PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Bloodstream infections, antibiotic resistance and the practice of blood culture sampling in Germany – study protocol of a Thuringia-wide prospective population-based study (AlertsNet)
AUTHORS	Karch, André; Schmitz, Roland; Rißner, Florian; Castell, Stefanie; Töpel, Sandra; Jakob, Matthias; Brunkhorst, Frank; Mikolajczyk, Rafael

VERSION 1 - REVIEW

REVIEWER	Kevin B Laupland Royal Inland Hospital, Kamloops, BC, Canada
REVIEW RETURNED	11-Jul-2015

GENERAL COMMENTS	Bloodstream infection (BSI) is of major importance. A requisite step in the diagnosis of BSI is the sampling of blood for culture; if a culture is not taken then it is impossible to diagnose a BSI. It therefore follows that in regions/institutions where sampling rates are higher (lower) that rates of BSI will be higher (lower). While a small number of studies have provided evidence supporting this, published literature evaluating the effect of sampling on BSI incidence is notably scanty. In particular, the optimum sampling frequency (that which will identify nearly all BSI but not waste resources by oversampling and identification of excessive contaminants) is not known. This study proposed by Karch and colleagues therefore represents a major undertaking aimed at evaluating the role of sampling and occurrence of BSI. My main comments and suggestions 1. Population-based studies are those where all cases in a defined geographic region are included (or estimated using a non-biased random sampling procedure). The advantages are that the incidence in a population can be established and selection bias is minimized or eliminated. Most centers worldwide that have reported on population-based surveillance for BSI have had ascertainment rates approaching 100% (in other words all labs in the surveillance region are included). While no set standard has been agreed upon, generally accepted that 90% or more of cases occurring in a population should be identified in a population-based study. As I understand the current expected rate for this study is 75% of cases are expected to be included. Ideally the authors will recruit these remaining centres. If not, some means of dealing with this bias will need to be defined. 2. It is impressive that the investigators have managed to recruit so

	many participating institutions on a voluntary basis across such a large region. However, it is well established that voluntary submitted data often misses cases. In addition, data abstraction will be subjected to potential variability by the number of data collectors. It is imperative that a system of audit be done to identify misses or poorly collected data. This needs to be done on a randomly selected sample of cases to ensure validity. 3. It is critically important to separate out community-onset BSI (those occurring in outpatients or among those admitted to hospital with first culture positive within the first 48 hours from admission) from hospital-onset BSI (those first identified more than 48 hours after admission or within 48 hours of hospital discharge). Notably identification of all the community-onset cases requires inclusion of community-based labs in addition to hospital labs. It is very important to discern community-onset and hospital-onset cases as they are clearly distinct clinically and epidemiologically. For example, length of stay and sampling of inpatients is critically important for hospital-onset cases but essentially irrelevant for community-onset cases where sampling practices in the emergency department is the single most important determinant. In my opinion the investigators need to clearly define and distinguish community-onset and hospital-onset cases and complete independent assessments of the determinants of these separately. 3. Establishment of contaminants is a challenging area that is potentially highly subjective. I suggest that explicit objective criteria are used. All organisms that may be considered to be potential contaminants (ie coagulase negative staphylococci, viridans group streptococci, micrococci etc) should be clearly stated along with the objective criteria for classification as contaminants or not. These should not be open for individual assessment. Consistency in establishment of contaminants should be subjected to an audit to ensure that there is no misclassification. 4. Establishment of an episode of a BSI is challenging. In almost all cases, a repeat positive blood culture within 30 (90 days?) days represents the same episode with either treatment failure or relapse. In addition, where multiple positive organism isolates be identified from a single patient the question of whether this is a single (ie poly-microbial infection) or multiple mono-microbial infections is raised. I strongly recommend that the authors use objective criteria for establishing these and not use individual assessment. For example, all positive isolates for the same organism within 30 days are considered the same episode, all isolates obtained within 48 hours are considered the same episode or something of the like.

REVIEWER	Keng Sheng Chew Universiti Sains Malaysia, MALAYSIA
REVIEW RETURNED	28-Sep-2015

GENERAL COMMENTS	1) On page 5, lines 11-13, the authors said that findings from previous surveillance networks are not easily transferable to other countries. On what basis, would AlertsNet findings are generalizable to other countries since AlertsNet is a German-based surveillance and does not include data from other countries?

