Antimicrobial Stewardship with and without Infectious Diseases Specialist Services to Improve Quality-of-Care in Secondary and Tertiary Care Hospitals in Germany: Study Protocol of the ID ROLL OUT Study

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ABSTRACT

Background: Antimicrobial stewardship (AMS) programs aim to secure the rational prescription of antibiotics through implementing department- or hospital-level activities. Infectious disease (ID) specialists improve the quality of care and outcomes in infection patients predominantly by individual consultations and patient-level interventions. While hospital AMS programs are established to various extents in

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Germany, ID specialist services are rarely available in this country. In the ID ROLL OUT study, we will implement and evaluate hospital-level AMS tools with and without ID specialist services in secondary and tertiary care hospitals. We aim to identify means to comprehensively and sustainably improve the quality of care of patients with infectious diseases.

Methods: This project is a clustered, two-armed intervention study, which will be conducted in ten secondary and tertiary (non-university) care hospitals in Germany. The intervention groups are stratified by key characteristics of the hospitals. We will compare two interventional strategies: implementation of AMS teams and implementation of AMS teams combined with the activities of ID specialists (AMS + IDS).

Planned Outcomes: The primary outcome is the quality of care as measured in changes in a *Staphylococcus aureus* bacteremia (SAB) score (as an indicator of difficult-to-treat infections) and a community-acquired pneumonia (CAP) score (as an indicator of common infections) compared to a baseline pre-interventional period. Our secondary outcomes comprise patient- and hospital-level outcomes, such as the quality and frequency of antibiotic treatment, in-hospital mortality, duration of hospitalization, and *C. difficile* incidence (associated diarrhea episodes). The study may provide urgently needed key information for the aspired advancement of ID care in Germany.

Key Summary Points

Infectious disease (ID) specialist services are known to improve ID patients' quality of care, but are rarely implemented in German hospitals

The ID ROLL OUT study is a prospective clustered two-armed interventional trial with a pre-post design conducted in ten secondary and tertiary care hospitals in the Federal state of Baden-Württemberg, Germany

We will evaluate the impact of implementing Antimicrobial stewardship (AMS) teams or AMS teams combined with the activities of ID specialists by measuring patient- and hospital-level outcomes

We hypothesize that the interventions will improve adherence to diagnostic and therapeutic quality-of-care indicators, enhance rationale antibiotic prescribing without increasing in-hospital mortality, reduce costs, and shorten the hospital length of stay

The study aims to provide important data on measures to improve the quality of ID care and will delineate structural and personnel requirements that may be used to guide innovations in routine ID care in Germany

INTRODUCTION

Background

Even before the current SARS-CoV-2 pandemic, it had become evident that infectious diseases constitute a major threat to human health [1, 2], showing, once again, an optimal diagnostic and therapeutic management of infections is essential. Due to the growing numbers of patients with implanted foreign devices, or profound immunosuppression [3] and (multi)-drug-resistant pathogens causing severe healthcare-associated infections [2], the management of infectious diseases (ID) will become increasingly complex [4].

Antimicrobial Stewardship (AMS) programs aim to optimize antimicrobial treatments and avoid overuse through a rational and responsible prescription of antimicrobials. It has been reported that about one third of antimicrobial prescriptions in hospitals are considered eligible for optimization [5, 6]. The proportion of inappropriate antimicrobial prescriptions in Germany is described as similar [7]. AMS programs establish strategies and measures in a systematic, i.e., hospital level, or institutional approach resulting in a shorter hospital length of stay, reduced mortality, and better patient safety [8–12].

The involvement of ID specialists enhances the quality of care primarily by a more patient-level approach [13, 14]. There is convincing evidence that ID specialist consultations improve adherence to diagnostic and therapeutic management standards (e.g., for community-acquired pneumonia [CAP]), which translates to improved survival, particularly in the context of severe infections, such as *Staphylococcus aureus* bacteremia (SAB), candidemia, or infective endocarditis [9, 15–20]. Moreover, ID specialist services play a major role in the rational prescription of antimicrobials and the containment of infections by (multi)drug-resistant pathogens [21]. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America claim that AMS programs are best led by ID

specialists with additional AMS training [10, 21].

While in Germany AMS programs are established to various and often limited extents, ID specialist services are implemented mainly in university hospitals and very rarely in secondary and tertiary care hospitals. Until recently, there have been fewer than five ID specialists per million inhabitants in Germany [22]. As the number of ID specialists diverges from the steadily increasing demand [21–23], the German government established an incentive program to strengthen the training of ID specialists. In spring 2021, the delegates of the German Medical Association enacted to implement an ID specialist training program with a 6-year curriculum, equivalent to other internal medicine specialist areas [24]. It has, as yet, been undetermined how and to which extent ID specialist services can be implemented in secondary and tertiary care hospitals, how collaboration with AMS teams should be organized, and at what intensity or staffing ratio this should ideally be performed.

