad representation across sub-Saharan Africa. Therefore, we assume that our collected data is representative of healthcare facilities in this region.

A different approach, which could be chosen for sampling for the quantitative strand would be snowball sampling (122). The concept of this approach is that already enrolled subjects recruit or provide information about additional potential prospective subjects. In a setting where the extend of the sampling frame is unknown, especially if research is conducted in hard to reach or stigmatised populations, this is highly beneficial and seems superior to purposive sampling (127). REVIVE principal Investigators (PI) could recruit colleagues at other healthcare facilities which would be suitable for the trial. However, the REVIVE trial provides a large number of sites and covers a vast geographical area across sub-Saharan Africa so that any extension beyond these might not be needed to identify sites for the

qualitative strand. Additionally, the vanguard phase will help to assess the number of available guidelines, which also informs on the sampling approach.

4.5.2 Qualitative strand

The results of the quantitative part will help to select participants for the qualitative part. A purposeful sampling method will be used, which allows the identification and selection of participants with specific characteristics (128). Participants will be included based on the availability of facility-specific antimicrobial guidelines, which helps to identify participants who are 'information rich' (128).

Based on the research question we will include all sites who provide facility-specific guidelines. This reflects homogenous purposeful sampling, because the study participants share several identical features such as participating in a trial, having interest in research and corresponding infrastructure, availability of facility-specific guidelines and a similar professional background as physicians (52). This is also referred to as 'criterion-I' sampling, because a clear inclusion criteria (availability of facility-specific guidelines) selects the participants (128). Other purposeful sampling approaches include maximum variation sampling, extreme or deviant case sampling, or the intensity sampling (52, 77, 128). These approaches aim to include specific set of participants which are either the most extreme participants (extreme or deviant case), or to cover the complete range of participants (e.g., maximum variation).

If the number of sites with facility-specific guidelines exceeds the preliminary defined sample size of about 12 participants for thematic analysis, which is estimated to achieve

saturation, participants will be approached based on a random selection within the sample identified using a purposeful sampling strategy (random purposeful sampling). All facilities with a facility-specific guidelines will construct the sample frame, and participants will be randomly selected using a computer-generated sequence. This will ensure representativeness of the complete group (77, 128).

4.5.3 Sample size

Based on the chosen sequential explanatory design the sample sizes can vary for the quantitative and qualitative part since it is not the intention to merge or compare the data (52).

Based on the restriction to the REVIVE trial, a total of 60 sites will be asked to provide guidelines for the quantitative part. To achieve saturation in the qualitative part, we estimate 12 participants are needed based on the chosen design, underlying framework, selection of participants and analysis approach. However, the sample size for the qualitative part is only an initial estimate and may be adjusted during the study, to achieve complete insights into the research question. Sample size and saturation in qualitative studies are discussed below in more detail.

4.6. Data collection and analysis

In explanatory sequential designs, data collection occurs at two timepoints. First, during the quantitative strand and second during the qualitative strand. However, since data of both strands are not independent, a three-step process is applied for the complete study:

1) Data collection of quantitative data and analysis of the collected data

2) Assessment if and how data from the quantitative strand will inform the qualitative strand

3) Data collection of the qualitative strand and analysis of the collected data.

Data will be analyzed using a strand specific analysis technique and then linked to each other (77).

4.6.1 Quantitative

4.6.1.1. Document collection

All PIs who oversee healthcare facilities participating in the REVIVE trial will be contacted, informed about the study purpose, and asked to provide the guidelines used at their site to manage infectious diseases. PIs not involved in clinical care will be asked to forward the request to another person in charge.

4.6.1.2. Data extraction, comparison, and analysis

Provided guidelines will be saved and data will be extracted into a spreadsheet for analysis. The extracted data will include the following items grouped in two categories:

1. Baseline characteristics: Year of publication, authority publishing the guideline, number of pages
2. Disease specific information:
    - Community-acquired pneumonia
    - Hospital-acquired pneumonia
    - Urinary tract infection

Data will then be analysed regarding the availability of facility-based guidelines (binary, yes/no). Guideline agreement will be assessed as overlap with information of the disease

specific guidance in the WHO AWaRe guidelines. Each item of every single guideline will be compared to the WHO AWaRe guidelines. Following items are extracted (total: 11)

Community-acquired pneumonia (5 items)

- Diagnostic approach (4 items)
    - Clinical presentation, Microbiology Tests, Imaging, Other treatment considerations
- First line treatment and treatment duration (1 item)

Hospital-acquired pneumonia (non-ventilator associated pneumonia (non-VAP)) (4 items)

- Diagnostic approach (3 items)
    - Clinical presentation, Microbiology Tests, Imaging
- First line treatment and treatment duration (1 item)

Urinary-tract infection (uncomplicated) (2 items)

- Treatment indication (1 item)
- First line treatment (1 item)

The agreement of these items with the WHO AWaRe book will be rated as follows:

- Not addressed (0 points): Information for the respective items is not found within the guidelines.
- Agreement (1 point): The extracted data for an item in the country guideline matches or is more extensive than the AWaRe guideline recommendations. In case of

antibiotic treatment only exact matching is counted as agreement since misuse is a driver of antibiotic resistance.

- Partial agreement (0.5 points): The provided information includes at least partially the same information as WHO but does not cover all aspects.
- No agreement (0 points): Facility-specific recommendation is not in line with the AWaRe guidelines.

Points will be added up for each guideline. Results will be displayed with appropriate graphs (e.g., bar graph).

4.6.2 Qualitative

Qualitative data will be collected in cooperation and coordination with a scientist with expertise in qualitative research methodology to ensure a high quality of the work, once the quantitative work has been completed. Mixed-methods research is complicated by the fact that two research paradigms are addressed, the qualitative and quantitative, which are based on different foundations. Therefore, there is benefit to work in teams to cover both research areas (52).

Before proceeding with the interviews, baseline characteristics of the participants will be collected (e.g., age, medical board certifications, work experience).

4.6.2.1. Interviews

Lived experiences of physicians regarding barriers and possible facilitators to implement antibiotic guidelines in sub-Saharan Africa will be collected in semi-structured interviews. All participants will provide a written informed consent. The interviews will be conducted

through a video call using a software (e.g., 'Microsoft Teams' (Microsoft Corporation, Redmont, USA)). All calls will be recorded and transcribed, using software-integrated tools. Transcripts will be reviewed and modified accordingly. All recordings and transcripts will be saved on a secured server, and access to the file will be password protected.

