GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections
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Antimicrobial resistance (AMR) is a growing public health concern, with a strong impact not only on human health but also on the economy and human development. Heads of States unanimously recognized this threat in September 2016 at the United Nations General Assembly, where they issued a declaration in support of implementation of the Global Action Plan on AMR that was adopted by WHO’s Member States at the Sixty-eighth World Health Assembly in 2015. AMR is considered a threat to achieving several Sustainable Development Goals, and the percentage of bloodstream infections due to two types of AMR has been defined as an indicator of progress in tackling this global threat.

Harmonized data collection is necessary to guide the world towards an optimal public health response and informed decision-making. In 2015, WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) – the first global system for collecting official national data on AMR in bacterial pathogens that cause common infections in humans. GLASS monitors the spread and frequencies of AMR in all regions of the world. But in addition to this monitoring, GLASS is also aiming to gather accurate estimates of the impact of AMR on human health to better inform strategies and investment to tackle this global threat.

Most estimates of the impact of AMR on human health are based on fragmented, very limited data, many of which are derived from epidemiological studies in high-income countries, often conducted by different methods, which makes consolidation for regional or global estimates impossible. The GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections is appropriate for generating robust estimates of the impact of AMR on human health. Like the SDG AMR indicator, the method addresses bloodstream infection with AMR organisms, which are considered to be among the most serious life-threatening infectious diseases.

Application of the GLASS method is expected to generate particularly robust estimates of the impact of AMR on global health through a systematic, harmonized approach in all countries.

WHO is grateful for the support of international, regional and national partners that contributed to the development of this harmonized, sound approach to broadening the evidence base for better-informed strategies to curb the impact of AMR on human health.

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## Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>BSI</td>
<td>Bloodstream infection</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Prevention and Control</td>
</tr>
<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
</tr>
<tr>
<td>DALYs</td>
<td>disability-adjusted life-years</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>ESBL</td>
<td>Extended-spectrum beta-lactamase</td>
</tr>
<tr>
<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
</tr>
<tr>
<td>GLASS</td>
<td>Global Antimicrobial Resistance and Use Surveillance System</td>
</tr>
<tr>
<td>HCF</td>
<td>Health-care facility</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IHME</td>
<td>Institute for Health Metrics and Evaluation</td>
</tr>
<tr>
<td>LIC</td>
<td>Low income country</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MDR</td>
<td>multi-drug resistance</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>MSSA</td>
<td>Methicillin-susceptible Staphylococcus aureus</td>
</tr>
<tr>
<td>NHSN</td>
<td>National Healthcare Safety Network</td>
</tr>
<tr>
<td>qSOFA</td>
<td>quick Sepsis related organ failure assessment</td>
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</table>
Rationale

1.1 Background

Antimicrobial resistance is a growing public health concern, which jeopardizes achievement of a number of sustainable development goals. However, the exact burden of disease associated with AMR is very difficult to establish, and in many settings no reliable estimates are available. Nevertheless, such findings are essential to inform policy makers about the potential health effects of interventions aimed at reducing AMR, to establish the amount of resources required to tackle this health concern, and to determine the most appropriate intervention strategies.
In population and public health, there are two main ways of thinking about and measuring burden of disease. The most common approach has been labelled “biomedical” [1]. It involves gauging the impact of disease and disability on patients, from the onset of illness to the outcome—recovery, chronic disease, disability, or death. It also involves assessing the potential of medical interventions to alter the course of diseases and future disability and illness. Information is gathered about how diseases and interventions affect individuals and these data are combined to create an overall picture of the health of the population. The other main approach to thinking of burden of disease is “economic.” It focuses on the financial costs of illnesses for individuals, households, healthcare systems, and societies.

In the Global Burden of Disease studies performed by the WHO [2] and the Institute for Health Metrics and Evaluation (IHME) [3] the burden of different diseases is measured in disability-adjusted life-years (DALYs) [4]. This combines the years of completely healthy life lost due to premature death and due to living with a disability. To calculate the latter, information is required about the frequency of disease sequelae, the duration of these sequelae, and the disability weight. These weights represent societal perceptions about the gravity of living with specific disease sequelae for a one-year period. Years lived in disability are especially important for chronic diseases, where people can have a reduced quality of life for extensive periods. In the case of acute infections, disease duration is often short, and sequelae are not so frequent. In a recent study by the European Centre for Disease Prevention and Control (ECDC) [5] it was estimated that 85% of BSI-associated DALYs consisted of healthy life years lost, due to the high attributable mortality. However, there is little data about the type, frequency, or duration of BSI sequelae, which are needed for correct DALY calculations [6]. These measures require active follow-up beyond hospital discharge, which would greatly complicate observational studies; it requires more resources, increases ethical complexities, and it would prolong study length, because, ideally, patients should be followed-up till death, or till sequelae have resolved or have become chronic.

At the international level, ECDC [5, 7] and the United States Centre for Disease Control and Prevention (CDC) [8] have published estimates for the number of deaths attributable to AMR in their respective settings. These estimates were based on region-specific AMR surveillance data and limited scientific evidence of attributable mortality rates from a small number of cohort studies. For many other regions, high quality surveillance data or AMR attributable mortality estimates have not been readily available. One effort at providing global estimates for AMR attributable mortality was carried out by the UK AMR Review Group in 2014 [9]. However, their results were extrapolated from AMR surveillance data in high-income countries and again lacked empirical evidence about attributable mortality. This emphasizes the need for two things; more comprehensive AMR surveillance data, especially for low- and middle-income countries, and more reliable and setting-specific estimates for AMR attributable mortality and morbidity. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) surveillance provides information about the frequency and geographical and temporal variance of AMR among clinically relevant bacteria at a global scale. However, detailed clinical outcome data of affected patients is currently not collected through this framework. Therefore, WHO GLASS proposes specifically designed studies to assess setting-specific by attributable mortality due to AMR within the GLASS framework to be offered to countries as ad-hoc protocols to better understand the impact of AMR. The current master template protocol is the GLASS method for estimating attributable mortality of AMR bloodstream infections.
GLASS currently collects information on infections in the bloodstream, urinary tract, gastrointestinal and genital tract, with an initial focus on *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Salmonella* spp., *Shigella* spp. and *Neisseria gonorrhoeae* [10]. In this first step towards the estimation of AMR health impact, GLASS will focus on one specific syndrome, namely bloodstream infections (BSIs). Identification of, and the definition for confirmed BSIs are very straightforward, namely the isolation of pathogens from blood cultures of patients. At the same time, these infections constitute one of the most serious and life-threatening infectious diseases. Moreover, in a recent study, it was found that mortality related to BSIs constitutes 72% of the total burden of AMR [5], at least in the European setting.

Considering technical and financial resources and study feasibility, this protocol specifically targets two pathogens with a specific resistance profile, to provide a framework that can later be expanded to cover other important bug-drug combinations:

- Extended-Spectrum Beta-lactamase-producing *E. coli* (ESBL *E. coli*)
- Methicillin-resistant *S. aureus* (MRSA)

These two resistant pathogens are responsible for a significant proportion of multi-drug resistant (MDR) BSIs; Cassini *et al.* in their analysis of the burden of resistant bacterial infections in Europe found that ESBL *E. coli* and MRSA had the highest impact on total DALYs per 100,000 population, contributing 41% of the total DALYs [5]. They are also part of the recommended core outcome indicators to monitor the impact of infectious diseases on human health for the WHO global action plan on antimicrobial resistance [11]. Based on the local epidemiology and availability of resources, the research team is encouraged to consider other BSI pathogens. Since carbapenem resistance is an increasing public health problem, which severely limits treatment options [12], the research teams may consider adding ESBL-producing or carbapenem-resistant *Klebsiella pneumoniae* or carbapenem-resistant *Acinetobacter* spp. whenever possible and relevant for the local disease epidemiology.

In settings where data is available from point prevalence surveys, or BSI surveillance, this could be used to identify other important AMR pathogens causing BSIs, which could be considered for this exercise as well. However, for harmonization purposes GLASS proposes that all participating sites at least include ESBL *E. coli* and MRSA BSIs.

Based on the above considerations, we selected in-hospital mortality as our primary outcome as it is the most pragmatic mortality measure. It is an easily available, objective and important endpoint, which does not require follow-up beyond hospital discharge. Discharge status “moribund” will be recorded as well for patients who are discharged to die elsewhere, and mortality 30 days after BSI (with follow-up beyond hospital discharge) will be added as an optional outcome measure.

There are several challenges when trying to estimate the impact of AMR BSIs on mortality. First of all, how do we establish whether mortality is associated with or a direct consequence of AMR BSIs? There are different methodologies that could be used:

- counting of cause-specific deaths through death certificates
- establishing AMR BSI case fatality rates
- determining excess mortality associated with AMR BSIs.
On death certificates, the main underlying cause of death for each patient is reported, plus secondary conditions contributing to death. Often, the main underlying cause of death involves a chronic condition; infections are seldom recorded as the main underlying cause of death. When looking at secondary conditions contributing to death, infections are reported more often, but the resistance profile of the causative pathogen is rarely included. Utilization of this method will therefore result in a large underestimation of the problem [13, 14].

When the relevant data is available, case-fatality rates for patients with AMR infections are relatively straightforward to obtain; it is the number of patients with a AMR BSI that died divided by the total number of patients with a AMR BSI within a certain time window. However, this proportion indicates whether a patient died with an infection, not whether the patient died because of the infection. It does not consider the possibility of that patient dying by the same infection caused by a susceptible strain of the same bacteria. Consequently, application of this measure will overestimate the excess of mortality associated with AMR.

Excess mortality, or attributable mortality, determines how many extra patients died because they acquired an AMR BSI. This method requires a comparison of case-fatality rates between patients with an AMR BSI and similar patients without such an infection (these different groups are called cohorts). This is the most often applied method and provides the most reliable estimates to determine the mortality attributable to AMR [13, 14]. Therefore, this is the approach that will be applied in this GLASS master template protocol.

The choice of comparator cohorts to include in a study looking at the impact of AMR BSI could be informed by the way interventions could change the occurrence of AMR BSIs. If one considers that interventions (like antimicrobial stewardship or vaccination) would reduce the number of AMR BSIs but replace (some of) them by drug-susceptible BSIs, patients with a drug-susceptible BSI would be an appropriate control group (replacement scenario) (Figure 1.1). However, if interventions (like infection prevention and control not specifically aimed at resistant infections) would reduce the number of AMR BSIs, and would either leave unchanged or reduce the number of drug-susceptible BSIs [15], then AMR and susceptible BSIs are independent entities (additive scenario), and non-infected patients should be the control group of choice (Figure 1.1). There is no definitive evidence indicating which scenario is more likely, and it may actually be different depending on the setting, level of resistance in the population, the causative pathogen, and whether the BSI is community-associated or hospital-associated [13, 15-18].

**Figure 1.1.** Additive and replacement scenarios in the context of AMR BSI epidemiology
Objective

Based on the above rationale, this GLASS master template protocol will allow for the generation of reliable estimates of in-hospital mortality attributable to AMR BSIs, at a minimum including ESBL E. coli and MRSA BSIs, both for community and hospital-origin infections, in the patient population that seeks care in a healthcare facility.
“Attributable mortality” is defined as the excess mortality among patients with AMR BSI when compared to patients without such an infection, adjusted for the influence of confounding factors (Paragraph 3.3 & Appendix 9.2.1). Countries can decide to recruit a number of healthcare facilities, preferably including different types of care and funding (Appendix 9.2.1). Duration of the study will depend on the required sample size, i.e. baseline mortality proportions and the magnitude of the desired detectable difference, combined with the number of participating hospitals, hospital size, and incidence of pathogen-specific BSIs.

It is important to note that the measurement of AMR BSI attributable mortality will be possible only for patients that are symptomatic, can access healthcare facilities, will have a blood culture result and for whom life status can be determined. In certain settings, particularly in low income countries (LICs), this may cause a large selection bias. In these cases, parallel studies should be designed to estimate the proportion of the population that cannot be captured by hospital-based studies, including health-seeking behaviour, community antibiotic use, and bias in selection of patients to undergo blood culture. Nevertheless, the patients targeted by this protocol will also be the ones that would benefit from improved prevention and treatment strategies. In addition, in certain contexts, discharge alive may not represent cure; dying patients are sometimes discharged to die at home for religious, cultural and/or financial reasons. To overcome this possible bias, the status at discharge for these patients will be recorded as “moribund”. In addition, mortality 30 days after the BSI, with follow-up beyond hospital discharge, will be included as an optional outcome measure. For hospital mortality, variability in length of stay, and thus follow-up, will be considered by applying appropriate survival models.
Method

This is a protocol for a **prospective cohort study** to estimate mortality attributable to community and hospital-acquired AMR BSIs for each selected AMR pathogen in selected healthcare facilities. For each target species of infection (e.g. MRSA), up to three cohorts of patients will be followed-up until hospital discharge, including patients with AMR BSIs of each target species, drug-susceptible BSIs of each target species and patients without BSI of the target species (at enrolment).
This study can be run in a single healthcare facility, or in a subset of healthcare facilities; considerations and selection procedures are detailed in paragraph 3.2. A formula to determine the target sample size of enrolled patients, including a way to determine the duration of the study is provided (see Chapter 4). To determine the attributable mortality associated with AMR BSIs, the first consideration is the selection of appropriate cohort groups. As discussed before, the type of comparator cohorts to be included in the study (drug-susceptible BSIs and patients without these infections) is intrinsically related to what the study aims to achieve. The comparison between patients with AMR BSIs and drug-susceptible BSIs assumes that every infection caused by resistant bacteria would be replaced by an infection caused by more susceptible bacteria if the spread of resistant pathogens was prevented [16]: this implies the assumption of the replacement scenario (Figure 1.1). Although easier to apply in a cohort study, this scenario is often not the case as the epidemiology of infections caused by susceptible and resistant bacteria is not necessarily analogous [19]. This approach will only generate data on the risk of dying from a resistant strain of a pathogen in an infected population. In contrast, for the additive scenario (Figure 1.1), patients with AMR BSIs and ‘non-infected’ patients are compared. This approach assumes that AMR BSIs affect a different type of patient than drug-susceptible BSIs, and if the AMR BSI would have been prevented these patients would not have experienced a BSI. Thereby, the occurrence of AMR BSIs would add to the total number of BSIs occurring in a healthcare facility [17, 18]. By considering both scenarios, the upper and lower limit of the impact of AMR can be determined.

A second consideration when implementing this cohort mortality study, is that patients in the control group will not be exactly the same as patients with an AMR BSI. For example, it is clear that a young, otherwise healthy girl, with a complicated fracture at the surgical department, will not have the same risk of dying as an old man with severe diabetes admitted to the ICU with heart failure, independent of the presence of an AMR BSI. Therefore, if groups are compared in an observational study, the analysis should always correct for the presence of underlying risk factors for death other than the exposure of interest. Information should be collected about demographics, as well as the patient’s acute disease severity, and their underlying chronic illnesses. The assessment of the underlying risks should be at least 48 hrs before the first signs of infection, to ensure they are not a consequence of the infection. Different clinical scores can be used to measure co-morbidities, like the Charlson score for underlying diseases [20, 21], and the (quick) SOFA score for acute illness [22-26].