Growing evidence reveals that AMS programs are less effective if they exclude the determining factors of the organizational, structural, personal, and psychological contexts [25, 26]. Key barriers to antimicrobial prescription behavior improvements are concerns about potentially negative patient-level outcomes, the hierarchical structures, lack of communication skills, and team dynamics [25, 27, 28]; we therefore address these determinants in our study.

Objectives

The present study aims to implement and examine the effect of AMS teams with and without ID specialist services (AMS + IDS) on patient- and hospital-level outcome measures. Besides evaluating diagnostic and therapeutic measures, we will perform a process evaluation to investigate the feasibility and intensity of the interventions' implementation from both a medical and pharmaceutical perspective. Generated insights may provide urgently needed key information for the optimized care of patients with ID in secondary and tertiary care hospitals in Germany.

We hypothesize that (1) patient- and hospital-level outcomes of both intervention groups (AMS teams and AMS + IDS) will be significantly different (improved) compared to the baseline. Furthermore, we presume that (2) the effects in the more complex intervention AMS + IDS will be greater than for AMS teams. We assume that the interventions will be accepted and deemed beneficial (3), AMS + IDS more than AMS teams.

METHODS

Study Design

We designed a 3-year multicenter, prospective, two-armed intervention study with a pre-post analysis. Ten secondary and tertiary care hospitals (accounting for ~ 10% of hospital beds in the federal state of Baden-Württemberg) will participate. The allocation to groups will be stratified by hospital key characteristics (e.g., number of hospital beds, type of departments). Structural characteristics in terms of baseline AMS activities will be described by using the ICATB2 score, a composite score for AMS framework, resources, and action [29]. During the initial baseline year (2021), we arrange project preparations and offer a test phase for data entry and a workshop with the entire study staff to assess the specific needs, while the hospitals provide care as usual. We document the primary and secondary outcomes at baseline. This study phase also includes the detailed planning of the interventions by tackling organizational, structural, personal, and psychological aspects as well as potential psychological barriers and approaching facilitators.

During the second year, which includes a wash-in phase, the interventions will be implemented in two intervention groups, resulting in five hospitals for each group. We will train the teams during the implementation of the interventions. To adapt the interventions, if necessary, we will conduct a further workshop midway through the intervention phase [30]. We perform a process evaluation with semi-
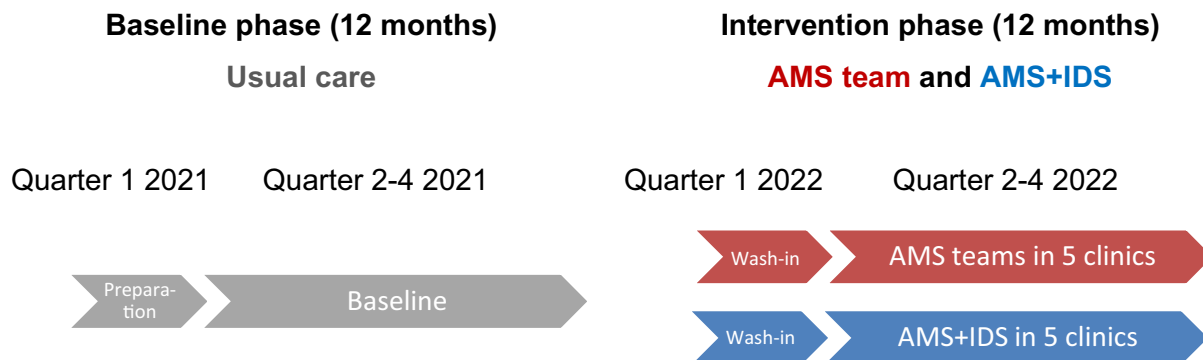
Baseline phase (12 months)

Usual care

Quarter 1 2021   Quarter 2-4 2021

Intervention phase (12 months)

AMS team and AMS+IDS

Quarter 1 2022   Quarter 2-4 2022

Fig. 1 Schedule of the study phases

structured interviews after 6 and 12 months during the intervention. Figure 1 shows the study schedule.