	2) On page 13, lines 1 - 4, the authors said that there are seven interventions that are aimed to be studied in order to improve the practice of blood culture. On what basis these seven interventions are chosen and not others?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name

Kevin B Laupland
Institution and Country
Royal Inland Hospital, Kamloops, BC, Canada

1. Population-based studies are those where all cases in a defined geographic region are included (or estimated using a non-biased random sampling procedure). The advantages are that the incidence in a population can be established and selection bias is minimized or eliminated. Most centers worldwide that have reported on population-based surveillance for BSI have had ascertainment rates approaching 100% (in other words all labs in the surveillance region are included). While no set standard has been agreed upon, generally accepted that 90% or more of cases occurring in a population should be identified in a population-based study. As I understand the current expected rate for this study is 75% of cases are expected to be included. Ideally the authors will recruit these remaining centres. If not, some means of dealing with this bias will need to be defined.

Response
Thank you for your comment. It is indeed our plan to recruit the remaining centres and we are at the moment negotiating final details. In case we are not successful we will have to take this into account at the analysis stage.
We added to the text:
“Negotiations with the remaining facilities have been started as it is the aim of AlertsNet to cover the entire population of Thuringia.” (Page 8, lines 23-24)
“If AlertsNet is not successful in maintaining a population-based data collection (equal to covering more than 90% of all bloodstream infection cases in Thuringia), this needs to be addressed in the analysis and interpretation stage.” (Page 14, lines 22-25)

2. It is impressive that the investigators have managed to recruit so many participating institutions on a voluntary basis across such a large region. However, it is well established that voluntary submitted data often misses cases. In addition, data abstraction will be subjected to potential variability by the number of data collectors. It is imperative that a system of audit be done to identify misses or poorly collected data. This needs to be done on a randomly selected sample of cases to ensure validity.
Response
Thank you for your comment and the supporting words. AlertsNet is indeed a voluntary network; however, once an institution and its collaborating lab have agreed to participate, all blood cultures received by the lab and their results are automatically and digitally transferred to the blood culture registry in the same way they are reported to the referring clinicians, thus, there will be no missing data with respect to the microbiological parameters. However, the collection of clinical data which is collected for further understanding of the clinical correlate of the bloodstream infection episode (including antimicrobial therapy) is indeed subject to potentially incomplete documentation. Therefore, we are constantly reviewing the data quality of the participating centers and are sending weekly reports to the centers. We agree that regular audits are good means to further improve the data quality in the institutions as well as for reviewing the data quality of the labs and added the following

paragraph:
“Moreover, data quality in the participating hospitals will be constantly evaluated and weekly reports will be sent back to the institutions. Regular audits will be implemented in addition for the participating laboratories and clinical institutions.” (Page 14, lines 25-27)

3. It is critically important to separate out community-onset BSI (those occurring in outpatients or among those admitted to hospital with first culture positive within the first 48 hours from admission) from hospital-onset BSI (those first identified more than 48 hours after admission or within 48 hours of hospital discharge). Notably identification of all the community-onset cases requires inclusion of community-based labs in addition to hospital labs. It is very important to discern community-onset and hospital-onset cases as they are clearly distinct clinically and epidemiologically. For example, length of stay and sampling of inpatients is critically important for hospital-onset cases but essentially irrelevant for community-onset cases where sampling practices in the emergency department is the single most important determinant. In my opinion the investigators need to clearly define and distinguish community-onset and hospital-onset cases and complete independent assessments of the determinants of these separately.
Response
We are grateful to you for bringing up the issue of community-onset BSIs. We agree with the reviewer that it is important to differentiate between hospital- and community onset BSIs and that it is crucial to counteract a potential selection bias against community-onset BSI. As patients with BSIs are generally treated in an inpatient setting (no matter if community- or hospital-onset BSI) we are confident that our hospital-based approach still captures all of the community-onset BSIs. Moreover, we address this issue in our eCRFs where we collect extensive data on the origin of the infection so that a differentiation is possible. This enables us as well to collect retrospective data about the disease period before admission to the hospital. A direct inclusion of the around 4000 general practitioner and registered doctors in Thuringia into AlertsNet is not feasible given that most of them are self-employed and their labs are spread over the whole of Germany.
We added the following sentence:
“This also includes community-onset bloodstream infections which can be differentiated in AlertsNet from hospital-onset bloodstream infections using the eCRF system; thus, retrospective data about the time before admission to the hospital can be gathered.” (Page 14, lines 5-8)

4. Establishment of contaminants is a challenging area that is potentially highly subjective. I suggest that explicit objective criteria are used. All organisms that may be considered to be potential contaminants (ie coagulase negative staphylococci, viridans group streptococci, micrococci etc) should be clearly stated along with the objective criteria for classification as contaminants or not. These should not be open for individual assessment. Consistency in establishment of contaminants should be subjected to an audit to ensure that there is no misclassification.
Response
Thank you for your comment. We will discuss comment 4 together with comment 5 as it is both related to the algorithm we use for generating bloodstream episodes from blood culture results.