Pathogen-related factors can also influence patient outcomes. It is clear from the scientific literature that not all BSIs have equal clinical impact; for example, *Acinetobacter baumannii* or *Klebsiella pneumoniae* BSIs more often result in a fatal outcome than *Escherichia coli* BSIs [27, 28]. Part of these differences may be associated with patient-related factors; vulnerable patients may be more prone to develop an infection by *A. baumannii*. However, two recent studies showed that even after adjusting for patient differences, pathogen related factors changed the mortality risk [29, 30]. Therefore, the impact of AMR BSIs needs to be determined separately for each pathogen.
Antibiotic treatment plays an important role as well in the relationship between AMR infections and mortality. Patients infected by multi-drug resistant infections have a higher chance of receiving inappropriate empirical treatment [31] and this has been associated with a smaller chance of survival [32]. In two meta-analyses the impact of multi-drug resistance in patients with BSIs was reduced after inappropriate empirical therapy was considered as well [32, 33]. Information about inappropriate treatment among patients with BSIs is important to assess current clinical management and could provide cues for improvement. Moreover, data about treatment strategies could help understand differences in the impact of AMR between healthcare facilities or clusters of healthcare facilities.

For example, settings with more available antimicrobial choices may be more likely able to provide adequate therapy for a resistant infection. As another example, settings with more multidrug resistance may be less able to provide adequate therapy for a resistant infection, and thus have higher AMR attributable mortality. However, since inappropriate empirical therapy is often a direct consequence of the presence of multi-drug resistance it can be considered part of the AMR concern and as such can be ignored when estimating the mortality associated with AMR. Since assessment of appropriateness of antibiotic treatment is very resource intensive as well, it will only be added as optional data to be collected in this protocol.

Finally, there are several technical considerations. In this method, the primary outcome is mortality at the end of hospital stay. This means that we are observing how long it would take for the event of interest, death, to occur and that the duration of follow-up will be different for all patients, and between different settings, as it depends on their length of stay and thus discharge policies. Therefore, survival analysis, which can consider heterogeneous duration of follow-up, needs to be applied. At the same time, it should be acknowledged that patients who are discharged can no longer die in hospital; hospital discharge and mortality are so-called competing events [34, 35]. This requires survival analysis adjusted for competing events; if regular survival analyses are performed the impact of an infection on hospital mortality will be overestimated [36].

In addition, the occurrence of a BSI is a time-dependent exposure; community-associated infections are present on admission, but hospital-associated infections only develop after at least two days in hospital. Some patients may only develop a hospital-associated infection after a number of weeks of hospital admission. If BSIs among hospitalised patients are considered as a fixed exposure in survival analysis, i.e. a risk factor that has been present from admission, this will underestimate the impact of AMR BSIs on mortality [36]. This is due to the fact that an artificial survival advantage is created; patients who acquire an infection had to survive long enough to be able to develop the infection (immortal time bias) [37].

All these factors have to be taken into consideration when trying to estimate the health impact of AMR BSIs [6]. However, to render the implementation of the current method feasible, some concessions will be inevitable.
3.2 Study population

The target population is the **adult**, **paediatric** and **neonatal** patient population seeking care in healthcare facilities. Inclusion and exclusion criteria are stratified according to the following levels [38]:

a) Healthcare facilities

b) Department

c) Patient

The inclusion criteria should first be applied to healthcare facilities, secondly to departments in the healthcare facilities that meet the inclusion criteria, then to patients in the selected departments. Table 1 provides a detailed overview of the inclusion criteria.

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>INCLUDE</th>
<th>EXCLUDE (EXAMPLES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare facility</td>
<td>Acute care healthcare facilities</td>
<td>Nursing homes Rehabilitation centres</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatric centres</td>
</tr>
<tr>
<td>Department</td>
<td>Acute care inpatient departments</td>
<td>Long-term care wards Day surgery wards</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day care wards (e.g. renal dialysis)</td>
</tr>
<tr>
<td>Patient</td>
<td>Patients hospitalized as an inpatient (requiring at least an overnight stay)</td>
<td>Outpatient clinic Day surgery/day treatment Outpatient dialysis Parents/relatives of admitted children</td>
</tr>
</tbody>
</table>

3.2.1 Healthcare facility

All types of acute care healthcare facilities where **appropriate antibiotic treatment for BSIs is available and used routinely** are eligible to carry out the method described in this protocol. Non-acute care facilities such as institutions providing only nursing care, rehabilitation centres or psychiatric centres should not be included (Table 1).

3.2.2 Department

All acute care inpatient departments in participating healthcare facilities should be included. Where distinction is possible, non-acute departments should be excluded (Table 1).

Excluded departments are defined as:

- Long-term care wards (e.g. nursing homes, post-treatment)
- Emergency departments (except for wards attached to this type of department where patients are monitored for more than 24 hours)
- Day-surgery wards, day-care wards (e.g. renal dialysis ward)
Within one department, some patients may fall into one of the above-mentioned excluded categories and other patients may meet the inclusion criteria. For example, a nephrology department may include both outpatient care (e.g. day-care dialysis patients) and inpatient care (e.g. kidney transplant patients). In this case all patients meeting the inclusion criteria (requiring at least an overnight stay) are selected irrespective of the nature of the department (Table 1). Department types included in the study are categorised according to the following wards types:

- Adult, paediatric or neonatal medical wards
- Adult, paediatric or neonatal surgical wards
- Obstetrics and gynaecology wards
- Adult, paediatric or neonatal intensive care units
- Haematology/oncology wards
- Emergency department wards where patients are monitored for more than 24 hours

### 3.2.3 Patients

All adult, paediatric and neonatal in-patients who are admitted to the defined departments and are expected to have at least one overnight stay during the study period are eligible for inclusion in the study. For cohort 1 all patients with a BSI caused by a drug-resistant target pathogen (f.e. MRSA and ESBL E. coli) will be included. Cohort 2 will consist of patients with a BSI caused by a drug-susceptible target pathogen (f.e. MSSA and non-ESBL E. coli). This will allow for the estimation of mortality in a replacement scenario (see 3.1). In order to be able to study the additive scenario as well (see 3.1), depending on available resources and chosen study objectives, a third cohort needs to be included. Cohort 3 can be included by selecting a random sample of patients without a BSI with the target pathogens at time of enrolment, this does not require confirmation by a negative blood culture but can be based on clinical presentation (Table 2). For further details regarding selection criteria, see paragraph 4.2.

<table>
<thead>
<tr>
<th>TARGET</th>
<th>ESBL E. COLI</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort-defining BSI</td>
<td>E. coli</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>ESBL</td>
<td>MRSA</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>Non-ESBL</td>
<td>MSSA</td>
</tr>
<tr>
<td>Cohort 3(^1)</td>
<td>Unexposed to target BSI at time of enrolment</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) If feasible, based on the resources and study objectives (see 3.1)
This study is based on the assumption that all patients with suspected BSIs will have a blood sample drawn according to best clinical practices, and that all blood samples undergo bacterial identification and antimicrobial susceptibility testing. This means that the patients included in this study will be representative for the selected healthcare facility.

However, if this assumption is not met and it is known that only a sample of patients would undergo testing this could limit the representativeness of the results; if only severely ill patients with a suspected BSI will undergo testing the study results will only be representative for this patient group. The same is true if blood culture testing depends on payment by patients. Another problem arises if only patients with a suspected BSI and failed empirical therapy will be tested. This will result in false estimates of the impact of resistance, because a large proportion of patients with drug-susceptible BSIs will not be identified.

In this case active case finding during the study period is strongly recommended to identify all individuals with suspected BSI (Appendix 9.2.2) in all the eligible departments [39]. Dedicated staff must be recruited to implement the study and support active case finding and referrals for microbiological testing.

### 3.3 Analytical methods

Descriptive statistics will provide a good overview of the characteristics of the enrolled patients as well as crude case fatality rates for BSIs per age group (neonatal, paediatric, adults), per infection origin (community-origin or hospital-origin), and per pathogen (\(S.\ aureus\) or \(E.\ coli\) BSI) and resistance profile (ESBL, MRSA).

In order to come to AMR mortality estimates, the crude case fatality rates for AMR BSIs (cohort 1) need to be compared to those for drug-susceptible BSIs (cohort 2) or to unexposed patients (cohort 3), and differences between patients like age, gender, and Charlson comorbidity score need to be considered as well. Moreover, not all patients enter the hospital with a BSI, some patients develop a BSI after a number of days in hospital, this time-dependency needs to be acknowledged as well [36]. Finally, hospital discharge prevents observation of in-hospital mortality, they are so-called competing events [34].

Different types of survival models can be applied that will be able to take all of the above challenges into account, including the sub-distribution (Fine and Gray) approach, and the cause-specific approach [55]. These models do assume proportional hazards, which should be graphically checked using scaled Schoenfeld residuals. The sub-distribution approach will provide a summary estimate of the impact of AMR BSIs on the outcome of interest, while adjusting for the competing event. It will provide estimates of the change in daily mortality rates among hospitalized patients due to AMR BSIs (hazard ratios, HR). The HRs derived from these types of models predict an individual's risk to experience a fatal outcome when acquiring an AMR BSI. The cause-specific model will provide estimates for the impact of AMR BSIs on the outcome of interest as well as the competing event, providing more insight into the etiology of the disease. Other models that can be considered include Aalen additive hazard models, or marginal structural models [56].

All potential confounders should be included in the final model; factors that are known risk factors for hospital mortality and influence the risk of a (AMR) BSI, which are not on the causal pathway from BSI to death. Potential confounders include gender, transfer from another hospital, regular hospital contact, ICU stay, surgery, Charlson score, qSOFA, Pitt bacteremia score, pathogen and the matching variables; age and type of admission. If multiple healthcare facilities delivered data, the model should be stratified by healthcare facilities to account for clustering effects and allowing heterogeneity in baseline hazards. This model can be used to compare cohort 1 to cohort 2, as well as cohort 1 to cohort 3 and cohort 2 to cohort 3. Since cohort 3 contains matched patients, this needs to be considered in the model as well through robust variance estimators.
Sample size and sampling strategy

4.1 Sample size calculation

For every study, it is important to determine the appropriate number of subjects required. If the number of included patients is too small, the study will not provide conclusive evidence and all the work will be in vain. If the number of subjects is very high, this will unnecessarily increase the workload.
In order to calculate the appropriate sample size for a reliable estimate of the attributable hospital mortality for AMR BSIs, the following items are required:

- The **expected mortality** among patients with BSIs (for the pathogen of interest)
- The clinically relevant difference in mortality risk one wants to detect between patients with AMR BSIs and drug-susceptible BSIs expressed as a **hazard ratio** (based on Cox regression, the technique required to analyse hospital mortality data)
- The **proportion of resistance**, number of AMR BSIs over all BSIs (for the pathogen of interest)
- The **probability of detecting the true difference** (1-beta, power)
- The **significance level** (alpha, precision)

The expected mortality and clinically relevant difference can be derived from published data. In previous, high-quality scientific studies, hospital mortality for patients with carbapenem-resistant Enterobacteriaceae [40], third-generation-cephalosporin resistant *E. coli* [41], and methicillin-resistant *S. aureus* [42] were all close to 35%, compared to mortality proportions between 17% and 23% for patients with BSIs caused by their susceptible counterparts, with an overall case fatality for patients with a BSI of 26% to 29%. The calculated hazard ratios comparing incidence of hospital mortality between patients with AMR BSIs and susceptible BSIs in these studies ranged from 1.68 to 2.90 [40-42].

Based on these data, using the most conservative approach, we can assume an overall mortality of 25% (pE) for patients with BSIs (AMR and drug-susceptible) and a relevant difference expressed as hazard ratio (HR) of 1.7. Then, the sample proportion of patients with AMR BSIs over the total number of BSIs is required, this is equal to the proportion of resistance (pA). This is specific to the study setting and should be determined for each of the AMR BSIs of interest, consequently for each setting and each AMR BSI under study a separate sample size needs to be calculated. For the probability of detecting a true difference and the significance level commonly used values can be applied: 80% power (z-score=0.84) and a precision of 0.05 (z-score=1.96).
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Different formulas exist to calculate sample sizes for survival models; some require more knowledge about the expected data than others, some are more easily applicable than others. Depending on the applied formula, the calculated number of patients that should be included in the study will slightly change. Here, we demonstrate how you can use the formula by Chow et al. [44]. This formula was developed for randomised clinical trials but will give an approximation of the required sample size for this observational study without requiring in-depth knowledge of the data structure. It is also available as a free online tool (powerandsamplesize.com). They apply the following formula for time-to-event data:

\[(1.96 + 0.84)^2\]
\[\text{Total sample size} = (\log (HR) - \log (1))^2 \times p_A \times (1 - p_A) \times p_E\]

Since some patients might be lost to follow-up it is best to add 10% to the calculated sample size and round it upwards.

**EXAMPLE: CALCULATING SAMPLE SIZE**

Healthcare facility A has reported 20 MRSA and 80 MSSA BSIs to GLASS the previous year, i.e. a MRSA resistance proportion of 20% \((20 \text{ MRSA BSI} / (20 \text{ MRSA BSI} + 80 \text{ MSSA BSI}))\).

Using the sample size tool, they can now calculate the required sample size for an AMR attributable mortality study in their setting. The general, conservative estimate for BSI mortality of 25% should be included as the probability of the event: \(p_E = 0.25\). The general, relevant difference of 1.7, should be included as Hazard Ratio: \(\theta = 1.7\). The power should equal 80%: \(\text{Power}, 1-\beta = 0.80\) (z-score=0.84), and precision should be 5%: \(\alpha = 5\%\) (z-score=1.96). Finally, we need to include the setting- specific MRSA sample proportion of 20%: \(p_A = 0.20\).

Inserting the above numbers in the tool, a total sample size \((\text{Sample Size}, n)\) of 696 patients is calculated, see Figure 3.1. The same can be achieved by using the formula above:

\[(1.96 + 0.84)^2\]
\[\text{Total sample size} = (\log (1.7) - \log (1))^2 \times 0.2 \times (1 - 0.2) \times 0.25 = 696\]

This means that, with a resistance proportion of 20%, 138 patients with a MRSA BSI (0.2*696), and 558 patients with a MSSA BSI (0.8*696) should be recruited. If it will be a multicentre study, data will be clustered, and this sample size should be increased by a design effect of 9%. In addition, some patients might be lost to follow-up so another 10% needs to be added to the minimum sample size. Therefore, the study should include 138*1.09*1.10=165 patients with a MRSA BSI, and 558*1.09*1.10=669 patients with a MSSA BSI, in total 834 patients with a S. aureus BSI.
Figure 3.1. Calculation of the sample size for time-to-event data using the formula by Chow et al., a hazard ratio of 1.7, 25% mortality, and a resistance proportion of 20% (Pa=0.2) (http://powerandsamplesize.com/Calculators/Test-Time-To-Event-Data/Cox-PH-2-Sided-Equality)

For ESBL *E. coli* BSIs, the same calculations can be performed, including the same conservative estimate for overall mortality of 25% for patients with BSIs (AMR and drug-susceptible) and a relevant difference expressed as a hazard ratio of 1.7, a power of 80% and a precision of 0.05. The only difference will be the sampling proportion of AMR BSIs, as this should be equal to the proportion of ESBL among *E. coli* BSIs in your setting.