Data storage and analysis will be supported using a qualitative data analysing software such as MAXQDA (Verbi Software, Berlin, Germany) or QDA Miner (Provalis Research, Montreal, Canada).

4.6.2.2. Interview protocol

The interview protocol refinement framework is used to develop the final semi-structured interview (129). This framework consists of four phases, with the final step involving the testing of the research instrument before its use in the study.

A mapping matrix and an outline of draft questions is provided in the appendix. The instrument will be finalized after the analysis of the quantitative data, so that questions might be modified to reflect unexpected findings.

A script will be developed based on the final questions to facilitate the conversation. The script will be piloted within the study team before its use.

4.6.2.3. Thematic analysis

Data analysis will be guided by a general-purpose thematic approach, which can be used to assess experiences of people and their perceptions and ideas on a given topic (130). One of its favorable characteristics is the possible wide range across frameworks, study questions, designs, and sample sizes, whereby it seems to match well to the constructivism worldview

(131). Sandelowski and Barroso described a continuum of qualitative research methods, reaching from analysis with no significant data transformation on one side to methods using deep interpretation and transformation of data on the other side (132). Kiger and Varpio put thematic analysis in the middle of this continuum, because it goes beyond describing and categorizing data, but is not highly interpretive and not used to develop theories (131).

The general-purpose thematic analysis is an inductive process, whereby the data is approached to look for patterns and themes to interpret them for meaning. The thematic analysis is commonly used for semi-structured interviews (130) and is applicable and feasible for this proposed mixed-methods research. Another option could be content analysis, which assesses the frequency, trends and patterns of the words used.

A thematic analysis of the transcript will be performed, following the outline for reflexive thematic analysis (133). This is also similar to other frameworks for thematic analysis (134). After familiarising oneself with the data, code generation, theme identification, reviewing and definition will lead to the creation of the final report. The identified themes will provide insights into the barriers against and facilitators promoting implementation and usage of existing guidelines for treatment of infectious diseases (133, 135).

4.7. Ethics

Data about practical guidance for mixed-methods research is limited, but indicates that research ethics training often does not cover this aspect in a sufficient manner (136). Ethical challenges arise throughout the complete mixed-methods research process and are based on the interplay between both research strands. Moreover, these issues can emerge and

amplify throughout the conduct of the research (137). Problems exist around obtaining informed consent in sequential designs using only a specific subset of participants for in-depth interviews without a confidentiality breach (138). However, the current proposed study does not collect any sensitive or personal information in the quantitative strand, and selection of the subset for the qualitative part will be based on availability of local guidelines. There will not be any harm, or benefit, in participating in any of these two research strands.

All sites will be informed about the purpose of requesting their guidelines.

Ethical approval will be obtained for the qualitative strand after the quantitative strand is completed. The ethical approval of the Hamilton integrated Research Ethic Board and of each of the applicable local agencies, which is responsible for the interview of participants, will be obtained prior to conduct. This will provide the option to include any additionally collected information or findings of the quantitative strand, which might influence the qualitative part. Therefore, the ethical submission will be more tailored towards the qualitative strain once the semi-structured interview questions are finalized. This prevents a submission of an amendment to include any changes.

A signed informed consent will be obtained from each participant before the interview and stored as electronic copy (password protected on a secured server).

5. Challenges

5.1. Sample size and Saturation in Qualitative Research

Determination of sample size is important for quantitative, qualitative and mixed-methods research to prevent exhaustion of time, resources or finances (139). In quantitative research an optimal sample size should detect any clinically relevant treatment effect, whereby in qualitative research sample size primarily aims to reach saturation (140-142).

5.1.1 Saturation

Glaser and Straus described in their work about the discovery of grounded theory the principle of theoretical saturation, whereby this refers to '…that no additional data are being found…' (143). The concept of saturation was also taken up in other areas of qualitative research, outside of the grounded theory, and it was listed as the most commonly used justification for sample size in 214 cross-sectional, interview-based studies (144, 145). However, there are several different definitions of saturation, whereby 'data saturation' or 'theme saturation', refers to the timepoint after which no relevant information will be captured anymore. Different approaches are used in literature, including frequency counts (saturation is reached when the number of new codes per transcript diminishes) or code meaning (assessing if the issues/dimensions/nuances are fully captured) to provide information about reaching saturation (146). However, the concept of saturation is debated in qualitative research, and its lack of a uniform definition results in various interpretations for different research designs (144, 146-148). Therefore it is not surprising that reporting on how sample size was calculated or saturation was defined is poor (149). Moreover, certain qualitative research approaches, such as the hermeneutic phenomenology, assume that

finite understanding can not be achieved and rounds of interpretation will lead to new understandings, as highlighted by Ironside and colleagues (150). In addition, quality of study was not correlated to sample size for hermeneutic studies but sample size in phenomenology research should be small enough to describe voices of participants (151). These issues, the possible infinite understanding, which questions if saturation can ever be achieved or how it is determined, and a sample size which might decrease quality after reaching a certain point because it might "*suppress the voices of participants and descriptions of phenomena"* (151), highlight the difficulties of identifying the correct amount of participants.

5.1.2 Sample Size Determination to reach Saturation

Despite being a guiding principle for sample size determination in qualitative research, it is not clearly described how to reach saturation, and researchers often do not mention how or on what assumption saturation was assessed or achieved (145, 146). In 2006, Guest, Bunce and Johnson described that in a retrospective analysis of conducted interviews 73% of content-driven codes were already detected within the first six transcripts. These results should be cautiously interpreted and cannot be applied universal since other characteristics such as participant selection or purpose of the research might require a larger number (152). Existing empirical recommendations provide information about the different types of saturation, whereby nine interviews are considered to be the minimal sample size for data saturation (148). Even if empirical sample size estimation has limitations and might be misused, it is the most commonly used approach (148). More recently suggested techniques

for inductive approaches also offer researchers to set a threshold about the confidence that sampling reached saturation (153).

Based on our qualitative analysis approach using thematic analysis, homogenous group of participants and literature regarding empiric estimation of sample size we assume that 12 interviews will be sufficient to achieve thematic saturation.

6. Vanguard phase

A vanguard phase was conducted to assess the feasibility of the proposed mixed-methods research study. Data about the availability of treatment guidelines for clinical infections, especially facility-based guidelines in sub-Saharan Africa, is limited. The vanguard phase therefore aimed to assess the availability of these guidelines in a small sample of sites participating in the REVIVE trial and obtained preliminary data about the proposed agreement indicators, which will be collected in the quantitative strand of the proposed main trial and inform participant selection of the qualitative strand.

