Survival following *Staphylococcus aureus* bloodstream infection; a prospective multinational cohort study assessing the impact of place of care

Running title: *S. aureus* mortality and quality of care

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Abstract

Background: *Staphylococcus aureus* bloodstream infection (SAB) is a common, life-threatening infection with a high mortality. Survival can be improved by implementing quality of care bundles in hospitals. We previously observed marked differences in mortality between hospitals and now assessed whether mortality could serve as a valid and easy to implement quality of care outcome measure.

Methods: We conducted a prospective observational study between January 2013 and April 2015 on consecutive, adult patients with SAB from 11 tertiary care centers in Germany, South Korea, Spain, Taiwan, and the United Kingdom. Factors associated with mortality at 90 days were analyzed by Cox proportional hazards regression and flexible parametric models.

Results: 1,851 patients with a median age of 66 years (64% male) were analyzed. Crude 90-day mortality differed significantly between hospitals (range 23% to 39%). Significant variation between centers was observed for methicillin-resistant *S. aureus*, community-acquisition, infective foci, as well as measures of comorbidities, and severity of disease. In multivariable analysis, factors independently associated with mortality at 90 days were age, nosocomial acquisition, unknown infective focus, pneumonia, Charlson comorbidity index, SOFA score, and study center. The risk of death varied over time differently for each infective focus. Crude mortality differed markedly from adjusted mortality.

Discussion: We observed significant differences in adjusted mortality between hospitals, suggesting differences in quality of care. However, mortality is strongly influenced by patient mix and thus, crude mortality is not a suitable quality indicator.

Introduction

Staphylococcus aureus is one of the commonest causes of nosocomial and community-acquired bloodstream infection (1). The associated mortality is substantial and varies between 20-30% at 90-days (2). Considerable efforts, including the use of quality targets, have been made in many healthcare systems to reduce the incidence and burden of *S. aureus* infection, and particularly of methicillin-resistant *S. aureus* (MRSA).

We have previously reported a pooled analysis of five prospective studies including 3395 patients with *S. aureus* bloodstream infection (SAB) from 20 hospitals in Europe and the USA and found marked differences in outcome between centers (3). Such differences might reflect variations in the quality of care received by patients with SAB, or alternatively, be the result of varying patient populations with different characteristics and access to hospital care and/or local variations in the prevalence of different *S. aureus* strains.

The impact of patient, pathogen, and management factors on outcome of SAB has been widely studied. Major patient factors include age, burden of comorbid disease, and the nature of the infective focus. Pathogen factors have been associated with particular disease manifestations (e.g. device related bacteremia) (4,5). Management of SAB is challenging and has been described as a major determinant of outcome. Choice of empiric and definitive therapy, extent of diagnostic investigation, source control, and duration of treatment are all identified as independent determinants of survival (6,7). Several studies have demonstrated the advantage of involving infection specialists and use of management bundles (8–10).

Quality measures have permeated medicine and are increasingly used for accountability and reimbursement. The measures inventory of the Center for Medicare and Medicaid Services in the United States lists several process measures concerning SAB (11). The National Health Service (NHS) in the United Kingdom employs the incidence of MRSA to compare healthcare-associated infection between hospitals (12). Although mortality of SAB is

currently not measured, comparable outcome measures are used in other disease areas. For example, mortality from breast cancer in females or mortality within 30 days of hospital admission for stroke are current NHS digital indicators (12).

Our objective was therefore to investigate whether crude mortality could serve as an objective and easy to implement quality indicator. In a multicenter, multinational, prospective, observational study on consecutive patients with SAB, we assessed between-center differences in mortality and how these differences are influenced by patient and disease factors.

Methods

Study design

We conducted a prospective, multicenter, international cohort study (ISAC-01 study, ClinicalTrials.gov identifier NCT02098850) in 11 tertiary care hospitals across 5 countries: Germany (2 centers), Korea (1 center), Spain (2 centers), Taiwan (1 center), and the United Kingdom (5 centers). All centers collected data on at least 80 consecutive patients with SAB.

Ethics approval

Ethics approval was obtained at each study center according to local regulations. Informed consent was sought from patients for follow-up visits. In some centers the study was conducted as part of a service evaluation and informed consent was waived by the Ethics Review Committee or relevant national authority.

Participants

Consecutive hospitalized patients with *S. aureus* cultured from blood between 01 January 2013 and 30 April 2015 were enrolled, unless bacteremia represented contamination as judged by an infectious diseases physician or clinical microbiologist. Patients with a previous episode of SAB within the prior 12 weeks and patients with polymicrobial bacteremia (except common skin contaminants) were excluded. 271 participants from the UK centers were co-enrolled in the "Adjunctive rifampicin for *Staphylococcus aureus* bacteremia (ARREST)" trial (EudraCT No. 2012-000344-10) (13); their data was provided from the ARREST trial database as the trial case report forms were shared.

Study size and Bias

Data collection was initially planned for a minimum of 2 years aiming for approximately 2,000 patients in the overall cohort. To avoid selection bias, only consecutive cases from centers with a minimum of 80 participants during the study period were included in this analysis. Each participating center regularly checked recruitment against their own hospital's laboratory reporting data to ensure cases were not missed. Information bias was avoided by agreeing a unified case report form applying the same definitions for the ISAC-1 and ARREST study patients.