For cohort 3, the unexposed cohort, sample size is easy. Each patient with a BSI should be matched to an unexposed patient, in a ratio of 1:1. The sample size of unexposed patients is therefore the same size as cohort 1 (AMR BSIs) plus cohort 2 (drug-susceptible BSIs). In the example of healthcare facility A, where 165 patients with a MRSA BSI and 669 patients with a MSSA BSI were needed, cohort 3 should consist of 834 unexposed patients.
4.2 Patient selection strategy

Individual-level patient data will need to be collected for all cohorts; patients with AMR BSIs (cohort 1), a cohort of patients with drug-susceptible BSIs (cohort 2), and a matched cohort of unexposed patients (cohort 3).

4.2.1 Active case finding (if study assumption about culturing all patients with a suspected BSI does not hold)

Active case finding of BSI cases for the study, as well as for good clinical practice, includes the following sequence of steps:

1. During routine hours, survey staff in inpatient wards and emergency/casualty units at the participating site will identify patients with suspected BSI (For definition, see Appendix 9.2.2)

2. If a patient has suspected BSI, then the patient must be referred for blood culture collection immediately, before administration of any antibiotic treatment (For methods, see Appendix 9.1).

3. At the laboratory, the specimen should be processed for bacterial isolation, identification, and AST. (For methods, see Appendix 9.1)

4.2.2 Cohort 1 and cohort 2

For identification of exposed patients for the targeted BSIs (cohort 1 and 2), blood culture results from the microbiological laboratory will need to be reviewed at least on a weekly basis for the duration of the study. Every patient who has a positive blood culture for *S. aureus* or *E. coli* (plus any extra target pathogens selected to be important for your setting) with antimicrobial susceptibility testing (AST) results should be enrolled. For all these patients demographic, clinical and outcome data will need to be recorded. They will form cohort 1, AMR BSIs, and cohort 2, drug-susceptible BSIs. Every patient can only be included in each cohort once. If a patient has multiple episodes of *S. aureus* or multiple episodes of *E. coli* BSIs during the study period, as per GLASS methodology only the first one will be considered [10]. If for one patient two target pathogens are isolated from the first blood culture set they should be treated as separate events and the patient included in the study twice. The enrolment date of these patients will be the date the blood culture was taken that was later confirmed to be positive (i.e. time 0). Exposed patients are enrolled until the target sample size is met (see paragraph 3.2.1).

4.2.3 Cohort 3

Cohort 3 should consist of unexposed patients, which means patients without a BSI with one of the target pathogens at the moment of enrolment. These can be both patients not diagnosed with suspected BSI, and therefore not blood sampled) of patients with confirmed BSIs by other pathogens or other type of infections. Cohort 3 should include randomly selected control patients for cohort 1 and 2 as it should enable a comparison of hospital mortality between patients with a AMR BSI (cohort 1) and no BSI, and between patients with a drug-susceptible BSI (cohort 2) and no BSI. For this cohort, patients should be selected in a random fashion using exposure density sampling [45] plus additional matching criteria (see below) to increase comparability.

Exposure density sampling means that for every patient with a BSI by a target pathogen an unexposed patient is matched based on duration of hospital stay before infection (LOS before BSI), on an individual level, with a 1:1 ratio. The unexposed patients should have a length of stay at least equal to the LOS before BSI of the infected patient and should have been free of BSIs by the target pathogens during that time. However, unexposed patients can develop a BSI with the target pathogen at a later point in time, because excluding patients based on a future event (a novel BSI) can introduce bias [46]. See figure 3.2 and the example below. To increase comparability of patients with a BSI (cohort 1 and 2) and unexposed patients (cohort 3) patients should also be matched on age group (neonatal, paediatric, adult), and reason for admission (elective or emergency admission). To further consider differences between adults and elderly patients, age will also be added as a covariate in the analytical models (Paragraph 3.3).
If an included unexposed patient develops a BSI with a target pathogen before death, discharge, (or the 30 day follow up if applied), this patient will remain in cohort 3, but will also be included in cohort 1 (AMR BSIs) or cohort 2 (drug-susceptible BSIs), depending on the susceptibility profile of the pathogen. Consequently, an extra unexposed patient needs to be selected for this newly infected patient. The best way to find eligible unexposed patients is to use the hospital admission registry to select all patients that were admitted on the same day or up to a week before the BSI patient. Then, select all patients that had a hospital admission at least equal to the LOS of the patient with confirmed BSI. Remember the LOS is calculated from the 1st full day of hospitalization to the day the blood culture was taken. Delete all patients that had a confirmed S. aureus or E. coli BSI and shorter LOS. From the remaining patients select the first one in the list who belongs to the same age group (neonatal, paediatric, or adult), and had the same reason for admission (elective or emergency admission).
Data collection

Data will be collected at healthcare facility-, and patient-level on standardized data collection forms (protocol supplementary material).
Healthcare facility form variables (Appendix 9.3):
For each healthcare facility participating in the study, hospital ownership, the type of healthcare facility, and healthcare facility activity data needs to be collected for the year prior to the study. The healthcare facility questionnaire should be completed at the beginning of the study and outcomes are used to adjust the analysis for healthcare facility characteristics, to interpret study results and to enable the possible modelling of the nation-wide estimates of attributable mortality among patients with bloodstream infection due to selected types of AMR.

Patient form variables (Appendix 9.4 & 9.5 & 9.6):
Patient-level data forms the basis of this study and consists of a set of demographic variables and clinical variables. Individual-level data will need to be collected (mainly) prospectively by a dedicated onsite investigator, based on information registered in hospital patient files. Most data will be collected at enrolment, then between enrolment and discharge. Variables are stratified by core and optional variables. Core variables should be collected in all healthcare facilities and are essential for this study to ensure valid results. Optional variables could provide more insight and more precise estimates but are not essential.

5.1 Individual patient data collection

Patients are enrolled until the necessary sample size is met, preferably this covers a full year to avoid any seasonal influences. Regardless of the cohort they belong to, or the end-date of the study, all enrolled patients are followed up until hospital discharge.

The onsite investigators will follow-up all patients for cohort 1, 2 and, if present, cohort 3. For every patient, data should be collected:

- At enrolment into the study (‘enrolment’): Date of blood culture for cohort 1 and cohort 2, and the date of enrolment for matched BSI patient for cohort 3 (in practice enrolment will be several days after the blood culture, since there is a delay in microbiological confirmation)
- At discharge (‘discharge’)
- At 30 days after enrolment if day 30 mortality is included as a secondary outcome

As soon as a patient is enrolled in the study, enrolment information should be collected from the patient file based on the patient enrolment questionnaire (Appendix 9.4), this will be retrospective data collection. From then onwards, the patient needs to be followed-up to make sure the patient will not be lost-to-follow-up and to collect additional clinical information (Appendix 9.5). Discharge information and day 30 mortality data can be collected based on the “Patient discharge form” (Appendix 9.6). If at day 30 after enrolment a patient is already discharged, life status can be determined through out-patient visits, mobile phone contact with patient or family members, or regional or national death registers.
Data management

Specialized database managers should develop a database necessary for data capture [39], with appropriate back-up options and data access rules. The computer housing the database will be password protected at login and on screensaver. If possible, data extraction from electronic information systems should be developed to feed the database, as this can improve data consistency and quality.
For all data not available for electronic extraction, electronic data entry forms need to be developed with incorporated validation rules (like consistencies of dates, format or logical age limits). Subsequently, data can be collected on paper forms and entered through these data entry forms, or they can be collected directly through completing the electronic data entry forms by study staff.

Each week, at each site, a site supervisor or his/her designee will perform quality control by reviewing a selection of completed forms for completeness and consistency. After entry of study data into the database, data quality procedures will be carried out, in addition to the validation rules, to identify problems such as missing data for core variables, inconsistencies between dates, etc. Entries flagged as errors will be recorded and communicated to study staff for correction.

Within one week of end of follow-up, the questionnaire and laboratory forms corresponding to the patient should be completed, checked for quality, and if a paper system is used, scanned electronically, and securely archived.

Once all individual patient data is collected, all data fields are validated, and all data queries have been finalized the database will be locked and the analysis can start.

GLASS will be able to assist with data management and analysis. It will have access only to coded data obtained during the study. GLASS will not have access to documents that link hospital identification numbers to study identification numbers. GLASS will not be involved in recruiting patients for the study, administering questionnaires to enrolled individuals, collecting clinical data, or testing specimens collected during the study. GLASS may be involved in evaluating case-finding practices, laboratory performance, and other study procedures.
7.1 Setting and frequency of the exercise

Contrary to other GLASS activities, application of this method is not a continuous activity. GLASS promotes to carry it out at least once, but the study can also be performed at regular intervals depending on local information needs. If there are large healthcare system changes, impact of AMR BSIs on mortality can change, and this could be a reason to repeat the exercise.
The research team, at a minimum, should consist of a principal investigator, a microbiologist, a research manager, a data manager, a statistician/epidemiologist, and an onsite investigator. Certain roles can be covered by the same person (e.g., principal investigator and microbiologist, or research manager and data manager).

The **principal investigator** should supervise the research team, ensure alignment with local ethical guidelines, is responsible for local ethical clearance, the quality of the data and the final output. This person should have previous research experience in the field of antimicrobial resistance, and preferably has a degree in infectious disease medicine, epidemiology, public health or microbiology.

The **microbiologist** is responsible for implementation of standard operating procedures for blood culture processing in the local laboratory, quality control, and high quality microbiological data, including species identification and AST results. This person is also responsible for providing access to the data to be able to identify eligible patients, and to record results in the study-specific electronic database.

The **research manager** is in charge of study logistics, like selecting and training the onsite investigators, making sure all required material is available (printed study method, digital or printed data entry forms, a database etc.), sticking to timelines, responding to queries, motivating onsite investigators, performing quality control checks etc. Previous experience as a clinical research manager is key.

The **data manager** organizes, implements, and enforces correct data collection policies and procedures, and needs to manage all incoming data files. If data is collected on paper, this person oversees digitalization of the data as well. If data is collected digitally, responsibilities include rolling out the digital data entry forms, encrypted transfer of data files, and compilation of data in one database. Data privacy and security are paramount. A strong IT profile, knowledge of database management, including application of data validation rules and data privacy are key.

The **statistician/epidemiologist** is responsible for data cleaning, data analysis and reporting, under the supervision of the principal investigator. Previous experience with setting up and analysing cohort studies, including survival analysis for competing outcomes would be very helpful.

The **onsite investigator** is responsible for data collection at the HCF level, in a standardized way, ensuring high data quality. This person will also transmit deidentified data to the data manager and is responsible to solve data queries from the data manager for missing data or data entry errors. The onsite investigators must be hospital staff who have routine access to patients’ blood culture results and antibiotic treatment records (e.g., the chief microbiologist or the infectious disease clinician).
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7.3 Ethical review and data privacy

According to general WHO guidelines, this study should include all standard safeguards for ensuring the confidentiality of patient information. Importantly, data that will be transmitted to the data manager should not allow identification of individual patients. Only de-identify data can be transferred to anyone who does not have routine access to patients’ medical records. The onsite investigator will hold a file providing the key to connect individual patient identifiers created for the study to individual patient identifiers within the hospital. This is required for data completion and correction issues after data collection has finished. Once the database is locked, this file should be destroyed, and anonymization should be irreversible. If files are transmitted electronically to the principal investigator, file(s) should be encrypted and transmitted via a safe online file sharing platform.

7.3.1 Informed consent

For this is a prospective observational study where routine clinical care data will be gathered from patient notes or other medical records, patients informed consent is required even if no interaction with the patient is necessary to obtain additional information (Informed consent form templates can be found at the end of this document). However, this is not an intervention study, so no experimental changes will be made to the care or treatment regime. The research study must be adequately explained to the patient, and the patient must have the capacity to consent. If active case finding during the study period is required, because routine clinical care does not include blood cultures for all suspected BSIs, informed consent for blood sampling may also be required (Informed consent form templates can be found at the end of this document). The consent can be oral or written. If a patient does not have decision-making capacity, treatment will be routinely offered as per the clinic/hospital standard procedures.

If required, it is advisable that the informed consent is obtained by someone who has no direct impact on patient care, due to power balances. For example, if the treating health professional requests for consent, the patient may feel obliged to accept. In cases where patient interaction is unavoidable, for example if the medical records and clinical notes are kept with the patient, an information and consent procedure may be necessary also in cases where informed consent is not required. In countries that do not require informed consent by individual patients, a broader informed consent can be sought as substitution. This can be achieved through an informed opt-out procedure, i.e. the medical records and associated patient documentation are reviewed unless the patient in question explicitly objects.
According to the International Ethical Guidelines for Health-related Research Involving Humans [47], the informed opt-out procedure must fulfil the following requirements:

- Patient should be aware that the study is taking place
- Patient should be provided with sufficient information about the study
- Patient should be informed that they can withdraw from the study and be given a genuine opportunity to do so. In practice, this can be achieved through several means, and patients may be informed verbally or in writing, for example through posters and pamphlets at the HCF.
- Patients should be informed that if they choose not to participate in this research project or to withdraw, they will still be offered the treatment that is routinely offered in the clinic/hospital for the selected infections and their samples will be used and stored as per the facility standard procedures.

A set of informed consent templates are available with the protocol supplementary material.

In addition to the studied patients, hospital staff and in some cases medical associations and unions should also be informed about the study. Necessary information includes:

- Purpose of the survey
- How and when the data collection will take place
- How data related to their practice will be used

This information should be conveyed to the staff by the hospital management and onsite investigator.

7.3.2 Patient privacy

It is mandatory to pseudonymize individual patient data during data collection and anonymize the data once the database is locked. In this study, two identifiers should be created; one for local use ("Patient ID"), and one for use in the analysis phase ("Patient Code"). The Patient ID should not contain any directly identifiable information, such as name and/or date of birth, but an existing hospital registration number or patient record number consisting of numbers and letters can be used. This identifier can be used by the onsite investigator to identify the patient and complete the data entry forms during the study period, and to solve data queries from the data manager. This identifier will not be entered into the electronic database or on paper forms.
The onsite investigator should also assign a study-specific anonymous code to each included patient (i.e. "Patient Code"). This code should be unique for each included patient at the hospital level and should not be related in any way to the Patient ID, or any other identifiable information. This identifier will be used on all data entry forms, and during data analysis to recognize each unique patient, without revealing the patient's identity. The "Patient Code" will be the patient identifier entered in the database. In multicentre studies, the combination of a HCF identifier (an anonymized HCF code for study purposes) and the "Patient Code" will generate unique identifiers for all patients.