6.1. Methods:

6.1.1 Aims:

The proposed main study will be conducted using a mixed-methods research design. The design of the main trial is an explanatory sequential design, starting with a quantitative strand which assesses the availability of the guidelines and agreement with the WHO AWaRe book. This is followed by a qualitative strand, whereby potential participants for semi-qualitative interviews will be approached based on the provision of facility-based antimicrobial guidelines. To conduct the interviews a certain number of sites with facility-

specific guidelines must be available to reach saturation in the qualitative data analysis. The proposed agreement indicators need to be accessible, so that the qualitative data collection (semi-structured interviews) can incorporate the findings. The aim of the vanguard phase is therefore to assess the availability of guidelines and the presence of agreement items. The feasibility will be judged using an ample scheme outlined in table 4 below:

***Table 4**: Traffic light scheme to assess the outcome of the vanguard phase*

Availability of guidelines	Availability of facility-specific guidelines	Extraction of agreement items for >50% of guidelines	Action
>66% AND	>20% AND	>50%	Proceed with main study as proposed
50% - 66% AND	10% - 20% OR	25% - 50%	Proceed with main study but either focus on non-facility-specific guidelines or adapt agreement indicators
<50% OR	<10% OR	<25%	Main study not feasible

6.1.2 Data collection:

Nine national leaders (NL) responsible for the trial conduct across the countries, or PIs of sites of the REVIVE trial were asked to provide antibiotic guidelines which are used in daily routine at their site. Standardized emails were sent out to the NL/PIs informing them about the purpose of collection of guidelines, and if no response was received, a minimum of two follow-up emails were sent at least seven days apart. If guidelines were obtained, data was extracted into a prespecified table to assess characteristics of the guidelines (e.g., year of

publication, issuing body, number of pages, etc.). The agreement of the guidelines was assessed by investigating if the guideline provided information about cornerstones of treatment of three key bacterial infections, namely community- and hospital-acquired pneumonia and urinary tract infections, to assess four indicators of agreement:

- Providing guidance for diagnostics/treatment indication
- Providing a treatment regimen
- Providing the dosage of the chosen drug
- Providing the treatment duration
- The assessment of necrotizing fasciitis was added to the study protocol after the vanguard phase was completed. Therefore, no data for this infectious syndrome was extracted.

6.1.3 Choice of indicators and infectious diseases

The chosen indicators are cornerstones of antibiotic use and are highly important for the correct administration of drugs. All these items are covered in the WHO AWaRe book, which was used as a reference. This document was developed to address the global need for improving antibiotic prescribing (44).

Focusing on community-acquired and hospital-acquired pneumonia, this vanguard covers two important infectious syndromes which are linked to high mortality especially in the setting of antimicrobial resistance. Lower respiratory tract infections were the leading cause for death attributable to antimicrobial resistance in 2019 (>400.000 deaths) (8, 9, 154). Therefore, comprehensive and high-quality recommendations are needed to counteract any

further emerge of resistance resulting in an even higher number of deaths. In contrast, community acquired urinary tract infections are not associated with high mortality rates. However, they are one of the most common infectious syndromes and therefore a frequent reason for antibiotic consumption, which is a driver of the development of AMR (155). Correct recommendations can therefore have a large impact.

6.1.4 Analysis

Data was analyzed as outlined in the proposal for the main study. In brief, baseline characteristics of the guidelines, overall treatment considerations and treatment recommendations were extracted into a table. Proportion of facilities with available guidelines or facility-specific guidelines were calculated. The following eleven agreement items were extracted:

Community-acquired pneumonia (5 items)

- Diagnostic approach (4 items)
    - Clinical presentation, Microbiology Tests, Imaging, Other treatment considerations
- First line treatment and treatment duration (1 item)

Hospital-acquired pneumonia (non-ventilator associated pneumonia) (4 items)

- Diagnostic approach (3 items)
    - Clinical presentation, Microbiology Tests, Imaging
- First line treatment and treatment duration (1 item)

Urinary-tract infection (uncomplicated) (2 items)

- Treatment indication (1 item)
- First line treatment (1 item)

Items were compared to the WHO AWaRe book. Agreement was judged as follows:

- Not addressed (0 points): Information for the respective item was not found within the guidelines.
- Agreement (1 point): The extracted data for an item in the country guideline matched or was more extensive than the AWaRe guideline recommendations. In case of antibiotic treatment only exact matching was considered as agreement since misuse is a driver of antibiotic resistance.
- Partial agreement (0.5 points): The provided information included at least partially the same information as WHO but did not cover all aspects.
- No agreement (0 points): Facility-specific recommendations were not in line with the AWaRe guidelines.

6.2. Results:

A total of nine sites in seven countries were asked to provide guidelines for the treatment of bacterial infections.

6.2.1 Availability

6.2.1.1. Guidelines

Responses were received from all nine facilities. Six guideline documents were provided, covering seven facilities (78%) across five countries. Two facilities provided the same national guidelines (Facility 1 and 2). Out of the two facilities not providing any guideline, one facility reported not having a single document, and physicians use a mix of different guidelines addressing specific infectious diseases in their area (e.g., endocrinology and

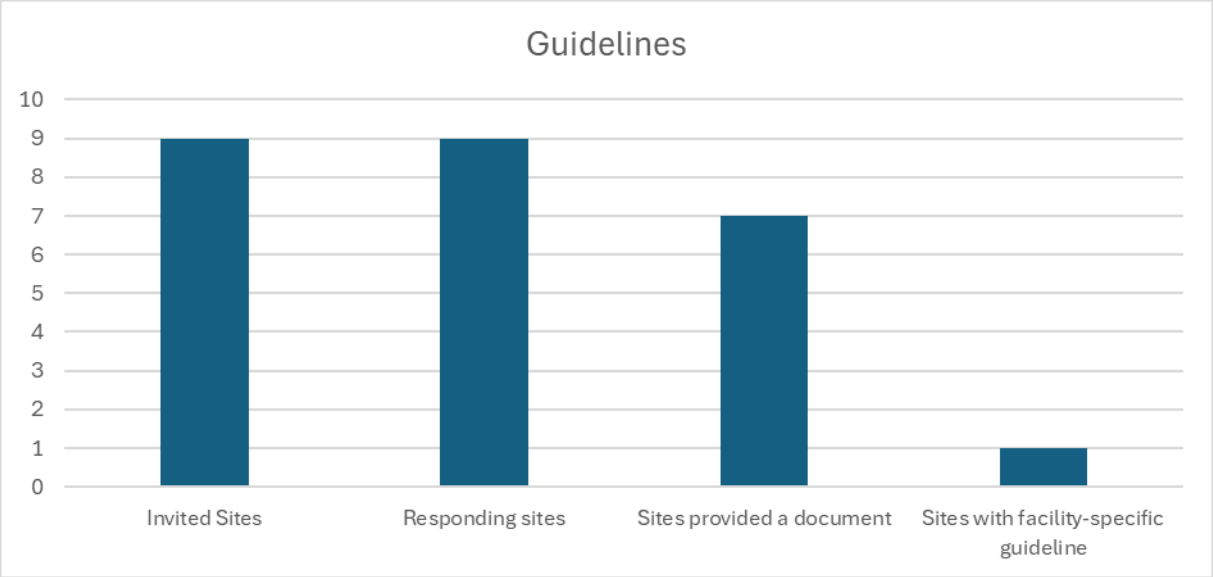

***Figure 3**: Overview of responses to the survey of antibiotic treatment guidelines of nine healthcare facilities across sub-Saharan Africa*