Interventions

We introduce a bundle of AMS interventions in all hospitals in varying degrees between the two groups (AMS teams vs. AMS + IDS) (Table 1). The interventions are planned and conducted following the national AMS Guideline [31]. The bundle includes:

– introducing formal AMS teams
– preparation and implementation of local prescribing guidelines and dosing recommendations for antimicrobials
– defining antimicrobial restrictions and implementation of mandatory prescription authorizations for reserve antibiotics, in agreement with the local institutional policies
– regular prescription audits through the AMS-team members (hospital-level point-prevalence surveys)
– regular educational events for prescribers, lectures and interactive workshops carried out by the AMS-team members, focusing on ID diagnostic, antimicrobial prescribing and case reviews, including feedback on antimicrobial use and resistance patterns
– local AMS team visits on selected wards (intensive care units and wards with high antimicrobial use) conducted by local AMS Team members. The visits comprise the review of antimicrobial therapies

(verification of the indication, review of drug, dosing, route of administration, and duration) and peer-to-peer discussion of the recommendations with the prescriber
– local IDS visits on selected wards (intensive care units and wards with high antimicrobial use) conducted by ID specialists. The visits comprise the complex evaluation of infections (site of infection, pathogen, susceptibility), the clinical condition of the patients, the review of the antimicrobial therapies (see above), peer-to-peer discussion of the recommendations with the prescriber, and a brief written recommendation
– availability of an ID consultation service

Sample Selection

Concerning our primary and secondary outcome variables (for further details, see Table 3), we will have two samples: sample A and sample B. Sample A comprises the primary patient-level outcome variables, diagnosed with one of the two indicator diseases (SAB or CAP). Sample B refers to the hospital-level outcome variables.

Regarding those secondary outcomes that will be provided by the health insurance company, the *Allgemeine Ortskrankenkasse* (AOK), the sample includes all newly admitted AOK-insured patients who have been diagnosed with SAB or CAP during the specified inclusion period. The AOK covers approximately 50% of Baden-Wuerttemberg's health insured population [32].

For the interviews within the process evaluation, we will apply the purposeful sampling technique to select the most promising sample, i.e., participants of the intervention team [33].

Inclusion and Exclusion Criteria

Inclusion criteria for sample A are either SAB or CAP (for further details, see Table 4 in the electronic supplementary material). For sample B, all inpatients of the respective hospitals are included, except for patients of the pediatric clinic and psychiatric departments. We will exclude incomplete data regarding the indicator diseases from the analysis.

Sample Size

Considering a dropout of 50%, our sample regarding CAP will contain 335 cases. Regarding the endpoint SAB, our sample will contain 110 cases in total. According to case numbers of SAB and CAP from previous years (which were reviewed by the centers involved), we assume we will be able to recruit the outlined numbers of cases, as we calculated with conservative recruitment rates, and it is highly unlikely that a significant decrease in incidence rates will occur. To prevent missing values, we plan a post-processing phase to complete the data should the maximum missing value of $> 5\%$ be exceeded. Concerning the power analysis, we assume that the effects (additional variance clarification by including group membership in our regression model) in the group AMS + IDS will be within the range of medium-high effects ($f2 = 0.12$) and for group AMS teams within the range of low to medium-high effects ($f2 = 0.08$) for our primary outcomes, SAB and CAP. We suppose, in accordance with standard conventions, a power of 0.80 and an alpha level of 5%, which was calculated by using the software "G*Power" [34, 35].

Measurements

The primary patient-level outcome is a 5-item SAB score and a 4-item CAP score (see Table 2), developed by the study staff based on current literature [36, 37]. Both dichotomous scores rate appropriate diagnostic and adequate treatment.

Table 1 Comparison of interventions

AMS teams	AMS + IDS
Antimicrobial prescribing guidelines	Antimicrobial prescribing guidelines
Dosing recommendations	Dosing recommendations
Educational events for prescribers (1 × 10 min lecture per department; 1–2 × 45 min. workshop/s per hospital)	Educational events for prescribers (3 × 10 min lecture per department; > 3–4 × 45 min workshop per hospital)
Antimicrobial restriction and prescription authorization	Antimicrobial restriction and prescription authorization
Prescription audit (hospital-level point-prevalence survey every 3 months)	Prescription audit (hospital-level point-prevalence survey every 3 months)
AMS team visits (intensive care units, wards with high anti-infective prescription rate) 1–2 × weekly	IDS visits (intensive care units, wards with high anti-infective prescription rate) 2–4 × weekly
	ID consultation service

Table 3 provides a detailed overview of the outcome measures, data source, and analysis.