The onsite investigator should create an encrypted file, where the link between the two identifiers for each patient are recorded. The "Patient ID" and the key between the "Patient ID" and the "Patient Code" may be stored safely for up to 6 months for validation purposes but should be eliminated after this time-period to irreversibly de-identify the individual patients. The principal investigator is responsible for ensuring that the de-identification of patient data takes place within the specified time-period and that the data collected at the HCF is safely stored. Some information may be difficult to de-identify, especially when the diagnosis or treatment is rare. In the context of this study, most diagnosis or treatments are general. However, it is important that data continue to be stored safely and be accessible only to authorized personnel after de-identification.

7.3.3 Data storage

Since the data collected for this study may contain sensitive information identifiable at the patient level, it is important that the data are stored safely with only authorized personnel able to obtain access. The means of storage may vary depending on the resources of the hospital, but the principal and onsite investigator should ensure that safe storage is achieved and is in accordance with the ethical and data safety regulations in that country. For example, all computers, electronic devices and data files will be encrypted with a password. When available, data files should preferably be stored on secure networks and VPNs of a hospital or university; permanent storage on external disks, e.g. USBs, should be avoided, as these devices may be lost. Regular back-ups of electronic data are paramount. Best practices include: 1) an original database on a local network/disk maintained by the data manager, 2) a copy on an external network/disk, 3) a copy on an external network/disk that is physically hosted at a different location. These databases should be synced at least weekly.
7.3.4 Ethical committee

Before conducting the study, the principal and onsite investigator must seek ethical clearance from the hospital management and/or the national, regional or local ethical committees as per institutional policies. As the scope of the method is public health surveillance, ethical clearance should be sought for surveillance and not for medical research when applicable. WHO published guidelines addressing ethical considerations in public health surveillance in 2016 [47].

In addition to approval for data collection, it is also advisable to simultaneously seek clearance for sharing of deidentified data with the WHO if desirable. It is important to note that different rules may apply for local or national use versus international use of the collected data. For example, local regulations may not require informed consent for local use of data collected by means of this survey but may require informed consent if the data are to be shared outside of the national borders. In these cases, the principal investigator is responsible for ensuring that necessary requirements are met before sharing data with the WHO. It is important that the results of the study are shared with the hospital administration, and relevant hospital staff.

7.3.5 Publications

Publications based on data collected by means of this method should reference the method and the version number.
References


Appendices
9.1 Currently recommended blood culture practices

For adults, the Clinical and Laboratory Standards Institutes (CLSI) guidelines recommend four 10-ml bottles of blood (e.g., two sets of blood cultures, each consisting of an aerobic and anaerobic bottle, equivalent to 40ml of blood) from independent puncture sites to be able to detect about 90-95% of BSIs [48]. If resources are limited, preference should be given to two 10-ml aerobic bottles, anaerobic bottles have a lower priority.

Multiple sets can be collected simultaneously or over a short period of time; timing doesn't seem to significantly affect the recovery of clinically relevant pathogens. Venipuncture is the preferred method, as arterial blood samples do not increase diagnostic yield, and blood specimens from intravascular lines have demonstrated increased rates of contamination [48]. For children the volume should be adapted to the patient’s total blood volume and weight, and should consist of 1-2 aerobic bottles, anaerobic bottles should only be included when deemed clinically relevant. Recommendations include one 2-ml aerobic bottle for children <1kg, two 2-ml aerobic bottles for children 1.1-2kg, one 4-ml and one 2-ml aerobic bottle for children 2.1-12.7kg, two 10-ml aerobic bottles for children >12.7kg, and for those >36.3kg adult standards can be followed [49].

Proper skin sepsis with a tincture of iodine, chlorine peroxide or chlorhexidine gluconate (not appropriate for enfants<2 months) prior to blood sampling is required to reduce blood culture contamination rates [48]. Blood specimens should be collected prior to administration of antibiotics.

Blood culture specimens should be sent to the laboratory as promptly as possible, preferably within 12 hours, they should never be refrigerated or frozen, or held at room temperature for more than a few hours. A significant reduction in pathogen recovery has been observed when blood culture bottles have been held for >24h between 4-18 degrees Celsius or >12h at 37 degrees Celsius. Lengthy incubation of blood culture bottles prior to entering them into a continuous-monitoring blood culture instrument may delay or impede the detection of growth and is discouraged [48].

9.2 Definitions

In this protocol the following definitions have been used, apply to the data collection forms as well and should be applied during data collection.

9.2.1 Country/HCF level

HCF type of care

When a hospital has facilities with different levels of care, then the highest hospital category should be reported. For example, if one facility of the hospital belongs to the primary level and another facility belongs to the tertiary level, then the reported category should be tertiary hospital.

**Primary care** (typically 30-250 beds):

a. Few specialties (mainly internal medicine, obstetrics-gynaecology, paediatrics, general surgery or only general practice);

b. Limited laboratory services are available for general, but not for specialised pathological analysis;


**Secondary care** (typically 200-800 beds):

a. Hospital is highly differentiated by function with five to ten clinical specialities, such as haematology, oncology, nephrology, intensive care unit (ICU);

b. Takes some referrals from other (primary) hospitals;

c. Could have teaching activities;

Tertiary care (typically 300-1500 beds)
a. Highly specialised staff and technical equipment (ICU, haematology, transplantation, cardio-thoracic surgery, neurosurgery);
b. Clinical services are highly differentiated by function.
c. Specialised imaging units;
d. Regularly takes referrals from other (primary and secondary) hospitals;
e. Often a university hospital or associated to a university;
f. Commonly referred to as ‘national hospital’, ‘central hospital’, or ‘academic or university hospital’.

Specialized hospital
a. Single clinical specialty, possible with subspecialties
b. Highly specialized staff and technical equipment

HCF ownership
For the purpose of the study, HCFs will be categorized based on the type of care and funding [50]. If hospital ownership is unclear, prioritize management over ownership of the building and/or funding. For instance, if a hospital is managed privately (for profit) but the building is state-owned, or the hospital receives public funding, then select “private, for profit”.

Public
Healthcare facilities that are owned or controlled by a government unit or a public corporation (where control is defined as the ability to determine the general corporate policy).

Private, not for profit
Healthcare facilities that are legal or social entities created for the purpose of producing goods and services, whose status does not permit them to be a source of income, profit, or other financial gain for the unit(s) that establish, control or finance them.

Private, for profit
Healthcare facilities that are legal entities set up for the purpose of producing goods and services and are capable of generating a profit or other financial gain for their owners.

Other or unknown
Healthcare facility ownership cannot be categorised as one of the above, or healthcare facility ownership is unknown.

Hospital group
A hospital group consists of multiple hospitals (sites) linked together administratively. Hospital groups can be referred to as trusts, mergers, fusions, boards, chains, and so forth. As part of a hospital group, the hospitals must follow the same common rules in terms of management, care to patients, policies or guidelines, and so forth. This tight relationship between hospitals of the same hospital group may affect their individual results by making them more homogenous than when compared with hospitals not belonging to the hospital group.

It is not mandatory for all hospitals (sites) belonging to a particular hospital group to participate in the study; however, data must be reported separately for each participating hospital (site). When hospital groups participate in the survey, the variable “HospitalGroupCode” will anonymously identify the hospital group. All hospitals belonging to the same hospital group have the same value under “HospitalGroupCode”, making it possible to group them together for analysis. The principal investigator should provide an unique “HospitalGroupCode” to all hospitals from the same hospital group.
High risk wards

High risk wards are defined as units or wards that have higher number of patients with serious infections due to the type of care they provide. High risk units consist of wards with the following specialties:

- Haematology
- Oncology
- Burns
- Transplantation
- Infectious diseases (general or specialized infectious disease wards; e.g. HIV units, neonatal units) Attributable mortality

Excess mortality among patients with AMR BSI when compared to patients without such an infection, adjusted for the influence of confounding factors

9.2.2 Patient-level

Suspected blood stream infection (BSI) in adults

All adult patients (>17 years old) with two or more of the following clinical signs (adapted from [51]):

- Hyperthermia (>38 degrees Celsius) or hypothermia (<36 degrees Celsius)
- Respiratory rate ≥ 20 breaths per minute
- Heart rate > 90 beats/min

Suspected blood stream infection (BSI) in children

All children (>28 days and <18 years old) with two or more of the following clinical signs (adapted from [52]):

- Hyperthermia (>38 degrees Celsius) or hypothermia (<36 degrees Celsius)
- Respiratory rate more than 2 standard deviations above the normal for age (see table below), or mechanical ventilation for an acute pulmonary process
- Heart rate more than 2 standard deviations above normal for age (see table below), or for children < 1 year of age, mean heart rate<10th percentile for age

Table 3. Age-specific criteria for suspected bloodstream infection

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>HEART RATE (BEATS/ MINUTE)</th>
<th>RESPIRATORY RATE (BREATHS/ MINUTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (1 month – 1 year)</td>
<td>&gt;180 or &lt;90</td>
<td>&gt;34</td>
</tr>
<tr>
<td>Toddler and preschool (&gt;1 to 5 years)</td>
<td>&gt;140</td>
<td>&gt;22</td>
</tr>
<tr>
<td>School age (5-12)</td>
<td>&gt;130</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Adolescent</td>
<td>&gt;110</td>
<td>&gt;14</td>
</tr>
</tbody>
</table>
Suspected blood stream infection (BSI) in neonates [53]

All neonates (<29 days) with **two or more** of the following clinical signs

- Temperature >=37.5 degrees Celsius or <35.3 degrees Celsius
- Respiratory rate >60 breaths per minute or severe chest indrawing or grunting or cyanosis
- Change in level of activity
- History of feeding difficulty
- History of convulsions

**Confirmed bloodstream infection (BSI)**

Isolation of a clinical relevant pathogen from a blood sample of a patient (all ages) seeking healthcare at a healthcare facility.

**Confirmed AMR bloodstream infection (AMR BSI) for selected pathogens:**

- **ESBL E. coli:** E coli isolates resistant to third generation cephalosporins as defined by current internationally recognized clinical breakpoints for third generation cephalosporins (e.g. EUCAST or CLSI) [45, 54], with confirmed ESBL-production according to EUCAST/CLSI guidelines.
- **MRSA:** presumptive methicillin-resistant S. aureus isolates as defined by oxacillin MIC and cefoxitin disc diffusion tests according to current internationally recognized clinical breakpoints (e.g. EUCAST or CLSI) [45, 54].

**Community-origin BSI**

A confirmed BSI occurring in an individual who has been admitted to a hospital for two or less calendar days, with calendar day one equal to the day of admission without prior significant healthcare exposure in preceding 48 hours (transferred from another hospital or discharged from a hospital (same hospital or another one)).

**Hospital-origin BSI**

Confirmed BSI occurring in an individual who has been admitted to a hospital for more than two calendar days, with calendar day one equal to the day of admission.

**Age groups**

- Neonatal: Patients of less than 28 days of age
- Paediatric: Patients between 29 days of age and 17 years of age
- Adult: Patients older than 17 years of age

**9.2.3 Surgical categories**

Surgery is classified as NHSN or non-NHSN surgery. NHSN surgery is defined in the list below. Any surgery not included in this list is considered as non-NHSN surgery, adapted from ECDC [50].
### NHSN SURGERIES

<table>
<thead>
<tr>
<th>NHSN Surgeries</th>
<th>Non-NHSN Surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal aortic aneurysm repair</td>
<td>Laminectomy</td>
</tr>
<tr>
<td>Abdominal hysterectomy</td>
<td>Limb amputation</td>
</tr>
<tr>
<td>Appendix surgery</td>
<td>Liver transplant</td>
</tr>
<tr>
<td>Bile duct, liver or pancreatic surgery</td>
<td>Neck surgery</td>
</tr>
<tr>
<td>Breast surgery</td>
<td>Open reduction of fracture</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Ovarian surgery</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>Pacemaker surgery</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>Peripheral vascular bypass surgery</td>
</tr>
<tr>
<td>Colon surgery</td>
<td>Prostate surgery</td>
</tr>
<tr>
<td>Coronary artery bypass graft with chest and/or donor site incisions</td>
<td>Rectal surgery</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>Refusion of spine</td>
</tr>
<tr>
<td>Exploratory laparotomy</td>
<td>Shunt for dialysis</td>
</tr>
<tr>
<td>Gallbladder surgery</td>
<td>Small bowel surgery</td>
</tr>
<tr>
<td>Gastric surgery</td>
<td>Spinal fusion</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>Spleen surgery</td>
</tr>
<tr>
<td>Herniorrhaphy</td>
<td>Thoracic surgery</td>
</tr>
<tr>
<td>Hip prosthesis</td>
<td>Thyroid and/or parathyroid surgery</td>
</tr>
<tr>
<td>Kidney surgery</td>
<td>Vaginal hysterectomy</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>Ventricular shunt</td>
</tr>
<tr>
<td>Knee prosthesis</td>
<td></td>
</tr>
</tbody>
</table>

### EXAMPLES OF NON-NHSN SURGERIES

<table>
<thead>
<tr>
<th>Examples of Non-NHSN Surgeries</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsillectomy</td>
<td>Hysteroscopic removal of fibroids; evacuation of retained products of conception</td>
</tr>
<tr>
<td>Application of external fixator/Olizarov</td>
<td>Extraventricular drain</td>
</tr>
</tbody>
</table>
## 9.2.4 Bacteria

List of bacteria that are relevant for this study, including codes for and reference to the specific variables from the Patient Form.