diabetic foot infections). The other facility, despite stating that it had guidelines, did not provide any document by the time of the submission of this thesis. Only one out of the nine sites (11%) provided a facility-specific document (Facility 3). Results of the responses are shown in Figure 3.

6.2.1.2. Overview of received guidelines

Six of the seven facilities providing a document used a country-specific guideline (87%), whereby five facilities used guidelines which were not infectious disease specific (5/7; 71%). These guidelines included, besides treatment recommendations for infectious diseases, also information on a variety of other diseases such as psychotic disorders or diabetes. Guidelines were published between 2017 to 2022, and therefore mostly before the publication of the agreement reference (2022). The number of pages varied between 46 and 1202 for the received documents. Extracted data is shown in Table 5.

6.2.2 Agreement

6.2.2.1. Community-acquired pneumonia

Guidance regarding the diagnostic approach for CAP was outlined in six of seven facilities (85%). Clinical presentation varied, but covered the information provided by the WHO in all documents. Facilities 3, 4, and 6 provided an even more detailed description of clinical presentation.

The WHO AWaRe book states that no microbiological testing is needed for mild cases of CAP, however blood cultures, urinary antigen for *Legionella pneumophila* and *Streptococcus pneumoniae* should be performed in severe cases. This recommendation is only partially represented in four documents, whereby for Facilities 1, 2 and 5 no approach was specified. Facilities recommend collecting blood cultures, but none provided a statement about the use of urinary antigens.

Performing a chest X-ray is listed in all guidelines of the facilities except Facility 5. None of the documents consider a specific patient population. The WHO AWaRe book indicates that

chest X-ray is not necessary for mild cases, but this is not reflected in any of the included guidelines.

Determining disease severity is essential to provide the correct choice of treatment according to the AWaRe book. This approach is also noticed in Facilities 3, 4, and 6. Guidelines covering the remaining four sites did not mention an approach to determine the severity of the diseases.

Several drug options for treating both, mild and more severe, cases of community-acquired pneumonia are provided by the WHO AWaRe book. Treatment duration should be five days for mild cases and can be longer in severe cases. Even if facilities recommend similar drugs, dosage or duration of treatment vary widely resulting in no agreement.

6.2.2.2. Hospital-acquired pneumonia

Three facilities (43%) did not provide any information about HAP (Facilities 1,2 and 5). Of the remaining four facilities, three have the same diagnostic approach for CAP and HAP. Since the clinical presentation provided by the WHO AWaRe book is quite similar for HAP and CAP, this is in agreement for all four facilities providing any information. The microbiological diagnostics includes blood cultures, respiratory samples (microscopy and culture), and urinary antigens in the WHO AWaRe document. However, none of the facilities recommend all these diagnostics, but all provided at least one of them. Facilities 3 and 4 recommend at least sputum cultures and blood cultures, Facility 6 cultures from lower respiratory samples and Facility 7 blood cultures.

The WHO recommends chest radiography and all four facilities providing information were in line with this recommendation.

Discrepancies exist for treatment recommendations. None of the provided guidelines is in agreement with the WHO AWaRe book regarding drug, dosage or duration. Recommended drugs at facilities include substances such as vancomycin, carbapenems or the addition of azithromycin in specific cases, which are all not recommended by the AWaRe book. Dosage of drugs which would be in line often do not match (e.g., Amoxicillin-Clavulanate 625g instead of 1000g). Most regimens promoted at facilities are longer than seven days (the recommended duration in the WHO AWaRe). Only Facility 6 reflects the identical treatment duration as the WHO AWaRe. Facility 7 recommends continuing treatment for up to 14 days. However, the guideline includes the option to discontinue treatment if a patient is afebrile for 48-72h, which might result in a shorter treatment duration than the 14 days. Facility 5 recommends a shorter course than the WHO AWaRe (five days).

6.2.2.3. Urinary tract infection

The guidelines of four facilities (Facilities 1, 2, 3, 6) include information about the treatment of non-complicated urinary tract infections. All four provide information about the treatment indication of suspected urinary tract infection, which includes a mix of clinical and laboratory findings. This reflects the WHO AWaRe approach, which also combines clinical and laboratory results to initiate treatment.

Even if the WHO AWaRe book and guidelines used by the facilities provide several treatment options, there is only one regimen with overlap for drug, dosage and duration. Facility 6 recommends the use of Cotrimoxazole 160/800mg every 12h for three days. All other options

of Facility 6, and of Facilities 1,2 and 3 are not aligned, resulting in partial agreement for this item, only.

***Table 5a**: Extracted data of all provided guidelines (facilities 1-4)*

Item	WHO AWaRe	Facility 1 + 2	Facility 3	Facility 4
Availability				
- **Guidelines available**		Yes	Yes	Yes
- **Infectious disease specific**		No	Yes	No
- **Facility-specific**		No, national	Yes	No, national
Allergy				
- **Section on general principles**	Yes	No	No	No
Characteristics				
- **Year of publication**	2022	2020	2022	2017
- **Pages**	160	459	112	708
Community-acquired pneumonia				
- **Diagnostic approach**				
- **Clinical presentation**	New onset (<2 weeks) or worsening cough with fever (≥ 38.0 °C), sputum production, dyspnea, tachypnea, reduced oxygen saturation, crepitations on lung auscultation, chest pain/discomfort without alternative explanation	Clinical features These are usually of sudden onset. Symptoms - Fever - Dry or productive cough - Chest pain - Chills - Breathlessness	Common symptoms: Cough with or without purulent sputum, fever (can be >39°C), pleuritic chest, fast breathing – On chest examination: decreased breath sounds, dullness, localized foci of crepitations, bronchial breath sounds – Signs of serious illness (severe pneumonia) include: - Cyanosis (lips, oral mucosa, fingernails)	- Fever - short history - Productive cough - Sputum - rusty or blood stained, yellowish, greenish - Pleuritic chest pain - worse on deep breathing or coughing - Breathlessness - Sweating - Muscle aches - Elderly and immunocompromised patients may have minimum or no symptoms