5. Establishment of an episode of a BSI is challenging. In almost all cases, a repeat positive blood culture within 30 (90 days?) days represents the same episode with either treatment failure or relapse. In addition, where multiple positive organism isolates be identified from a single patient the question of whether this is a single (ie poly-microbial infection) or multiple mono-microbial infections is raised. I strongly recommend that the authors use objective criteria for establishing these and not use individual assessment. For example, all positive isolates for the same organism within 30 days are considered the same episode, all isolates obtained within 48 hours are considered the same episode or something of the like.
Response

We totally agree with the reviewer that definition of contaminants and episodes is crucial for our study. However, this definition is far from trivial. We have therefore defined already early on in the process an algorithm which helps us in doing so. The algorithm first differentiates between obligate pathogens and facultative pathogenic bacteria. Detection of an obligate pathogen results automatically in the definition of a BSI episode, while for facultative pathogenic bacteria at least two positive blood cultures with the same pathogen within 96 hours are necessary.
For the definition of an episode, we also used the 96 hour margin. If the same organism is cultured at least 96 hours after the last positive blood culture, a new episode is defined (for facultative pathogenic bacteria then, again, 2 positive blood cultures within 96 hours are necessary). We added information on the algorithm:
"Documentation of patient-related clinical data will be performed exclusively for clinically relevant positive BC results. For this, positive blood cultures collected in the registry undergo an automated algorithm aiming at differentiating contaminants from clinically relevant pathogens. For this, blood culture results are compared to predefined lists of obligate and facultative pathogenic bacteria. Obligate pathogens are automatically defined as clinically relevant at their first occurrence while facultative pathogenic bacteria must be cultured at least twice within 96 hours in the same patient [10]. Documentation will be performed for each new episode. A new episode is generated only If the same organism is cultured at least 96 hours after the last positive blood culture in the same patient (for facultative pathogenic bacteria then, again, 2 positive blood cultures within 96 hours are necessary). In the case of a first or new episode, patient characteristics listed in Appendix 2 need to be documented." (Page 10/11, lines 20-27 and 1-3)

Reviewer: 2
Reviewer Name

Keng Sheng Chew
Institution and Country
Universiti Sains Malaysia,
MALAYSIA

1) On page 5, lines 11-13, the authors said that findings from previous surveillance networks are not easily transferable to other countries. On what basis, would AlertsNet findings are generalizable to other countries since AlertsNet is a German-based surveillance and does not include data from other countries?
Response
Thank you for your comment. We didn't want to imply that AlertsNet data is more generalizable than data from previous surveillance networks. In contrast, we tried to argue that AlertsNet will be a valuable tool for assessing the situation in Germany as none of the surveillance network data is truly transferable to other health-care systems. Thus, the available networks and AlertsNet complement each other. We clarified our statement and adapted the sentence to:
"Although the members of the IBSC have already published important research results from their surveillance networks [17], results of these types of studies are not easily transferable to other countries; a study reflecting the pathogen and antibiotic resistance profiles in Germany as well as the properties of the German healthcare system will complement the available surveillance networks perfectly." (Page 4, lines 12-15)

2) On page 13, lines 1 - 4, the authors said that there are seven interventions that are aimed to be studied in order to improve the practice of blood culture. On what basis these seven interventions are chosen and not others?

Response

Thanks for this helpful comment. The planned interventions will be derived in a two-step process. First, a literature review on deficits and potential intervention aims has been performed. Second, a comprehensive mixed methods study (including focus groups and a quantitative survey) is currently conducted, aiming at identifying underlying causes for the deficits in blood culture testing. Based on these results, a multifaceted intervention concept is currently being developed and piloted. The seven areas reported are preliminary and based on the literature review. We replaced the sentence by: "Potential areas of improvement based on a systematic literature review are."