<table>
<thead>
<tr>
<th>PATHOGENS</th>
<th>PATHOGEN CODE</th>
<th>APPLICABILITY (VARIABLE NAME)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATHOGENS OF PRIMARY INTEREST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>ESCCOL</td>
<td>BSIPathogen</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>STAAUR</td>
<td>BSIPathogen</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>ACIBAU</td>
<td>BSIPathogen / BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>KLEPNE</td>
<td>BSIPathogen / BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>STRPNE</td>
<td>BSIPathogen / BSIAdditionalPathogen</td>
</tr>
<tr>
<td><strong>GRAM-POSITIVE ADDITIONAL PATHOGENS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GRAM-POSITIVE COCCI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>STAEPI</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>STAEPI</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
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<tr>
<td>Coagulase-negative staphylococci, not specified</td>
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<td>BSIAdditionalPathogen</td>
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<tr>
<td>Other coagulase-negative staphylococci</td>
<td>STAOTH</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>STRPNE</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae (B)</em></td>
<td>STRAGA</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes (A)</em></td>
<td>STRPYO</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td>Other haemolytic streptococci (C, G)</td>
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</tr>
<tr>
<td><em>Streptococcus spp., other</em></td>
<td>STROTH</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><em>Streptococcus spp., not specified</em></td>
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<td>BSIAdditionalPathogen</td>
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<td><em>Enterococcus faecium</em></td>
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<td>BSIAdditionalPathogen</td>
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<tr>
<td><em>Enterococcus spp., not specified</em></td>
<td>ENCNSP</td>
<td>BSIAdditionalPathogen</td>
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<tr>
<td>Gram-positive cocci, not specified</td>
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<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td>Other Gram-positive cocci</td>
<td>GPCOTH</td>
<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td>PATHOGENS</td>
<td>PATHOGEN CODE</td>
<td>APPLICABILITY (VARIABLE NAME)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>GRAM-POSITIVE BACILLI</strong></td>
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<tr>
<td>Corynebacterium spp.</td>
<td>CORSPP</td>
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<td>Listeria monocytogenes</td>
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<tr>
<td>Other Gram-positive bacilli</td>
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<td>BSIAdditionalPathogen</td>
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<tr>
<td><strong>GRAM-NEGATIVE ADDITIONAL PATHOGENS</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>GRAM-NEGATIVE COCCI</strong></td>
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<td></td>
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<td>MORCAT</td>
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<td>Moraxella spp., not specified</td>
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<td>BSIAdditionalPathogen</td>
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<td><strong>ENTEROBACTERIAECEAE</strong></td>
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<td>Citrobacter koseri (e.g. diversus)</td>
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<tr>
<td>Enterobacter aerogenes</td>
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<td>Enterobacter sakazakii</td>
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<td>Enterobacter gergoviae</td>
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<td>Enterobacter spp., other</td>
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<tr>
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<td><strong>ENTEROBACTERIACEAE (CONTINUED)</strong></td>
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<td>Proteus vulgaris</td>
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<td>Serratia liquefaciens</td>
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<td>Hafnia spp.</td>
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</tr>
<tr>
<td>Morganella spp.</td>
<td>MOGSPP</td>
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<tr>
<td>Providencia spp.</td>
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<td>BSIAdditionalPathogen</td>
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<tr>
<td>Salmonella enteritidis</td>
<td>SALENT</td>
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</tr>
<tr>
<td>Salmonella typhi or paratyphi</td>
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<td>Salmonella typhimurium</td>
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<tr>
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<tr>
<td>Yersinia spp.</td>
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</tr>
<tr>
<td><strong>GRAM-NEGATIVE BACILLI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>ACIBAU</td>
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</tr>
<tr>
<td>Acinetobacter calcoaceticus</td>
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<tr>
<td>Acinetobacter haemolyticus</td>
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<tr>
<td>Acinetobacter lwoffii</td>
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<td>Acinetobacter spp., other</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>Stenotrophomonas maltophilia</td>
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<tr>
<td>PATHOGENS</td>
<td>PATHOGEN CODE</td>
<td>APPLICABILITY (VARIABLE NAME)</td>
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</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
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<td>Achromobacter spp.</td>
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</tr>
<tr>
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<tr>
<td>Agrobacterium spp.</td>
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<td>Alcaligenes spp.</td>
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<tr>
<td>Campylobacter spp.</td>
<td>CAMSPP</td>
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<td>Flavobacterium spp.</td>
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<tr>
<td>Gardnerella spp.</td>
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<td>Helicobacter pylori</td>
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<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td>Gram-negative bacilli, not specified</td>
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<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td>Other Gram-negative bacilli, non enterobacteriaceae</td>
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<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td><strong>ANAEROBIC BACILLI</strong></td>
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<td></td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
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</tr>
<tr>
<td>Bacteroides other</td>
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<td>BSIAdditionalPathogen</td>
</tr>
<tr>
<td>Clostridium difficile</td>
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</tr>
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<tr>
<td>Propionibacterium spp.</td>
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<td>Prevotella spp.</td>
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</tbody>
</table>
### 9.2.5 Antibiotic and enzyme inhibitor names

List of antibiotics that are relevant to report on, specified per GLASS pathogen, including codes to be used in the patient form.

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>ANTIBACTERIAL CLASS</th>
<th>ANTIBACTERIAL AGENT</th>
<th>CODE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td>Sulfonamides and trimethoprim</td>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td>Fluoroquinolones</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Levofloxacin</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td>Third generation cephalosporins</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Ceftazidime</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Cefotaxime</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td>Fourth generation cephalosporins</td>
<td>Cefepime</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Imipenem</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Ertapenem</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td></td>
<td>Doripenem</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td>Polymixins</td>
<td>Colistin</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><strong>Klebsiella pneumonia</strong></td>
<td>Penicillins</td>
<td>Ampicillin</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td></td>
<td>Tetracyclines</td>
<td>Tigecycline</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td></td>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td></td>
<td>Aminoglyco-sides</td>
<td>Gentamicin</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td></td>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td>Penicillinase-stable Beta-lactams</td>
<td>Cefoxitin</td>
</tr>
</tbody>
</table>
### 9.3 Healthcare facility form variables

<table>
<thead>
<tr>
<th>VARIABLE NAME</th>
<th>DEFINITION</th>
<th>ANSWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HospitalID</td>
<td>Official identifier of the hospital to be discarded before sending the data to the study coordinator.</td>
<td>Free text</td>
</tr>
<tr>
<td>HospitalCode</td>
<td>Anonymous code of the hospital that uniquely identifies the hospital. The code should be provided by the study coordinator.</td>
<td>Free text</td>
</tr>
<tr>
<td>StudyStartDate</td>
<td>Starting date of the data collection in the hospital.</td>
<td>Date YYYY-MM-DD</td>
</tr>
<tr>
<td>StudyEndDate</td>
<td>End date of the data collection in the hospital.</td>
<td>Date YYYY-MM-DD</td>
</tr>
<tr>
<td>HospitalGroup Code</td>
<td>Anonymous code of the hospital group to allow for grouping of hospitals from the same hospital group. The code should be provided by the study coordinator.</td>
<td>Free text</td>
</tr>
<tr>
<td>HospitalGroup AllSitesIncluded</td>
<td>Do all sites of the hospital group participate in the study?</td>
<td>Boolean Y: yes N: no</td>
</tr>
<tr>
<td>HospitalType</td>
<td>Type of hospital</td>
<td>Coded value: PRM: Primary, SEC: Secondary, TRT: Tertiary, SPEC: Specialized</td>
</tr>
<tr>
<td>Hospital Specialty</td>
<td>Specialty of the specialized hospital</td>
<td>Free text</td>
</tr>
<tr>
<td>Hospital Ownership</td>
<td>Ownership according to public/private status.</td>
<td>Coded value: PUB: Public, PRVNFP: Private, not-for-profit, PRVFP: private, for-profit, OTH: Other, UNK: Unknown</td>
</tr>
<tr>
<td>Hospital TotalBeds</td>
<td>Total number of beds in the hospital including acute and non-acute beds.</td>
<td>Number Positive integer</td>
</tr>
<tr>
<td>Hospital AcuteBeds</td>
<td>Number of acute care beds in the hospital.</td>
<td>Number Positive integer</td>
</tr>
<tr>
<td>Hospital ICU Beds</td>
<td>Number of ICU beds in the hospital.</td>
<td>Number Positive integer</td>
</tr>
<tr>
<td>Hospital Annual Admissions</td>
<td>Annual number of overall admissions in the year prior to the study. If the number of admissions is not available, use the number of discharges.</td>
<td>Number Positive integer</td>
</tr>
<tr>
<td>Hospital Annual PatientDays</td>
<td>Annual number of overall patient-days in the year prior to the study. If the number of patient-days is not available use the number of bed-days.</td>
<td>Number Positive integer</td>
</tr>
<tr>
<td>Hospital Catchment</td>
<td>Based on the number of patient discharges from the previous year: proportion of patient discharges of the selected hospitals, divided by the total number of patient discharges from all hospitals in the Member State.</td>
<td>Number Positive integer</td>
</tr>
</tbody>
</table>
## 9.4 Patient enrolment form variables

<table>
<thead>
<tr>
<th>VARIABLE NAME</th>
<th>DEFINITION</th>
<th>ANSWER</th>
<th>VARIABLE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Code</td>
<td>Anonymous code of the patient that uniquely identifies the patient. Only the onsite investigator should be able to link this code to the official PatientID.</td>
<td>Free text</td>
<td>Core variable</td>
</tr>
<tr>
<td>Match Number</td>
<td>Code to identify patients that are matched, only relevant if an unexposed cohort is included in the study. Patients matched to each other should have the same number.</td>
<td>Free text</td>
<td>Core variable</td>
</tr>
<tr>
<td>AgeYear</td>
<td>Age of the patient in number of years for patients 2 years of age or older.</td>
<td>Number Integer&gt;=2</td>
<td>Core variable</td>
</tr>
<tr>
<td>AgeMonth</td>
<td>Age of the patient in number of months for patients younger than 2. When the baby is less than a month, enter 0.</td>
<td>Number Integer between 0 and 23</td>
<td>Core variable</td>
</tr>
<tr>
<td>Gender</td>
<td>Gender of the patient</td>
<td>Coded value M: Male F: Female T: Transgender UNK: Unknown</td>
<td>Core variable</td>
</tr>
<tr>
<td>Admission Date</td>
<td>Admission date of the patient to the hospital</td>
<td>Date YYYY-MM-DD</td>
<td>Core variable</td>
</tr>
<tr>
<td>VARIABLE NAME</td>
<td>DEFINITION</td>
<td>ANSWER</td>
<td>VARIABLE NAME</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Admission Ward</td>
<td>Responsible medical specialty at time of admission</td>
<td><strong>Coded value</strong></td>
<td>Core variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MED: Adult medical ward</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMED: Paediatric MED</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NMED: Neonatal MED</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRG: Adult surgical ward</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSRG: Paediatric SRG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSRG: Neonatal SRG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OBS: Obstetrics /gynaecology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICU: Adult intensive care unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PICU: Paediatric ICU</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NICU: Neonatal ICU</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HON: Haematology/oncology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMR: Emergency department</td>
<td></td>
</tr>
<tr>
<td>Admission Diagnosis</td>
<td>Registered primary admission diagnosis for acute care episode resulting in admission of the patient to the hospital</td>
<td><strong>Coded value</strong></td>
<td>Optional variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ORT: Orthopaedic condition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CARD: Cardiovascular condition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMD: Endocrine/Metabolic disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GIT: Gastrointestinal disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GUD: Genitourinary disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>INF: Infectious disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMD: Haematological disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRD: Neurological disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMD: Pulmonary disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRA: Trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GYN: Gynaecological disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTD: Connective tissue disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRM: Dermatological disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ONC: Oncologic disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UDT: Undetermined</td>
<td></td>
</tr>
<tr>
<td>Emergency Admission</td>
<td>Whether a patient arrived at the hospital in need of immediate care, i.e. a non-scheduled admission</td>
<td><strong>Boolean</strong></td>
<td>Core variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMR: Emergency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ELT: Elective</td>
<td></td>
</tr>
<tr>
<td>Transfer From Hospital</td>
<td>Patient came directly from another hospital.</td>
<td><strong>Boolean</strong></td>
<td>Optional variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y: Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N: No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UNK: Unknown</td>
<td></td>
</tr>
<tr>
<td>Transfer From Non Hospital Facility</td>
<td>Patient came directly from a health facility that is not a hospital; for example long term care facility or rehabilitation centre.</td>
<td><strong>Boolean</strong></td>
<td>Optional variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y: Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N: No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UNK: Unknown</td>
<td></td>
</tr>
<tr>
<td>Hospitalization 90Days</td>
<td>If the patient had a hospitalization in the 90 days before admission.</td>
<td><strong>Boolean</strong></td>
<td>Optional variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y: Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N: No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UNK: Unknown</td>
<td></td>
</tr>
<tr>
<td>Regular Hospital Contact</td>
<td>If the patient had regular hospital contact, for example for dialysis, cancer treatment etc. in the previous 90 days.</td>
<td><strong>Boolean</strong></td>
<td>Optional variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y: Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N: No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UNK: Unknown</td>
<td></td>
</tr>
<tr>
<td>ICUStay 48hours</td>
<td>If the patient stayed more than 48 hours at the ICU between admission and blood culture.</td>
<td><strong>Boolean</strong></td>
<td>Optional variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y: Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N: No</td>
<td></td>
</tr>
<tr>
<td>VARIABLE NAME</td>
<td>DEFINITION</td>
<td>ANSWER</td>
<td>VARIABLE NAME</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td>--------</td>
<td>---------------</td>
</tr>
</tbody>
</table>
| SurgerySince Admission | Surgery between admission and blood culture, requiring local or general anaesthesia. | Boolean | Y: Yes  
N: No  
UNK: Unknown | Optional variable |
| TypeSurgery Since-Admission NumberDoctors | Type of surgery between admission and blood culture (See Appendix 9.2.3). | Coded value | MIN: minimal invasive surgery/Non-NHSN  
NHSN: NHSN coded surgery  
UNK: unknown | Optional variable |
| Central Vascular Catheter | Presence of central vascular catheter in the 48 hours prior to the blood culture. | Boolean | Y: Yes  
N: No  
UNK: Unknown | Optional variable |
| Peripheral Vascular-Catheter NumberDoctors | Presence of peripheral vascular catheter in the 48 hours prior to blood culture. | Boolean | Y: Yes  
N: No  
UNK: Unknown | Optional variable |
| Urinary Catheter | Presence of urinary catheter in the week prior to the blood culture. | Boolean | Y: Yes  
N: No  
UNK: Unknown | Optional variable |
| Intubation NumberDoctors | Presence of invasive intubation device in the week prior to the blood culture. | Boolean | Y: Yes  
N: No  
UNK: Unknown | Optional variable |
| Comorbidities (list) | Comorbidities present at hospital admission for the Charlson comorbidity score. These can be derived from ICD- codes* and include: Congestive heart failure  
Chronic pulmonary disease  
Mild liver disease  
Moderate or severe liver disease  
Connective tissue disease  
Peptic ulcer  
Diabetes  
Diabetes with end organ damage  
Hemi- or paraplegia  
Cancer/leukaemia  
Metastatic solid tumour  
AIDS  
Dementia  
Malaria  
HIV on ART  
HIV without ART  
Malnutrition  
Tuberculosis | Boolean | Y: Yes  
N: No  
UNK: Unknown | Core variable |