			- Nasal flaring - Intercostal or subclavian indrawing - RR > 30 breaths/minute - Heart rate > 125 beats/minute - Altered level of consciousness (drowsiness, confusion)	
- **Microbiology Tests**	- Mild cases: not needed - Severe cases: blood cultures, urinary antigen for L. pneumophila and S. pneumoniae	Not addressed	For severe disease: - Sputum culture - Blood culture	- Sputum gram stain and culture and sensitivity - Ziehl-Neelsen stain for acid-fast bacilli (to exclude TB) - Blood culture and sensitivity
- **Imaging**	Mild cases: X-ray not necessary	May support clinical findings	For all cases Chest X-ray	Chest X-ray
- **Other treatment considerations**	Determining disease severity	Not addressed	Determining disease severity	Determining disease severity
- **First line treatment and treatment duration**	**Mild** - Amoxicillin 1g q8h - Phenoxymethylpenicillin 500mg q6h **Severe** - Cefotaxime 2g q8h - Ceftriaxone 2g q24h - Adding Clarithromycin 500mg q12h (if CURB-65 >=2) - 5 days for mild. Consider longer for severe disease	- Benzylpenicillin 1-2 Mio U q6h for 5 days - Ceftriaxone 1g-2g q24h for 7 days - Erythromycin 500mg q6h for 7 days	**Mild** If there are no comorbidities or recent antibiotic use: - Amoxicillin 1 g q8h for 7 days - Azithromycin 500 mg q6h for three days OR - Doxycycline 100 mg q12h for 7 days If there are comorbidities or recent antibiotic use (within 3 months) - Amoxicillin/clavulanate 2 g q12h for 7 days PLUS - Azithromycin 500 mg q24h for three days - Doxycycline 100 mg q12h for 7 days **Severe** Inpatient (severe CAP) Non-ICU (not in respiratory failure) - Ceftriaxone 2 g q6h. Once patient is stable, shift to Amoxicillin/clavulanic acid 1 g q12h to complete total course of 7 days.	**Ambulatory patients:** Amoxicillin 1g q8h for 7 days AND - Azithromycin 500mg q24h for 6 days or - Erythromycin 500mg q6h for 7 days **Hospitalised patients:** Amoxicillin + Clavulanic acid 1.2g q8h for 7-10 days AND Azithromycin 500mg q24h for 3-7 days

			ICU (in respiratory failure or comorbidity) - Ceftriaxone 2g q24h 7 days PLUS Azithromycin 500 mg q24h for three days	
Hospital-acquired pneumonia (non-VAP)				
- **Diagnostic approach**				
- **Clinical presentation**	New or worsening cough +/- sputum production, difficult and rapid breathing, reduced oxygen saturation, crepitations on lung auscultation, or chest pain/discomfort with no alternative explanation; fever ≥ 38.0 °C usually present (may be absent, especially in the elderly)	Not addressed	Common symptoms: Cough with or without purulent sputum, fever (can be >39°C), pleuritic chest, fast breathing – On chest examination: decreased breath sounds, dullness, localized foci of crepitations, bronchial breath sounds – Signs of serious illness (severe pneumonia) include: - Cyanosis (lips, oral mucosa, fingernails) - Nasal flaring - Intercostal or subclavian indrawing - RR > 30 breaths/minute - Heart rate > 125 beats/minute Altered level of consciousness (drowsiness, confusion)	- Fever - short history - Productive cough - Sputum - rusty or blood stained, yellowish, greenish - Pleuritic chest pain - worse on deep breathing or coughing - Breathlessness - Sweating - Muscle aches Elderly and immunocompromised patients may have minimum or no symptoms
- **Microbiology Tests**	- Blood cultures (ideally before starting antibiotics) - Microscopy and culture of respiratory samples (ideally before starting antibiotics) - Urinary antigens for and L. pneumophila S. pneumoniae	Not addressed	For severe disease: - Sputum culture - Blood culture	- Sputum gram stain and culture and sensitivity - Ziehl-Neelsen stain for acid-fast bacilli (to exclude TB) - Blood culture and sensitivity
- **Imaging**	Chest radiograph needed	Not addressed	For all cases Chest X-ray	Chest X-ray
- **First line treatment and treatment duration**	- Amoxicillin + Clavulanic acid 1000/200mg iv or 875+125mg oral q8h - Cefotaxime 2g q8h - Ceftriaxone 2g q24h	Not addressed	Ceftazidime 1g q8h + Vancomycin 1g q12h	**Ambulatory patients:** Amoxicillin 1g q8h for 7 days AND

	- Piperacillin + tazobactam 4000/500mg q6h - 7 days			- Azithromycin 500mg q24h for 6 days or - Erythromycin 500mg q6h for 7 days **Hospitalised patients:** Amoxicillin + Clavulanic acid 1.2h q8h for 7-10 days AND Azithromycin 500mg q24h for 3-7 days
Urinary-tract infection (uncomplicated)				
- **Treatment indication**	Compatible clinical presentation AND a positive test[a]	This is made by history, physical examination and laboratory investigations. Midstream specimen urine is collected for microscopy, culture and sensitivity. The diagnosis is based on colony count of bacteria of more than 10/5/ml on culture.	Patients with symptomatic UTI often require antibiotic treatment	Not addressed
- **First line treatment**	- Amoxicillin + clavulanic acid 500/125mg q8h 3-5days - Nitrofurantoin 100mg q12h (modified release) or 50mg q6h (immediate release) for 5 days - Sulfamethoxazole + trimethoprim 800/160mg q12h for 3 days - Trimethoprim 200mg q12h for 3 days	- Nitrofurantoin 50-100mg q12h for 5-7 days - Nalidixic acid 250mg q8h for 5 days	- Norfloxacin 400mg q12h - Ciprofloxacin 500mg q12h - Amoxicillin/clavulanate 1g q12h - Trimethoprim-sulfamethoxazole 480 q12h	- Ciprofloxacin 500mg q12h - Female 5-7 days - Male: 10-14 days - Cefuroxime 250-500mg q12h - Female 5-7 days - Male: 10-14 days