Primary Outcomes

SAB The SAB data set comprises 171 variables, with a SAB score consisting of five variables. The variables were selected as several studies demonstrated that adherence to these diagnostic and therapeutic quality-of-care indicators are

Table 2 Overview of SAB and CAP scores

Five-scale SAB score (1 point, if applicable)	Four-scale CAP score (1 point, if applicable)
Follow-up blood cultures drawn within 48 h after initial treatment	Blood culture drawn prior to antibiotics
Antimicrobial treatment according to guidelines concerning agent and duration	Adequate treatment duration (< 7 days on the regular ward)
Performance of TTE and/or TEE	Initial therapy according to guidelines
Adequate search for SAB focus and metastatic manifestations	Recommendation of influenza and pneumococcal vaccination
Focus eradication control	

associated with improved outcomes in SAB patients [17, 36, 38].

CAP The CAP data set is composed of 159 variables, including a CAP score composed of 4 variables, which are already used (and validated) as process indicators of quality of care in the German health care system and shown to be associated with improved survival/outcome [39–43].

Secondary Outcomes
Patient Level As secondary patient-level outcomes, we will analyze in-hospital mortality, length of hospital stay, 30-day readmission rates, *C. difficile* incidence, and overall costs (including anti-infective and diagnostic costs).

Hospital Level Secondary hospital-level outcomes are antimicrobial prescription quality and density ascertained via a point prevalence survey, adherence to quality indicators, and overall cost calculations, such as diagnostic and anti-infective costs, hospital length of stay, personnel, and intervention costs.

Claims Data of Insurance Records The health insurance company will provide aggregated data on patient mortality (number of patients who died during a 30-day follow-up period after discharge), hospital length of stay, inpatient re-admission, case mix index of the participating hospitals, patient age, and the number of patients selected during the inclusion period and *C. difficile* incidence.

Process Evaluation For the process evaluation, we will conduct interviews 6 and 12 months after starting the intervention phase to analyze the implementation process and, if necessary, to optimize the interventions during the workshop. The interview will be semi-structured and conducted by our staff. The focus of the process evaluation will be the interventions' execution, barriers, and solutions as well as feasibility and benefits. We will also consider organizational, structural, personal, and psychological aspects.

Data Collection

Study physicians and pharmacists of the ten secondary or tertiary hospitals will collect and record the primary, patient-level, and some hospital-level secondary outcomes. We will therefore provide the study staff with the RED-Cap online data collection tool, version 10.6.13. The hospital-level secondary outcomes will be recorded across all patients by the responsible hospital. The health insurance company will provide us with the aggregated hospital-level secondary outcomes. Due to the anonymized data collection process, an informed consent will not be required; however, all the patients will be informed about the study upon their hospital admission.

Regarding the process evaluation, we will conduct semi-structured individual and focus group interviews at two time points (intermediate and at the end of the project) with participants of the intervention team after obtaining informed consent. Semi-structured interviews are suitable for problem-based and dialogical research questions, which match our purposes [44, 45]. Focus group interviews will be

Table 3 Overview of measurements and outcomes

Measurements	Instruments	Groups	Data Source	Data analysis
Primary outcomes				
SAB data set	Questionnaire	Baseline/AMS teams and AMS + IDS	Anonymous patient records	Quantitative analysis
CAP data set	Questionnaire	Baseline/AMS teams and AMS + IDS	Anonymous patient records	Quantitative analysis
Secondary outcomes				
Patient level[a]	Questionnaire	Baseline/AMS teams and AMS + IDS	Anonymous patient records	Quantitative analysis
Hospital level[b]	Questionnaire and point prevalence analysis	Baseline/AMS teams and AMS + IDS	Anonymous patient records, hospital records	Quantitative analysis
Claims data of insurance records	Aggregated data	All patients insured by the AOK	Health insurance company, AOK	Quantitative analysis
Process evaluation	Focus group and individual interviews	Medical staff (physicians and pharmacists)	Medical staff	Qualitative analysis

[a]The patient-level variable contains in-hospital mortality, length of hospital stay, 30-day readmission rates, *C. difficile* incidence, and costs

[b]The hospital-level variable contains antibiotic prescription quality and density, adherence to quality indicators, cost calculations (diagnostic and anti-infective costs, hospital length of stay, personnel, and intervention costs)

applied to explore the attitudes and experiences of the different groups [46].

The data collection process for the baseline phase started in April 2021. We will collect data for the intervention phase by the end of 2022.