<table>
<thead>
<tr>
<th>VARIABLE NAME</th>
<th>DEFINITION</th>
<th>ANSWER</th>
<th>VARIABLE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>PittBSIScore</td>
<td>The following five criteria are graded within 48 hours before, or on the day of, the positive blood culture. The highest score is recorded, and all are summed: Fever &lt;35.1°C or &gt;39.9°C (2 points) 35.1-36 or 39.0-39.9°C (1 point) Hypotension Acute hypotensive event with drop in systolic blood pressure (BP) &gt;30mmHg and diastolic BP &gt;20mmHg, or requirement of intravenous vasopressor agents, or systolic BP &lt; 90mmHg (2 points) Mechanical ventilation (2 points) Cardiac arrest (4 points) Mental status Alert (0 points) Disoriented (1 point) Stuporous (2 points) Comatose (4 points)</td>
<td>Number 0 or Positive integer</td>
<td>Core variable</td>
</tr>
<tr>
<td>NumberDoctors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QSOFAScore</td>
<td>The patients scores 2 or all 3 items from the Quick Sequential Organ Failure Assessment score within 48 hours before, or on the day of, the positive blood culture: Respiratory rate ≥22/min Change in mental status Systolic blood pressure ≤100 mmHg</td>
<td>Boolean Y: Yes N: No UNK: Unknown</td>
<td>Core variable</td>
</tr>
<tr>
<td>AntibioticsYN</td>
<td>Only for hospital-origin BSIs. Patient received antibiotics between admission and up to two days prior to the blood culture.</td>
<td>Boolean Y: Yes N: No UNK: Unknown NA: Not applicable</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Antibiotics YNName</td>
<td>Name of the antibiotics the patient received between admission and up to two days prior to the blood culture.</td>
<td>Coded value ATC code</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Antibiotics Before Culture</td>
<td>Patient received antibiotics in the 48 hours before the blood culture.</td>
<td>Boolean Y: Yes N: No UNK: Unknown</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Antibiotics Before CultureName</td>
<td>Name of the antibiotics the patient received in the 48 hours prior to the blood culture.</td>
<td>Coded value ATC code</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Immunosuppresion</td>
<td>Immunosuppression in the 48 hours prior to the blood culture, this includes any of the following: HIV (CD4 ≤ 200/mm3), end-stage renal disease requiring dialysis, insulin-dependent diabetes mellitus, active malignancy, cytotoxic chemotherapy ≤ 6 months, prednisone therapy ≥ 10 mg/day, Child C cirrhosis, neutropenia ≤500/mm3, hematopoietic stem-cell transplantation (HSCT), solid organ transplantation (SOT).</td>
<td>Boolean Y: Yes N: No UNK: Unknown</td>
<td>Optional variable</td>
</tr>
<tr>
<td>BSIDate</td>
<td>Date the blood culture was taken that identified the bloodstream infection.</td>
<td>Date YYYY-MM-DD</td>
<td>Core variable</td>
</tr>
<tr>
<td>VARIABLE NAME</td>
<td>DEFINITION</td>
<td>ANSWER</td>
<td>VARIABLE NAME</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td>--------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>BSIWard</strong></td>
<td>Responsible medical specialty at time of the blood culture that identified the bloodstream infection.</td>
<td><strong>Core variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BSIPathogen</strong></td>
<td>Pathogen of interest identified in blood culture: <em>E. coli</em>, <em>S. aureus</em> or additional pathogens selected for the study. Additional codes for selected pathogens.</td>
<td><strong>Core variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pathogen Susceptibility NumberDoctors</strong></td>
<td>Presence of methicillin resistance for <em>S. aureus</em> or resistance to third generation cephalosporins for <em>E. coli</em>, indicate other for additional pathogens and resistance profiles selected for the study.</td>
<td><strong>Core variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pathogen ESBLconf</strong></td>
<td>In case of third generation cephalosporin resistant <em>E. coli</em> isolate report whether ESBL production was detected.</td>
<td><strong>Core variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pathogen Susceptibility Tot NumberDoctors</strong></td>
<td>SIR results for other antibiotics as reported by the microbiological laboratory.</td>
<td><strong>Optional variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Polymicrobial</strong></td>
<td>Additional pathogens identified in the same blood sample (can be several culture bottles) from which the pathogen of interest for the study was identified.</td>
<td><strong>Core variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BSIAdditional Pathogen NumberDoctors</strong></td>
<td>The additional pathogens identified in the same blood sample (can be several culture bottles) from which the pathogen of interest for the study was identified.</td>
<td><strong>Core variable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BSISource</strong></td>
<td>Indicate whether the bloodstream infection was a primary infection (unknown origin / central line), or a secondary infection. <strong>Primary</strong>: Pathogens are introduced directly into the blood stream e.g., by central line, translocation from mucous membranes, by trauma, nosocomial introduction, or infections of intravascular sites such as heart valves, intravascular devices, aneurisms, etc. <strong>Secondary</strong>: Pathogens enter the bloodstream from an infection at an anatomically defined site (focus), like pneumonia, peritonitis, soft tissue infection, cysts etc.</td>
<td><strong>Optional variable</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Core variable**

**Coded value**

**Boolean**

**MED**: Adult medical ward  
**PMED**: Paediatric MED  
**NMED**: Neonatal MED  
**SRG**: Adult surgical ward  
**PSRG**: Paediatric SRG  
**NSRG**: Neonatal SRG  
**OBS**: Obstetrics / gynaecology  
**ICU**: Adult intensive care unit  
**PICU**: Paediatric ICU  
**NICU**: Neonatal ICU  
**HON**: Hematology/oncology  
**EMR**: Emergency department

**ESCCOL**: *E. coli*  
**STAAUR**: *S. aureus*  
**MRSA**: Methicillin resistant *S. aureus*  
**G3CEP**: *E. coli* resistant to third generation cephalosporins  
**Y**: Yes  
**N**: No  
**UNK**: Unknown  

**Antibiotics list**, see Appendix 9.2.5.
### 9.5 Patient follow-up form variables

<table>
<thead>
<tr>
<th>VARIABLE NAME</th>
<th>DEFINITION</th>
<th>ANSWER</th>
<th>CORE/ OPTIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated <em>S. aureus</em> BSI</td>
<td>Presence of <em>S. aureus</em> bloodstream infection and an implanted prosthesis (pacemaker/implanted cardiac defibrillator, cardiac valve, endovascular implant, prosthesis joint, spondylodesis, other bone implants), or duration of <em>S. aureus</em> BSI &gt;2 days, or <em>S. aureus</em> BSI related fever &gt;3 days.</td>
<td>Boolean</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Empirical Treatment</td>
<td>Name of the antibiotics the patient received to treat the blood culture before microbiological results were available.</td>
<td>Coded value</td>
<td>Core variable</td>
</tr>
<tr>
<td>Empirical Administration</td>
<td>Administration route for EmpiricalTreatment.</td>
<td>Coded value</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Date Empirical</td>
<td>Date EmpiricalTreatment was administered.</td>
<td>Date YYYY-MM-DD</td>
<td>Core variable</td>
</tr>
<tr>
<td>Enddate Empirical</td>
<td>Date EmpiricalTreatment was stopped.</td>
<td>Date YYYY-MM-DD</td>
<td>Core variable</td>
</tr>
<tr>
<td>DateAST</td>
<td>Date antimicrobial susceptibility results were reported back to attending medical doctor, electronically, on paper, by phone, or by direct communication.</td>
<td>Date YYYY-MM-DD</td>
<td>Optional variable</td>
</tr>
</tbody>
</table>
### 9.6 Patient discharge form variables

<table>
<thead>
<tr>
<th>VARIABLE NAME</th>
<th>DEFINITION</th>
<th>ANSWER</th>
<th>CORE/OPTIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge date</td>
<td>Date the patient was discharged from the hospital, dead or alive.</td>
<td>Date YYYY-MM-DD</td>
<td>Core variable</td>
</tr>
<tr>
<td>Discharge status</td>
<td>Whether the patients were discharged alive, discharged to die elsewhere, or death.</td>
<td>Coded value ALV: Alive MRB: Moribund; discharged alive but expected to die soon DTH: Death</td>
<td>Core variable</td>
</tr>
<tr>
<td>Discharge destination</td>
<td>The discharge destination of the patient.</td>
<td>Coded value HOM: Home LTC: Long-term care facility HOS: Other hospital NA: Not applicable if death</td>
<td>Optional variable</td>
</tr>
<tr>
<td>Day30 Mortality</td>
<td>Life status 30 days after enrolment (=date of blood culture, for cohort 3 patients this equals to hospital admission date+ number of days between admission and blood culture for their matched exposed patient)</td>
<td>Coded value ALV: Alive DTH: Death UNK: Unknown</td>
<td>Optional variable</td>
</tr>
</tbody>
</table>
Healthcare Facility Form

This form is part of the WHO AMR attributable mortality master template protocol designed to determine the impact of AMR on in-hospital mortality among patients with bloodstream infection due to selected types of antimicrobial resistance in your hospital, region, or country. Through this form, general information about your hospital will be collected to provide the context for the individual patient data that will be collected as well.

(For definitions with regards to the below questions, see Appendix 9.2.1 & 9.4 in the master template protocol.)

1. Hospital Name

2. Hospital code (assigned by study coordinator):

3. Start date of patient recruitment in your hospital:
   DD/MM/YYYY

4. End date of patient recruitment in your hospital:
   DD/MM/YYYY

5. If your hospital is currently part of a hospital group (linked administratively, like a trust), please provide the group code provided by the study coordinator:

6. If your hospital is part of a hospital group, please indicate whether all sites participate in the study (if unknown, check with study coordinator):
   - Yes
   - No
   - Unknown

7. Please provide type of your healthcare facility:
   - Primary
   - Secondary
   - Tertiary
   - Specialized
   - Other (please specify):

8. If it is a specialized hospital, please provide the specialty:
9. What (other) important specialties are available in your hospital:

- SOT: Solid organ transplant
- BMT: Bone marrow transplant
- BUR: Burns unit
- NEN: Neonatal unit
- OBS: Obstetrics unit
- HEM: Clinical haematology without transplantation
- ONC: Oncology
- OTH: Others

10. Please indicate what type of ownership describes your hospital best:

- PUB: Public
- PRVNFP: private, not-for-profit
- PRVFP: private, for-profit
- OTH: Other
- UNK: Unknown

11. Please provide the total number of in-patient beds (acute and non-acute) at the start of the study:

12. Please provide the total number of acute care in-patient beds (exclude wards, like long-term care/psychiatric wards) at the start of the study:

13. Please provide the total number of admissions in the previous calendar years. If the number of admissions is not available, use the number of discharges.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of admissions</th>
<th>Number of discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. Please provide the total number of patient-days in the previous calendar year. If the number of patient-days is not available use the number of bed-days.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patient-days</th>
<th>Number of bed-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
15. Please provide the proportion of the national healthcare seeking population that is serviced by your hospital (catchment population) as percentage of national population: e.g., proportion of patient discharges of the selected hospitals, divided by the total number of patient discharges from all hospitals in the Member State.

16. Please provide the total number of medical doctors in full-time equivalent (FTE), who work in your hospital at the start of the study (f.e. two doctors working half-time equal 1 FTE):

17. Please provide the total number of qualified nurses in full-time equivalent (FTE), who work in your hospital at the start of the study (f.e. two doctors working half-time equal 1 FTE):

---

**Patient Enrolment Form**

This form is part of the WHO AMR attributable mortality master template protocol designed to determine the impact of AMR on in-hospital mortality among patients with bloodstream infection due to selected types of antimicrobial resistance in your hospital, region, or country. Through this form, individual patient data will be collected for patients eligible for the study. It must be completed once the patient is enrolled.

Question with (*) are compulsory.

*(For definitions with regards to the below questions, see Appendix 9.2.2, 9.5, 9.6 & 9.7 in the master template protocol)*

**1. Demographic information**

1. Hospital patient identifier (for local use only)*

2. Patient Code (assigned, anonymous code)*

3. If an unexposed cohort (cohort 3) is included in the study, please report here the matching code that identifies the exposed and unexposed patients that are matched to each other (i.e. the exposed and unexposed patient should have the same uniquely identifying code). Match code: *

4. If the patient is 2 years of age or older, please report the age in years*

5. If the patient is younger than 2 years, please report the age in months* (report 0 for patients younger than 31 days)
6. Gender of the patient*

- Male
- Female
- Transgender
- Unknown

2. Microbiological data

7. What date was the blood culture taken that later confirmed a bloodstream infection with the pathogens selected for this study (MRSA, ESBL *E. coli*, ...)? For unexposed patients for cohort 3, include date of matched exposed patient*

DD/MM/YYYY

8. What pathogen was identified in the blood culture that resulted in inclusion in the study?*

- *E. coli*
- *S. aureus*
- NA (unexposed patient cohort 3)
- Other pathogen of interest (please specify):

9. Please indicate susceptibility of the above reported pathogen*

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>S</th>
<th>I</th>
<th>R</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-trimoxazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
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<tr>
<td>Cefazidime</td>
<td></td>
<td></td>
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<tr>
<td>Cefotaxime</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Cefepime</td>
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</tr>
<tr>
<td>Imipenem</td>
<td></td>
<td></td>
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<tr>
<td>Meropenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doripenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Minocycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
10. In case of third generation cephalosporin resistant *E. coli*, was ESBL production detected? If not tested report ‘unknown’ *  
- Yes  
- No  
- Unknown

11. Was this a polymicrobial bloodstream infection (i.e. additional pathogens were detected in the blood sample from the same date)? *  
- Yes  
- No  
- Unknown

12. Indicate the additional pathogens identified in the same blood sample (can be several culture bottles) from which the pathogen of interest for the study was identified  
A.  
B.  
C.  
D.  
E.  

13. Was the bloodstream infection a primary infection (unknown origin / central line): pathogens are introduced directly into the blood stream e.g., by central line, translocation from mucous membranes, by trauma, nosocomial introduction, or infections of intravascular sites such as heart valves, intravascular devices, aneurisms, etc.  
- Yes  
- No  
- Unknown

14. Was the bloodstream infection a secondary infection (unknown origin / central line): pathogens enter the bloodstream from an infection at an anatomically defined site (focus), like pneumonia, peritonitis, soft tissue infection, cysts etc.  
- Yes  
- No  
- Unknown

15. If secondary, please indicate the source of infection:  
- SST: Skin/soft tissue  
- PUL: Pulmonary  
- DIG: Digestive tract  
- UTI: Urinary tract  
- SSI: Surgical site  
- OTI: Other infection sites (diabetic foot, pacemaker, endocarditis)  
- Unknown
16. What was the responsible medical specialty the patient was admitted to at time of the blood culture that identified the bloodstream infection*
- MED: Adult medical ward
- PMED: Paediatric MED
- NMED: Neonatal MED
- SRG: Adult surgical ward
- PSRG: Paediatric SRG
- NSRG: Neonatal SRG
- OBS: Obstetrics / gynaecology
- ICU: Adult intensive care unit
- PICU: Paediatric ICU
- NICU: Neonatal ICU
- HON: Haematology/oncology
- EMR: Emergency department
- Unknown

3. Clinical data
17. Admission date*

DD/MM/YYYY

18. Responsible medical specialty at time of admission*
- MED: Adult medical ward
- PMED: Paediatric MED
- NMED: Neonatal MED
- SRG: Adult surgical ward
- PSRG: Paediatric SRG
- NSRG: Neonatal SRG
- OBS: Obstetrics / gynaecology
- ICU: Adult intensive care unit
- PICU: Paediatric ICU
- NICU: Neonatal ICU
- HON: Haematology/oncology
- EMR: Emergency department
19. Did the patient arrived at the hospital in need of immediate care, i.e. a non-scheduled admission? *

- EMR: emergency
- ELT: elective
- Unknown

20. Comorbidities present at hospital admission for the Charlson comorbidity score. These can be derived from ICD-codes* and include: *

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild liver disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderate or severe liver disease</td>
<td></td>
<td></td>
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<tr>
<td>Connective tissue disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemi- or paraplegia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer/leukaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic solid tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV on ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV without ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please specify):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

21. Please indicate the patient’s temperature on the day of the positive blood culture (degrees Celsius). If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

22. Please indicate the patient’s respiratory rate on the day of the positive blood culture (breaths/minute). If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*
23. Please indicate the patient’s heart rate the day of the positive blood culture (beats/minute). If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

24. Please indicate the patient’s systolic blood pressure on the day of the positive blood culture (mmHg). If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

25. Please describe the patient’s mental status on the day of the positive blood culture (date of blood culture)? If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

- Alert
- Disoriented
- Stuporous
- Comatose
- None of the above

26. If neonatal patient, please indicate changes in level of activity on the day of the positive blood culture. If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

- Yes
- No
- Unknown

27. If neonatal patient, please indicate history of feeding difficulty on the day of the positive blood culture. If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

- Yes
- No
- Unknown

28. If neonatal patient, please indicate history of convulsion on the day of the positive blood culture. If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

- Yes
- No
- Unknown
29. Did the patient suffered an acute hypotensive event with drop in systolic blood pressure (BP) >30mmHg and diastolic BP >20mmHg any on the day of the positive blood culture. If the information is not available for the day of the blood culture, the most recent measurement within 48h of obtaining the culture must be used.*

- Yes
- No
- Unknown

30. Registered primary admission diagnosis for acute care episode resulting in admission of the patient to the hospital

- ORT: Orthopaedic condition
- CARD: Cardiovascular condition
- EMD: Endocrine/Metabolic disorder
- GIT: Gastrointestinal disorder
- GUD: Genitourinary disorder
- INF: Infectious disease
- HMD: Haematological disease
- NRD: Neurological disease

31. Did the Patient came directly from another acute care hospital

- Yes
- No
- Unknown

32. Did the patient come directly from a health facility that is not a hospital; for example long term care facility or rehabilitation centre?