***Table 6b**: Extracted data of all provided guidelines (facilities 5-7)*

Item	WHO AWaRe	Facility 5	Facility 6	Facility 7
Availability				
- **Guidelines available**		Yes	Yes	Yes
- **Infectious disease specific**		Yes	No	No
- **Facility-specific**		No, national	No, national	No, national
Allergy				
- **Section on general principles**	Yes	No	No	No
Characteristics				
- **Year of publication**	2022	2022	2021	2020
- **Pages**	160	46	1202	112
Community-acquired pneumonia				
- **Diagnostic approach**				
- **Clinical presentation**	New onset (<2 weeks) or worsening cough with fever (≥ 38.0 °C), sputum production, dyspnea, tachypnea, reduced oxygen saturation, crepitations on lung auscultation, chest	Not addressed	**Typical**[b] - Acute onset of fever, cough with purulent sputum, dyspnea - Consolidation on CXR. **Atypical**[c] - More insidious onset of dry cough	- Breathing is rapid, shallow and difficult - Fever - Cough may be dry, or produce thick yellow, green, brown or blood-stained phlegm - Chest pain

	pain/discomfort without alternative explanation		- Extrapulmonary symptoms may be present (nausea/vomiting, diarrhea, headache, myalgias, sore throat) - Patchy interstitial infiltrates on CXR - Elevated transaminases & low serum sodium with Legionella	
- **Microbiology Tests**	- Mild cases: not needed - Severe cases: blood cultures, urinary antigen for L. pneumophila and S. pneumoniae	Not addressed	- Severe cases: - Blood cultures, sputum	- Blood cultures
- **Imaging**	Mild cases: X-ray not necessary	Not addressed	All patient chest X-ray	Chest X ray
- **Other treatment considerations**	Determining disease severity	Not addressed	Determining disease severity	Not addressed

- **First line treatment and duration**	**Mild**
	- Amoxicillin 1g q8h
	- Phenoxymethylpenicillin 500mg q6h
	Severe
	- Cefotaxime 2g q8h
	- Ceftriaxone 2g q24h
	- Adding Clarithromycin 500mg q12h (if CURB-65 >=2)
	- 5 days for mild. Consider longer for severe disease
		Low severity:
		- Amoxicillin 500mg q8h for 5 days
		High severity:
		- Amoxicillin + clavulanic acid 500/125 q8h for 5 days
			CAP outpatients (5-7 days):
			Amoxicillin 1000mg q8h 5-7 days
			CAP outpatients with comorbidities (5-7 days):
			Amoxicillin-Clavulanate 625 q8h or 1000/2125 q12h AND
			- Clarithromycin 500mg q12h OR
			- Azithromycin 5-7 days 500mg first day, 250mg for next 4 days
			CAP for hospitalized patients (5-7 days):
			- Ceftriaxone 1-2g q12h OR
			- Ceftriaxone 1-2g q12h AND
			  - Clarithromycin 500mg q12h OR
			  - Azithromycin 500mg first day, 250mg for next 4 days
				- Amoxicillin 500mg + clavulanic acid 125 every 8 hours for 14 days
				- Ceftriaxone IV or IM 1 to 2 g divided every 12 to 24 hours (Max: 4 g/day) depending on severity of illness and causative organism
				- Amoxicillin 500 mg every 8 hours for 10-14 days
				If received antibiotics within the past 3 months or with comorbidities:
				ADD Azithromycin oral 500 mg at once, then 250 mg daily

Hospital-acquired pneumonia (non-VAP)				

- **Diagnostic approach**				
- **Clinical presentation**	New or worsening cough +/- sputum production, difficult and rapid breathing, reduced oxygen saturation, crepitations on lung auscultation, or chest pain/discomfort with no alternative explanation; fever ≥ 38.0 °C usually present (may be absent, especially in the elderly)	Not addressed	- A new onset of fever - Purulent sputum - Leukocytosis/leukopenia - Decline in oxygenation. - Time of presentation: after 48 hours of admission for HAP	- Breathing is rapid, shallow and difficult - Fever - Cough may be dry, or produce thick yellow, green, brown or blood-stained phlegm - Chest pain
- **Microbiology Tests**	- Blood cultures (ideally before starting antibiotics) - Microscopy and culture of respiratory samples (ideally before starting antibiotics) - Urinary antigens for and L. pneumophila S. pneumoniae	Not addressed	Culture from lower respiratory samples	Blood cultures
- **Imaging**	Chest radiograph needed	Not addressed	Chest radiography is needed	Chest X ray
- **First line treatment and duration**	- Amoxicillin + Claculanic acid 1000/200mg iv or 875+125mg oral q8h - Cefotaxime 2g q8h - Ceftriaxone 2g q24h - Piperacillin + tazobactam 4000/500mg q6h - 7 days	**Non-severe and low risk of resistance:** - Amoxicillin + clavulanic acid 500/125 q8h for 5 days **Non-severe and high risk of resistance:** - Doxycycline 200mg on day 1, then 100mg q24h for 5 days	**HAP with one of the following: septic shock, mechanical ventilation, antibiotic in the last 90 days:** - One of the following o Cefepime 2 g IV q8h - Ceftazidime 2 g IV q8h - Meropenem 1 g IV q8h - Imipenem 500 mg IV q6hd - Piperacillin-tazobactam 4.5 g IV q6h PLUS **One of the following** - Gentamicin 5–7 mg/kg IV q24h - Ciprofloxacin 400 mg IV q8h **PLUS** - Vancomycin 15 mg/kg IV q8–12h (for severe cases, loading	- Amoxicillin 500mg + clavulanic acid 125 every 8 hours for 14 days - Ceftriaxone IV or IM 1 to 2 g divided every 12 to 24 hours (Max: 4 g/day) depending on severity of illness and causative organism - Amoxicillin 500 mg every 8 hours for 10-14 days **If received antibiotics within the past 3 months or with comorbidities:** ADD Azithromycin oral 500 mg at once, then 250 mg daily

			dose 25–30 mg/kg, maximum 3g) **HAP with none of the following: septic shock, mechanical ventilation, antibiotic in the last 90 days:** - **One of the following** - Ceftazidime 2 g IV q8h - Meropenem 1 g IV q8h - Imipenem 500 mg IV q6hd - Piperacillin-tazobactam 4.5 g IV q6h **PLUS** - Vancomycin 15 mg/kg IV q8–12h (for severe cases, loading dose 25–30 mg/kg, maximum 3g)	
Urinary-tract infection (uncomplicated)				
- **Treatment indication**	Compatible clinical presentation AND a positive test[a]	Not addressed	The diagnosis is based on clinical findings plus urine analysis	Not addressed
- **First line treatment**	- Amoxicillin + clavulanic acid 500/125mg q8h 3-5days - Nitrofurantoin 100mg q12h (modified release) or 50mg q6h (immediate release) for 5 days - Sulfamethoxazole + trimethoprim 800/160mg q12h for 3 days - Trimethoprim 200mg q12h for 3 days	Nitrofurantoin 100mg	- Ciprofloxacin 250- 500mg q12h for 3 days - Norfloxacin 400mg q12h for 3 days. - Nitrofurantoin 50mg q6h for 5 days - Cotrimoxazole (TMP-SMO) 160/800mg q12h for 3 days	- Amoxicillin 500mg q8h for 7 days - Amoxicillin + clavulanic acid oral 625 q8h for 7 days - Cotrimoxazole 960 q12h for 7-14 days - Nitrofurantoin 100mg q6h for 7-14 days