There is no reason to assume that our interventions might lead to unfavorable patient outcomes. Moreover, our study is neither a Medicinal Products Act study nor does it involve experimental or high-risk interventions which necessitate a Data Safety Monitoring Board sensu stricto. Nevertheless, outcomes such as antimicrobial prescription quality and density (ascertained via point prevalence surveys) and adherence to quality indicators are measured every 3 months. Thus, if a negative impact of the intervention is observed, we will be able to approach the specific hospital and study team.

Data Analysis

During the third year of the study, we will evaluate the gathered data and publish the findings.

Analysis of the Primary and Secondary Outcomes

Even with a number of just ten clusters, multi-level modeling may result in unbiased estimations for the regression coefficients and standard errors [47]. We will use a restricted maximum likelihood compared to the use of maximum likelihood estimation as this is recommended in such situations. If so, propensity score-weighted estimators for clustered data will be applied. The patients of AMS teams and AMS + IDS having similar propensity scores can be considered as comparable, even though their scores on the individual factors influencing

group membership may differ [48]. Furthermore, the study will explore the proportion of outcome variance explained by hospitals (high proportions argue for hospital-specific factors of success) and conduct patient subgroup analysis.

We will apply a generalized multilevel analysis with a log link and a gamma distribution for the cost indicator analysis to account for the right skewness common in cost data as well as for the point prevalence survey. We will then correlate the outcome variables with the total costs as part of a cost-effectiveness analysis and compare the reduction of antimicrobial with hospitals of comparable size in Germany. We will conduct sensitivity analyses of the samples. The number of patients with inpatient re-admission (for any reason) includes a 95% confidence interval. We will further analyze the patients' age (mean, standard deviation) and check for gender effects.

As the data provided by the AOK will be aggregated for data protection reasons, we will use, among others, meta-analytical techniques. These enable inferential statistics about target variables by combining statistical parameters of individual samples, although no data on individuals are available.

Analysis of the Process Evaluation

The interview data's valuation will be based on the multi-stage qualitative content analysis procedure according to Mayring [49] and using the Max QDA Plus software.

Compliance with Ethics Guidelines

This study was approved by the Institutional Review Board of the Ethics Committee at Albert Ludwig University of Freiburg (reference no. 21-1073, 23-03-2021) as well as the Ethics Committee of the State Medical Council of Baden-Württemberg (reference no. B-F-2021-037, 12-04-2021). We confirm that the necessary steps were taken to adhere to the legislation in Germany and that the ethics committees at each site were consulted as required. The Institutional Review Board of the Albert Ludwig University of Freiburg waived the need for written informed consent. We performed all procedures in accordance with the ethical standards of the institutional or national research committee as well as the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards. This study protocol adheres to the recommended SPIRIT checklist. This study is funded by the Innovation Committee of the Federal Joint Committee (G-BA) supported by the Innovation Fund (proposal-ID: NVF2_2019-062). We will report important protocol amendments to and adapted by the Ethics Committee at Albert Ludwig University of Freiburg.

STRENGTHS AND LIMITATIONS

While AMS programs are established to various extents, ID specialist services are rarely implemented in routine care in Germany. In the ID ROLL OUT study, we will implement and evaluate holistic AMS tools with and without ID specialist services in secondary and tertiary care hospitals. We aim to identify means to comprehensively and sustainably improve the quality of care of patients with infections. The results of the two-armed study will be directly transferable to secondary and tertiary care hospitals throughout Germany.

The project is also designed to assess implementation barriers and promoting factors. We hypothesize that by analyzing these factors the investigated strategies can be implemented in clinical practice of other secondary and tertiary care hospitals without major transfer efforts. To successfully and sustainably realize the holistic intervention and to achieve an effective roll-out, we will consider relevant organizational, structural, personal, and psychological aspects to capture the diversity of the study staff. The idea is to not enforce the change in behavior on the participating medical staff, but rather to develop the innovation collaboratively. Studies have demonstrated that a participatory approach when implementing change is more likely to be accepted by individuals [25, 26].

There might be limitations due to non-randomization. However, we will stratify the hospitals by their specific characteristics, which is an appropriate approach due to the relatively

small number of hospitals. During the current pandemic situation, the patient population and hospital admission rates may differ from our case calculation, which might impact upon recruitment and infection rates.

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Data Availability. Data sharing is not applicable to this article as no datasets were yet generated or analyzed during the current study. The data files, statistical details and codes will be available from the corresponding authors. However, unrestricted, unreasonable data-sharing is not planned.

Dissemination. We will publish the study results in impactful peer-reviewed journals and present them at scientific conferences to provide data for health care professionals, the wider ID, and public health research communities.

Monitoring. A data monitoring committee (DMC) will not be needed as known risks are minimal.

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