- Yes
- No
- Unknown

33. Was the patient hospitalized in an acute care hospital any time during the 90 days before this admission?

- Yes
- No
- Unknown

34. Did the patient have regular hospital contact, for example for dialysis, cancer treatment etc. during the previous 90 days before this admission?

- Yes
- No
- Unknown
35. Did the patient spent more than 48 hours in the ICU between admission and the day the blood culture was taken (date of blood culture)?
- Yes
- No
- Unknown

36. Did the patient have surgery requiring local or general anaesthesia between admission and detection of the bloodstream infection (date of blood culture)?
- Yes
- No
- Unknown

37. If the patient had surgery before detection of the bloodstream infection, was invasive (NHSN-coded) surgery?
- MIN: minimal invasive surgery/ Non-NHSN
- NHSN: NHSN coded surgery
- None
- Unknown

38. Did the patient have a central vascular catheter in place any time during the 48 hours prior to the bloodstream infection (date of blood culture)?
- Yes
- No
- Unknown

39. Did the patient have a peripheral vascular catheter in place any time during the 48 hours prior to the bloodstream infection (date of blood culture)?
- Yes
- No
- Unknown

40. Did the patient have a urinary catheter in place any time during the seven days prior to the bloodstream infection (date of blood culture)?
- Yes
- No
- Unknown

41. Did the patient have invasive intubation any time during the seven days prior to the bloodstream infection (date of blood culture)?
- Yes
- No
- Unknown
42. Did the patient require intravenous vasopressor agents any time during the 48 hours before the positive blood culture (date of blood culture)? *
   - Yes
   - No
   - Unknown

43. Did the patient need mechanical ventilation any time during the 48 hours before the positive blood culture (date of blood culture)? *
   - Yes
   - No
   - Unknown

44. Did the patient suffer a cardiac arrest any time the 48 hours before the positive blood culture.*
   - Yes
   - No
   - Unknown

4. Medication

45. In case the blood culture was taken >48 hours after admission, did the patient receive antibiotics between admission up to 48 hours before the blood culture?
   - Yes
   - No
   - Unknown

46. Name the antibiotics the patient received between admission and up to 48 hours prior to the blood culture
   - A.
   - B.
   - C.
   - D.
   - E.

47. Did the patient received antibiotics in the 48 hours before the blood culture?
   - Yes
   - No
   - Unknown
48. Name the antibiotics the patient received in the 48 hours before the blood culture

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.</td>
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<td></td>
</tr>
</tbody>
</table>

49. Was the patient immunosuppressed any time during the 48 hours prior to the blood culture. This includes any of the following:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV (CD4 ≤ 200/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease requiring dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxic chemotherapy ≤ 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone therapy ≥ 10 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child C cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia ≤ 500/mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematopoietic stem-cell transplantation (HSCT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid organ transplantation (SOT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient follow-up form

This form is part of the WHO AMR attributable mortality master template protocol designed to determine the impact of AMR on in-hospital mortality among patients with bloodstream infection due to selected types of antimicrobial resistance in your hospital, region, or country. Through this form, individual patient data will be collected for patients eligible for the study. It must be completed on a number of days after detection of bloodstream infection.

Question with (*) are compulsory.

(For definitions with regards to the below questions, see Appendix 9.2.2, 9.5, 9.6 & 9.7 in the master template protocol)

1. Please report all the antibiotics the patient received after the blood culture was taken, but before antimicrobial susceptibility results were reported to the attending medical doctor, including start- and stop-date, and route of administration *

<table>
<thead>
<tr>
<th>Name</th>
<th>Start date</th>
<th>End date</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. When were the antimicrobial susceptibility results from the laboratory reported back to the attending medical doctor (electronically / on paper / by phone / direct communication)? If not available before patient discharge, report first date after date of discharge.

DD/MM/YYYY

3. If the bloodstream infection was caused by S. aureus, was it a complicated bloodstream infection (presence of implanted prosthesis, duration of BSI > 2 days, BSI-related fever > 3 days)?

- [ ] Yes
- [ ] No
- [ ] Unknown
- [ ] Not applicable
# Patient discharge form

This form is part of the WHO AMR attributable mortality master template protocol designed to determine the burden of antimicrobial resistance in your hospital, region, or country. Through this form, individual patient data will be collected for patients eligible for the study. It must be completed at patient discharge.

Question with (*) are compulsory.

*(For definitions with regards to the below questions, see Appendix 9.2.2, 9.5, 9.6 & 9.7 in the master template protocol)*

1. Please report the patient discharge date*

   DD/MM/YYYY

2. Please report the patient discharge status*

   - ALV: Alive
   - MRB: Moribund; discharged alive but expected to die soon
   - DTH: Death
   - Unknown

3. What was the discharge ward?

   - MED: Adult medical ward
   - PMED: Paediatric medical ward
   - NMED: Neonatal medical ward
   - SRG: Adult surgical ward
   - PSRG: Paediatric surgical ward
   - NSRG: Neonatal surgical ward
   - OBS: Obstetrics/gynaecology
   - ICU: Adult intensive care unit
   - PICU: Paediatric ICU
   - NICU: Neonatal ICU
   - HON: Haematology/oncology
   - EMR: Emergency department
   - Unknown

4. Where was the patient discharged to?

   - HOM: Home
   - LTC: Long-term care facility
   - HOS: Other hospital
   - NA: Not applicable if death
   - Unknown
Notes to Researchers:

1. Please note that this is a template developed by the WHO ERC to assist the Principal Investigator in the design of their informed consent forms (ICF). It is important that Principal Investigators adapt their own ICFs to the outline and requirements of their study. The logo of the Institution must be used on the ICF and not the WHO logo.

2. The informed consent form consists of two parts: the information sheet and the consent certificate.

3. Do not be concerned by the length of this template. It is long only because it contains guidance and explanations which are for you and which you will not include in the informed consent forms that you develop and provide to participants in your research.

4. This template includes examples of key questions that may be asked at the end of each section, that could ensure the understanding of the information being provided, especially if the research study is complex. These are just examples, and suggestions, and the investigators will have to modify the questions depending upon their study.

5. In this template:
   - square brackets indicate where specific information is to be inserted
   - bold lettering indicates sections or wording which should be included
   - standard lettering is used for explanations to researchers only and must not be included in your consent forms. The explanation is provided in black, and examples are provided in red in italics. Suggested questions to elucidate understanding are given in black in italics.

TEMPLATE ON FOLLOWING PAGE
Informed Consent form for PATIENTS BLOODSTREAM INFECTION ACTIVE CASE FINDING

This Informed Consent Form is for men and women who attend clinic X, and who we are inviting to participate in research on health impact of AMR bloodstream infections.

You may provide the following information either as a running paragraph or under headings as shown below.

[Name of Principal Investigator]
[Name of Organization]
[Name of Sponsor]
[Name of Proposal and version]

This Informed Consent Form has two parts:
- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

A. Introduction

We are observing through this survey the health of patients with bloodstream infections caused by bacteria resistant to antibiotics.

I am going to give you more information and invite you to be part of this survey. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. Also, there may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Antibiotics are medicines that kills or stops the growth of bacteria. There are different types (classes) of antibiotics that can be used to treat bacterial infections. Depending on the bacterium, some antibiotic is more efficient than others. Your doctor will normally prescribe you the antibiotic that is more effective to treat your infection.

When the treatment is effective a bacterium is considered “susceptible” to the prescribed antibiotic. On the contrary, when a bacterium does not respond anymore to the prescribed antibiotic it is considered "resistant", and treatments become difficult and infections persist in the body, affecting patient health, and increasing the risk of spread to others.

Resistance to antibiotics (AMR) occurs naturally and over time when bacteria (such as bacteria, fungi, viruses, and parasites) come into contact with antibiotics. Luckily, there are laboratory tests that allow the doctors to identify if the bacterium is still susceptible or has become resistant to specific classes of antibiotics and choose the treatment accordingly.
Purpose of the survey
The consequences of AMR on patients’ health are still very difficult to establish and this information is essential to reduce its impact. For this reason, we will observe the clinical progress of patients with bloodstream infections (BSI) caused by bacteria resistant to specific antibiotics classes. Specifically, we will look at patients infected with two bacteria species and two specific classes of antibiotics that are often used to treat those infection:

1. *Escherichia coli* resistant to third generation cephalosporine (ESBL- E. coli)

To do so, information will be collected and compared from a group of patients with susceptible and resistant infections, and, if feasible, from a group of uninfected patients.

Type of Research
In stage 1 of this study patients are monitored for signs of suspected blood stream infection and blood sampled if necessary. Based on the obtained diagnostic results, patients might be asked to enrol into stage 2 of the study: a cohort study which involves comparing the future clinical progress of groups (cohorts) of patients infected with *E. coli* or *S. Aureus*, susceptible and resistant to chosen antibiotics, and a group of patients without infection.

Participant selection
We are inviting you to take part of this study is because you showed clinical signs of suspected bloodstream infection.

Voluntary Participation
Your participation in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will still offer the treatment that is routinely offered in this clinic/hospital for the selected infections. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol
Because you were diagnosed with a suspected bloodstream infection we will take blood from your arm using a syringe and needle to diagnose the possible cause of your infection. We will take about this much blood (show a spoon, vial or other small container with a small amount of water in it to match 40ml of blood) only once. This is done independently from the purpose of this study.

If you agree to take part to the study, some of your clinical data will also be recorded retrospectively, starting from the day you have been admitted, and prospectively. However, if you decide not to take part to the survey, the blood samples will still be sent for diagnostic and will be used and stored by the health care facility and the clinicians according to their common practices.
B. Description of the Process

Once your diagnostic results are obtained we might ask you to enrol in the second stage of the study and we might collect data from your medical records:

1. clinical data on the day we have received the laboratory results of your first routine blood sample.
2. the same information at 30 days of hospital admission (if feasible), and/or at your discharge.

If you choose to not consent for the information listed in point 1 and 2 to be acquired, unfortunately you will not be eligible to participate further to the survey, as those data are necessary for the study.

If you are selected as possible candidate for stage 2 of the study, we will take you through a second consent form for cohort enrolment and your participation will be entirely voluntary. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will still offer the treatment that is routinely offered in this clinic/hospital for the selected infections. You may change your mind later and stop participating even if you agreed earlier.

Risks
There is potential for breach confidentiality for data obtained from medical records. In the confidentiality section we explain how this risk can be minimized

Benefits
There may not be any benefit for you, but your participation is likely to help us find the answer to the a very important research question and start estimating the real health impact of AMR.

Confidentiality
The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is, and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc.].) Any of the results shared will be aggregated so that individuals cannot be identified.

Example of question to elucidate understanding: Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?

Sharing the Results
We will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw
You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all your rights will still be respected.

Who to Contact
If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail]
This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact [name, address, telephone number.]. It has also been reviewed by the Ethics Review Committee of the World Health Organization (WHO), which is funding/sponsoring/supporting the study.

> **Example of question to elucidate understanding:** Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study? Etc.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

**PART II: Certificate of Consent**

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked I have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant________________________

Signature of Participant _______________________

Date __________________________
   Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumbprint as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness __________________________ AND Thumb print of participant

Signature of witness __________________________

Date __________________________
   Day/month/year
Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1.
2.
3.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent __________________________

Signature of Researcher /person taking the consent __________________________
Date __________________________
   Day/month/year
Informed Consent form for PATIENTS BLOODSTREAM INFECTION ACTIVE CASE FINDING
This Informed Consent Form is for men and women who attend clinic X, and who we are inviting to participate in research on health impact of AMR bloodstream infections.

You may provide the following information either as a running paragraph or under headings as shown below.
[Name of Principal Investigator]
[Name of Organization]
[Name of Sponsor]
[Name of Proposal and version]

This Informed Consent Form has two parts:
- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

A. Introduction

(I am X, working for the Y Research Institute. We are observing through this survey the health of patients with bloodstream infections caused by bacteria resistant to antibiotics.

I am going to give you information and invite you to have your child participate in this research. You do not have to decide today whether you agree that your child may participate in the research. Before you decide, you can talk to anyone you feel comfortable with. Also, there may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Antibiotics are medicines that kills or stops the growth of bacteria. There are different types (classes) of antibiotics that can be used to treat bacterial infections. Depending on the bacterium, some antibiotic is more efficient than others. Your doctor will normally prescribe you the antibiotic that is more effective to treat your infection.

When the treatment is effective a bacterium is considered “susceptible” to the prescribed antibiotic. On the contrary, when a bacterium does not respond anymore to the prescribed antibiotic it is considered “resistant”, and treatments become difficult and infections persist in the body, affecting patient health, and increasing the risk of spread to others.)
Resistance to antibiotics (AMR) occurs naturally and over time when bacteria (such as bacteria, fungi, viruses, and parasites) come into contact with antibiotics. Luckily, there are laboratory tests that allow the doctors to identify if the bacterium is still susceptible or has become resistant to specific classes of antibiotics and choose the treatment accordingly.