[a] positive test (positive urine leucocytes/leucocyte esterase or positive urine culture)/ If tests could not be performed, treat based on clinical presentation

[b] *S. pneumonia, H. influenzae*

[c] Mycoplasma, Chlamydia, Legionella

***Table 7**: Agreement of items between provided guidelines and WHO AWaRe book*

Item	WHO AWaRe	Facility 1 + 2	Facility 3	Facility 4	Facility 5	Facility 6	Facility 7
Availability							
- **Guidelines available**		Yes	Yes	Yes	Yes	Yes	Yes
- **Infectious disease specific**		No	Yes	No	Yes	No	No
- **Facility-specific**		No, national	Yes	No, national	No, national	No, national	No, national
Allergy							
- **Section on general principles**	Yes	No	No	No	No	No	No
Characteristics							
- **Year of publication**	2022	2020	2022	2017	2022	2021	2020
- **Pages**	160	459	112	708	46	1202	112
Community-acquired pneumonia							
- **Diagnostic approach**							
- **Clinical presentation**	**Reference**						
- **Microbiology Tests**	**Reference**						
- **Imaging**	**Reference**						
- **Other treatment considerations**	**Reference**						

- First line treatment and treatment duration	Reference						
Hospital-acquired pneumonia (non-VAP)							
- Diagnostic approach							
- Clinical presentation	Reference						
- Microbiology Tests	Reference						
- Imaging	Reference						
- First line treatment and treatment duration	Reference						
Urinary-tract infection (uncomplicated)							
- Treatment indication	Reference						
- First line treatment	Reference						
Agreement		2	5	4	0	5	3
Partial Agreement		1	3	3	0	4	3
No Agreement		2	3	3	3	2	2
Not addressed		6	0	1	8	0	3
Points		2.5	6.5	5.5	0	7	4.5

6.2.2.4. Overall agreement

Overall agreement for all eleven items varied between 0 and 7 points, out of a total of 11 points (Table 6, Figure 4). The only facility-specific guideline scored 6.5 points, which was the second highest value. At three sites, guidelines did not provide information about >50% of the items (Figure 5). Facility 5 provided a document which included information on the recommended treatment regimen and epidemiological features (e.g., causative pathogens), but no recommendations about diagnostic approaches, nor did all treatment recommendations provide guidance on the antibiotic of choice, dosage and duration.

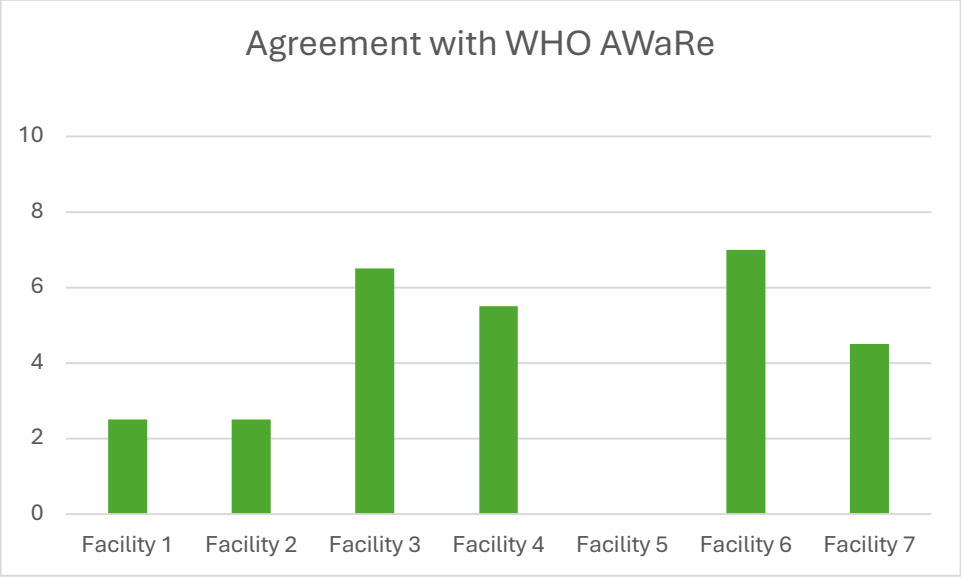

***Figure 4**: Overall agreement of the facilities with the WHO AWaRe book. Maximum number of points: 11*

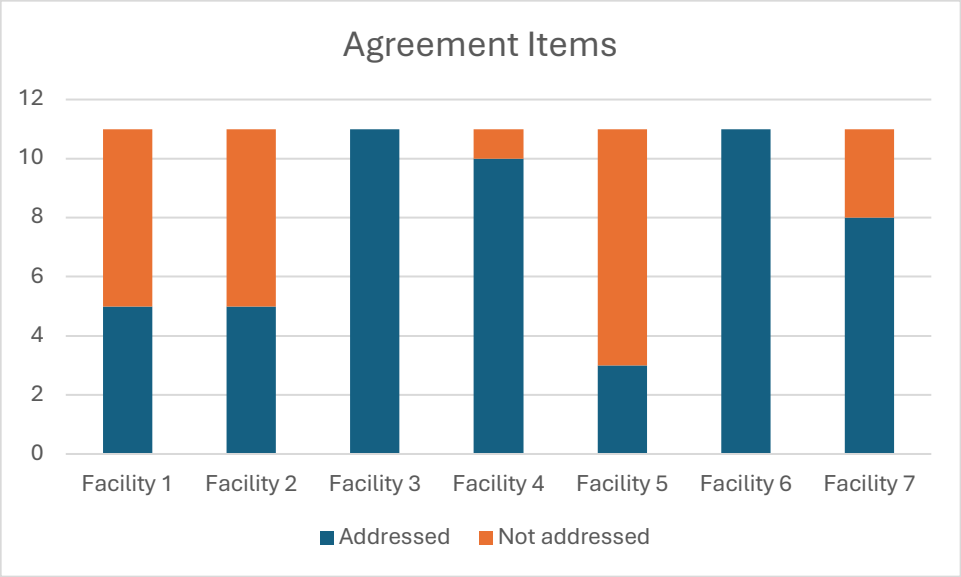

***Figure 5**: Number of addressed agreement items for each facility providing a guideline. Total number of items: 11*

6.2.3 Aims of the vanguard phase

Not all aims could be achieved. Guidelines were available for 78% (7/9) of facilities and 11% provided facility-specific documents. >50% of agreement items could be extracted for 57% of guidelines