**Purpose of the survey**

The consequences of AMR on patients’ health are still very difficult to establish and this information is essential to reduce its impact. For this reason, we will observe the clinical progress of patients with bloodstream infections (BSI) caused by bacteria resistant to specific antibiotics classes. Specifically, we will look at patients infected with two bacteria species and two specific classes of antibiotics that are often used to treat those infection:

1. *Escherichia coli* resistant to third generation cephalosporine (ESBL- *E. coli*)

To do so, information will be collected and compared from a group of patients with susceptible and resistant infections, and, if feasible, from a group of uninfected patients.

**Type of Research**

In stage 1 of this study patients are monitored for signs of suspected blood stream infection and blood sampled if necessary. Based on the obtained diagnostic results, patients might be asked to enrol into stage 2 of the study: a cohort study which involves comparing in the future clinical progress of groups (cohorts) of patients infected with *E. coli* or *S. Aureus*, susceptible and resistant to chosen antibiotics, and a group of patients without infection.

**Participant selection**

We are inviting your child to take part of this study is because your child showed clinical signs of suspected bloodstream infection.

**Voluntary Participation**

Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to have your child participate or not. If you choose not to consent, all the services you and your child receive at this clinic will continue and nothing will change, and your child will still be offered the treatment that is routinely prescribed for the diagnosed infection. You may also choose to change your mind later and stop participating, even if you agreed earlier, and the services you and/or your child receives at the clinic will continue.

**Procedures and Protocol**

Because you child was diagnosed with a suspected bloodstream infection we will take blood from your child arm using a syringe and needle to diagnose the possible cause of your infection. We will take about this much blood (show a spoon, vial or other small container with a small amount of water in it to match 40ml of blood) only once. This is done independently from the purpose of this study. If you agree for your child to take part to the study, some of your child clinical data will also be recorded retrospectively, starting from the day your child has been admitted, and prospectively. However, if you decide for your child to not take part to the survey, the blood samples will still be sent for diagnostic and will be used and stored by the health care facility and clinicians according to their common practices
B. Description of the Process

Once your diagnostic results are obtained we might ask you your consent for your child to enrol in the second stage of the study and we might collect data from your child medical records:

1. clinical data on the day we have received the laboratory results of your child first routine blood sample.
2. The same information at 30 days of hospital admission (if feasible), and/or at your child discharge.

If you choose to not consent for the information listed in point 1 and 2 to be acquired for your child, unfortunately your child will not be eligible to participate further to the survey, as those data are necessary for the study.

If your child is selected as possible candidate for stage 2 of the study, we will take you through a second consent form for cohort enrolment and your decision to have your child participate in this study will be entirely voluntary. It is your choice whether to have your child participate or not. If you choose not to consent, all the services you and your child receive at this clinic will continue and nothing will change. You may also choose to change your mind later and stop participating, even if you agreed earlier, and the services you and/or your child receives at the clinic will continue.

Risks
There is potential for breach confidentiality for data obtained from medical records. In the confidentiality section we explain how this risk can be minimized.

Benefits
There may not be any benefit for you or your child, but your participation is likely to help us find the answer to the a very important research question and start estimating the real health impact of AMR.

Confidentiality
The information that we collect from this research project will be kept confidential. Information about you child that will be collected during the research will be put away and no-one, but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your child number is, and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc.]. Any of the results shared will be aggregated so that individuals cannot be identified.

Example of question to elucidate understanding: Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?

Sharing the Results
We will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw
You do not have to agree to your child taking part in this research if you do not wish to do so and refusing to allow your child to participate will not affect your treatment or your child’s treatment at this Centre in any way. You and your child will still have all the benefits that you would otherwise have at this Centre. You may stop your child from participating in the research at any time that you wish without either you or your child losing any of your rights as a patient here. Neither your treatment nor your child’s treatment at this Centre will be affected in any way.)
Who to Contact
If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail])
This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact [name, address, telephone number.]). It has also been reviewed by the Ethics Review Committee of the World Health Organization (WHO), which is funding/sponsoring/supporting the study.

> **Example of question to elucidate understanding:** Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study? Etc.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?
PART II: Certificate of Consent

I have been invited to have my child participate in research of AMR bloodstream infections. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked I have been answered to my satisfaction. I consent voluntarily for the child in question to participate in this research as the child parents/guardian.

Print Name of Participant ____________________________
Signature of Participant ____________________________
Date__________________________________________
      Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumbprint as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness__________________________ AND Thumb print of participant
Signature of witness ____________________________
Date__________________________________________
      Day/month/year

Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1.
2.
3.
I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent__________________________

Signature of Researcher /person taking the consent__________________________
Date__________________________________________
      Day/month/year
Informed Consent form for PATIENTS COHORT ENROLMENT
This Informed Consent Form is for men and women who attend clinic X, and who we are inviting to participate in research on health impact of AMR bloodstream infections.

(Example: This Informed Consent Form is for men and women who attend clinic Z, and who we are inviting to participate in research on X. The title of our research project is "………………………….")

You may provide the following information either as a running paragraph or under headings as shown below.
[Name of Principal Investigator]
[Name of Organization]
[Name of Sponsor]
[Name of Proposal and version]

This Informed Consent Form has two parts:
- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

A. Introduction

I am X, working for the Y Research Institute. We are observing through this survey the health of patients with bloodstream infections caused by bacteria resistant to antibiotics.

I am going to give you more information and invite you to be part of this survey. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. Also, there may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Antibiotics are medicines that kills or stops the growth of bacteria. There are different types (classes) of antibiotics that can be used to treat bacterial infections. Depending on the bacterium, some antibiotic is more efficient than others. Your doctor will normally prescribe you the antibiotic that is more effective to treat your infection.

When the treatment is effective a bacterium is considered “susceptible” to the prescribed antibiotic. On the contrary, when a bacterium does not respond anymore to the prescribed antibiotic it is considered “resistant”, and treatments become difficult and infections persist in the body, affecting patient health, and increasing the risk of spread to others.
Resistance to antibiotics (AMR) occurs naturally and over time when bacteria (such as bacteria, fungi, viruses, and parasites) come into contact with antibiotics. Luckily, there are laboratory tests that allow the doctors to identify if the bacterium is still susceptible or has become resistant to specific classes of antibiotics and choose the treatment accordingly.

**Purpose of the survey**
The consequences of AMR on patients’ health are still very difficult to establish and this information is essential to reduce its impact. For this reason, we will observe the clinical progress of patients with bloodstream infections (BSI) caused by bacteria resistant to specific antibiotics classes. Specifically, we will look at patients infected with two bacteria species and two specific classes of antibiotics that are often used to treat those infection:

1. *Escherichia coli* resistant to third generation cephalosporine (ESBL- *E. coli*)

To do so, information will be collected and compared from a group of patients with susceptible and resistant infections, and, if feasible, from a group of uninfected patients.

**Type of Research**
This is a prospective cohort study and involves monitoring and comparing in the future clinical progress of groups (cohorts) of patients infected with *E. coli* or *S. Aureus*, susceptible and resistant to chosen antibiotics, and a group of patients without infection. Patients are selected based on the results of their first blood diagnostics test.

**Participant selection**
Cohort 1 and 2: We are inviting you to take part of this study is because *E. coli* or *S. aureus* were isolated in your first blood sample and the bacteria were ether susceptible or resistant to the classes of antibiotics we have mentioned before.

Cohort 3: We are inviting you to take part of this study is because no *E. coli* or *S. aureus* were isolated in your first blood sample taken for routine diagnostic, and because the duration of your hospital stay matches the duration of hospital stay of a patient infected by *E. coli* or *S. aureus*.

**Voluntary Participation**
Your participation in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will still be offered the treatment that is routinely offered in this clinic/hospital for the selected infections. You may change your mind later and stop participating even if you agreed earlier.

**Procedures and Protocol**
Your blood samples were sent for diagnostic and will be store and used by the health care facility according to their common practices. If you agree to take part to the study, some of your clinical data will also be recorded retrospectively, starting from the day you have been admitted, and prospectively.

### B. Description of the Process

During the study we will collect data from your medical records:

1. clinical data on the day we have received the laboratory results of your first blood sample.
2. the same information at 30 days of hospital admission (if feasible), and/or at discharge.
If you choose to not consent for the information listed in point 1 and 2 to be acquired, unfortunately you will not be eligible to participate further to the survey, as those data are necessary for the study.

**Duration**
The study will last from the day you have been enrolled in the study until your discharge.

**Risks**
There is potential for breach confidentiality for data obtained from medical records. In the confidentiality section of this form we explain how this risk can be minimized.

**Benefits**
There may not be any benefit for you, but your participation is likely to help us find the answer to the a very important research question and start estimating the real health impact of AMR.

**Confidentiality**
The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one, but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is, and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc.]. Any of the results shared will be aggregated so that individuals cannot be identified.

➢ **Example of question to elucidate understanding:** Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?

**Sharing the Results**
We will publish the results in order that other interested people may learn from our research.

**Right to Refuse or Withdraw**
You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all your rights will still be respected.

**Who to Contact**
If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail]

This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find out more about the IRB, contact [name, address, telephone number]. It has also been reviewed by the Ethics Review Committee of the World Health Organization (WHO), which is funding/sponsoring/supporting the study.

➢ **Example of question to elucidate understanding:** Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study? Etc.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?
PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have been asked and I have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant ___________________________
Signature of Participant ___________________________
Date ___________________________
               Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_________________________ AND Thumb print of participant
Signature of witness ___________________________
Date ___________________________
               Day/month/year

Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1.  
2.  
3.  
I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent ___________________________

Signature of Researcher /person taking the consent ___________________________
Date ___________________________
               Day/month/year
Estimating attributable mortality of AMR bloodstream infections

TEMPLATE FOR MINOR COHORT ENROLMENT

Informed Consent form for PATIENTS COHORT ENROLMENT

This Informed Consent Form is for men and women who attend clinic X, and who we are inviting to participate in research on health impact of AMR bloodstream infections.

(Example: This Informed Consent Form is for men and women who attend clinic Z, and who we are inviting to participate in research on X. The title of our research project is "..........................”)

You may provide the following information either as a running paragraph or under headings as shown below.

[Name of Principal Investigator]
[Name of Organization]
[Name of Sponsor]
[Name of Proposal and version]

This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

A. Introduction

(I am X, working for the Y Research Institute. We are observing through this survey the health of patients with bloodstream infections caused by bacteria resistant to antibiotics.

I am going to give you information and invite you to have your child participate in this research. You do not have to decide today whether or not you agree that your child may participate in the research. Before you decide, you can talk to anyone you feel comfortable with. Also, there may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Antibiotics are medicines that kills or stops the growth of bacteria. There are different types (classes) of antibiotics that can be used to treat bacterial infections. Depending on the bacterium, some antibiotic is more efficient than others. Your doctor will normally prescribe you the antibiotic that is more effective to treat your infection.

When the treatment is effective a bacterium is considered “susceptible” to the prescribed antibiotic. On the contrary, when a bacterium does not respond anymore to the prescribed antibiotic it is considered “resistant”, and treatments become difficult and infections persist in the body, affecting patient health, and increasing the risk of spread to others.)
Resistance to antibiotics (AMR) occurs naturally and over time when bacteria (such as bacteria, fungi, viruses, and parasites) come into contact with antibiotics. Luckily, there are laboratory tests that allow the doctors to identify if the bacterium is still susceptible or has become resistant to specific classes of antibiotics and choose the treatment accordingly.

**Purpose of the survey**

The consequences of AMR on patients’ health are still very difficult to establish and this information is essential to reduce its impact. For this reason, we will observe the clinical progress of patients with bloodstream infections (BSI) caused by bacteria resistant to specific antibiotics classes. Specifically, we will look at patients infected with two bacteria species and two specific classes of antibiotics that are often used to treat those infections:

1. *Escherichia coli* resistant to third generation cephalosporine (ESBL- E. coli)

To do so, information will be collected and compared from a group of patients with susceptible and resistant infections, and, if feasible, from a group of uninfected patients.

**Type of Research**

This is a prospective cohort study and involves monitoring and comparing in the future clinical progress of groups (cohorts) of patients infected with *E. coli* or *S. Aureus*, susceptible and resistant to chosen antibiotics, and a group of patients without infection. Patients are selected based on the results of their first blood diagnostics test.

**Participant selection**

Cohort 1 and 2: We are inviting your child to take part of this study is because *E. coli* or *S. aureus* were isolated in your child first blood sample and the bacteria were ether susceptible or resistant to the classes of antibiotics we have mentioned before.

Cohort 3: We are inviting your child to take part of this study is because no *E. coli* or *S. aureus* were isolated in your child first blood sample taken for routine diagnostic, and because the duration of your child hospital stay matches the duration of hospital stay of a patient infected by *E. coli* or *S. aureus*.

**Voluntary Participation**

Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to have your child participate or not. If you choose not to consent, all the services you and your child receive at this clinic will continue and nothing will change, and your child will still be offered the treatment that is routinely prescribed for the diagnosed infection. You may also choose to change your mind later and stop participating, even if you agreed earlier, and the services you and/or your child receives at the clinic will continue.

**Procedures and Protocol**

Your child blood samples were sent for diagnostic and will be store and used by the health care facility according to their common practices. If you agree to take part to the study, some of your child clinical data will also be recorded retrospectively, starting from the day your child has been admitted, and prospectively.
B. Description of the Process

During the study we will collect data from your child medical records:

1. clinical data on the day we have received the laboratory results of your child first blood sample.
2. the same information at 30 days of hospital admission (if feasible), and/or at your child discharge.

If you choose to not consent for the information listed in point 1 and 2 to be acquired for your child, unfortunately your child will not be eligible to participate further to the survey, as those data are necessary for the study.

Duration
The study will last from the day your child has been enrolled in the study until your child discharge.

Risks
There is potential for breach confidentiality for data obtained from medical records. In the confidentiality section of this form we explain how this risk can be minimized.

Benefits
There may not be any benefit for you or your child, but your participation is likely to help us find the answer to he a very important research question and start estimating the real health impact of AMR.

Confidentiality
The information that we collect from this research project will be kept confidential. Information about you child that will be collected during the research will be put away and no-one, but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your child number is, and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc.]. Any of the results shared will be aggregated so that individuals cannot be identified.

Example of question to elucidate understanding: Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?

Sharing the Results
We will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw
You do not have to agree to your child taking part in this research if you do not wish to do so and refusing to allow your child to participate will not affect your treatment or your child's treatment at this Centre in any way. You and your child will still have all the benefits that you would otherwise have at this Centre. You may stop your child from participating in the research at any time that you wish without either you or your child losing any of your rights as a patient here. Neither your treatment nor your child's treatment at this Centre will be affected in any way.

Who to Contact
If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail]
PART II: Certificate of Consent

I have been invited to have my child participate in research of AMR bloodstream infections. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked I have been answered to my satisfaction. I consent voluntarily for the child in question to participate in this research as the child parents/guardian.

Print Name of Participant __________________________
Signature of Participant __________________________
Date ____________________________________________
                        Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness___________________________ AND Thumb print of participant
Signature of witness ____________________________
Date __________________________________________
                        Day/month/year

Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1. __________________________
2. __________________________
3. __________________________
I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent__________________________

Signature of Researcher /person taking the consent___________________________
Date ____________________________
                        Day/month/year