Based on the pre-specified ample scheme the 'orange' area was met, which means that the main study can proceed after some modifications (Table 7). To conduct the qualitative part, it might be considered to focus on all provided guidelines instead of facility specific guidelines, only. This should help to achieve data saturation.

***Table 8**: Traffic light scheme presenting the outcome of the vanguard study*

Availability of guidelines	Availability of facility-specific guidelines	Extraction of agreement items for >50% of guidelines	Action
Achieved: 78%	**Achieved: 11%**	**Achieved: 57%**	

Aim: 50%-66% AND	Aim: 10% - 20% OR	25% - 50%	Procced with main study but either focus on non-facility-specific guidelines or adapt agreement indicators

6.3. Discussion

This vanguard phase demonstrates the feasibility of obtaining guidelines for follow up with in-depth semi-structured interviews in the qualitative strand of the proposed explanatory-sequential mixed-methods research study. Nevertheless, obtaining facility-specific guidelines of 11% of the 60 REVIVE sites would most likely not be enough to achieve saturation in the qualitative part (estimated target sample size: 12 interviews). Sufficient data about the agreement items of the guideline was obtained with the current survey. The goal to extract at least 50% of the predefined agreement items in the received guidelines was achieved in 57% of facilities (4/7) (target >50%). This ensures that enough data can be extracted on the selected items to provide an overview on the agreement with the WHO AWaRe, but also to include this information in the qualitative part.

Seven facilities provided guidelines (78%), whereby the missing guidelines were not obtained because there was no response of the PI/NL (1/9, 11%), or the clinician stated that no specific guideline for the treatment of infections was available at the facility (1/9, 11%). This is in contrast to Craig and colleagues, who reported that they identified national guidelines in only 36% of countries of the African Union from 2018 to 2021 (76). In our study,

the only facility-specific guideline was provided by a site from a country that also has a national guideline available which we obtained from another facility from the same country.

The limited number of facility-specific guidelines in this pilot highlights the possible challenges of treating bacterial infection in sub-Saharan Africa. Based on reported structural obstacles to identify and treat bacterial infection (154), these guidelines might be even more important to achieve optimal patient outcomes with the lowest risk of emerging resistance, and reduce the use of antibiotics with a high potential for developing resistance as currently reported (156). Unexpectedly, most guidelines provided are universal treatment guidelines and are not dealing solely with infectious diseases. This might hinder timely updates since these documents often cover several hundred pages.

The agreement of provided guidelines and WHO AWaRe guidelines varied across the included sites. Three facilities had less than 50% of items addressed, whereby one of these sites had not a single item in agreement with the WHO guideline. In order to capture not only which antibiotic is prescribed and for how long, we also tried to investigate possible misuse by looking at diagnostic approaches and treatment indications. The latter two items were, if provided, at a minimum partially in agreement with the WHO guidance.

Choice of first-line treatment and duration, however, was only in one case in partial agreement. This might be explained by different epidemiological settings and resistance rates. Nevertheless, the WHO AWaRe book provides several treatment options, which cover a wide range of settings. Also, the treatment duration of the guidelines used by the facilities,

which should be less influenced by local circumstances, was longer than recommended by the WHO for most infectious disease syndromes.

Using the full REVIVE trial network therefore seems to be a promising approach for the collection of guidelines and to capture a more detailed picture of the antibiotic treatment guideline landscape across sub-Saharan Africa. Also, the agreement of the guidelines can be assessed.

This vanguard has several limitations. Firstly, only three clinically relevant infectious syndromes were assessed. This might bias the results regarding agreement because less common infections might even be less common represented in the guidelines. Secondly, this approach included only one guideline per facility, which might not cover the complete spectrum. However, the practicability of the implementation of several guidelines to treat infectious diseases at the same facility is doubtful.

To summarize, the vanguard phase shows that the proposed mixed-method research study is feasible. Guidelines are available, even if most of them are not facility-based. Comparison of these guidelines used in facilities across sub-Saharan Africa with the WHO AWaRe is possible, even if the chosen agreement indicators could only be extracted in a little more than 55%. Future research, including this proposed mixed-methods study, should therefore not only focus on sites with facility-based guidelines, but instead include all sites providing any guidelines and look at the experience of clinicians using them. In addition, one or two other clinically relevant infectious syndromes (e.g., skin and soft tissue infections) should be included to provide a more comprehensive overview about the agreement with the WHO

AWaRe book. Also, the impact of unexpected findings, such as most guidelines not being infectious disease specific, can be further explored.

7. References

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8. Appendix

8.1. Mapping-matrix

Question	Background	Experience	Agreement	Limitations
Q1	X			
Q2	X			
Q3	X			
Q4		X		
Q5		X		
Q6		X		
Q7			X	
Q8			X	
Q9			X	
Q10			X	
Q11				X

8.2. Semi-structured interview questions - outline

Q1: What is your experience on antimicrobial resistance at your site?

Q2: What is your viewpoint with antimicrobial stewardship, especially the use of guidelines to treat bacterial infection?

Q3: What are antimicrobial stewardship interventions at your facility and what is your experience with these interventions?

Q4: What is your personal experience using the facility-specific guidelines?

Q5: What is your perception about the use of the guidelines by your colleagues?

Q6: What is your experience regarding treating community-acquired pneumonia, hospital-acquired pneumonia, and urinary tract infection (non-complicated)?

Q7: What is your viewpoint about the quality of the guidelines and their agreement with WHO AWaRe?

Q8: Can you recall any scenarios when you were not adhering to the guideline because you suspected misleading information?

Q9: Based on your viewpoint and experience, what are the main limitations of implementing the guidelines?

Q10: What content is missing or not adequately be covered in the guidelines?

Q11: What additional structural features or items would make the implementation easier?