Collected data

Data were prospectively collected by dedicated medical staff and reviewed by an infectious disease physician or clinical microbiologist. Data were collected during infectious disease consultations, patient visits, and from patient charts or registries. Factors measured comprised basic demographic data (age, gender) and comorbidity (Charlson comorbidity index [not age-adjusted] (14) and injecting drug use). We chose the Sepsis-related Organ Failure Assessment

(SOFA) score (15) to measure the severity of infection at the time the first positive blood culture was obtained. Mode of acquisition of SAB was categorized with slight variations to the Friedman criteria (16). When SAB onset (i.e. systemic signs of SAB or the first positive blood culture in the absence of systemic signs) occurred after more than 48hrs of hospital admission, SAB was classified as "nosocomial". When less than 48hrs after hospital admission had elapsed, patients were classified as "community-onset healthcare-associated" if there was a significant history of healthcare contact (defined as regularly receiving intravenous therapy or specialized wound care at home, or receiving hemodialysis or intravenous chemotherapy within 30 days, hospitalized for more than 1 day in the previous 90 days, residence in nursing-home or long-term care facility). The remaining patients were classified as "true community-acquired".

The infective focus was defined as the site of infection most likely to be responsible for seeding into the bloodstream, categorized into nine groups: endocarditis, osteoarticular (bone and joint infection with and without prosthetic device), pneumonia, skin and soft-tissue, surgical wounds, central venous catheter, peripheral venous catheter, and "other deep focus"; a substantial minority of foci were unknown. A hierarchical ranking of the infective focus (dominant focus) was established for multiple foci as defined previously (3,17), namely: endocarditis > osteoarticular > pneumonia > other deep focus > surgical wound > skin and soft-tissue > central venous catheter > peripheral venous catheter.

The primary outcome measure was survival through 90 days. Patients were followed-up by either in-person visits to the hospital, or by telephone. Where possible, survival data were confirmed by national death registry data. Patients lost to follow up were censored at the date of their last visit or last known date of interaction with healthcare (if available).

Statistical Methods

Categorical data were described by count and percentage, quantitative data as median and interquartile ranges, and compared between centers using Kruskal-Wallis and chi-squared tests for continuous and categorical data respectively. To investigate predictors of survival following SAB, we used Cox proportional hazards regression models including: age, gender, MRSA (vs methicillin-susceptible SAB), mode of acquisition (nosocomial, community-onset healthcare-associated, or true community-acquired), injecting drug use, comorbidity (Charlson comorbidity index), disease severity (SOFA score), dominant focus as described above, and study center. Charlson and SOFA scores were truncated at their 99th percentiles (10 and 17 respectively) to avoid undue influence from outliers. There was no evidence of non-linearity in the effect of any continuous factor (age, Charlson, SOFA) in multivariable models, assessed using multivariable fractional polynomials. Given the number of possible interactions between these factors, those with $p<0.001$ were included based on forward selection.

To estimate how the risk of mortality varied over time, a flexible parametric model (18) was also fitted to the data including the same factors and interactions as the final Cox model above, with the hazard as the underlying time scale to produce comparable hazard ratios. The underlying survival function for this model is based on natural cubic splines and the number of internal knots for the spline was chosen by minimizing the Bayesian Information Criterion (BIC). A single internal knot (at the 50th percentile of death times) was selected. Time-varying coefficients were included for dominant focus and SOFA based on improvements to the BIC. As the time-varying effects of SOFA were small in magnitude, we also considered time-varying coefficients for dominant focus and center to explore center effects.

All statistical analyses were performed in R, version 3.2.2 (R Development Core Team), in particular the rstpm2 package, version 1.3.4, and Stata version 15.1.

Role of the funding source

The ISAC-01 study did not receive dedicated funding. Funding for data acquisition of patients that were also enrolled in the ARREST study was provided by UK National Institute for Health Research Health Technology Assessment. The funding organizations had no influence on the design of the study, the collection, analysis, and interpretation of the data; and the decision to approve publication of the finished manuscript.

Results

In total, 2,080 patients met criteria for inclusion into the study and had complete evaluable data. 1,809 patients were recruited from ISAC-01 and 271 from ARREST. 145 patients were then excluded as SAB was found as part of a polymicrobial infection, and 84 were excluded as they had a documented prior episode of SAB in the 12 weeks prior to screening. A total of 1851 cases were therefore evaluated in the final analysis (Figure 1).

Patient Characteristics

Clinical and demographic variables are shown for each study center (Table 1). Median age was 66 years (IQR 52–77) and 1181 (64%) patients were male. There were highly significant between center differences (p<0.0001) in patient age, prevalence of MRSA, mode of acquisition, burden of comorbid disease as assessed by Charlson comorbidity index (CCI), proportion of patients injecting drugs, and severity of illness as determined by SOFA score (Table 1). Other than surgical wounds and endocarditis, there were marked differences between centers in the distribution of infective foci identified. Overall 370 cases (20%) had no infective focus identified; this varied substantially between centers (8%–33%).

MRSA was present in 302 (16%) patients. Of these 135 (45%) were nosocomial infections, 114 (38%) were community-onset healthcare-associated, and 53 (18%) were true community-acquired infections (p<0.0001 vs MSSA). Patients with MRSA were older (median 70 vs 65 years respectively, p=0.0001), had higher disease severity (median SOFA 5 vs 3 respectively, *p*=0.0001), and higher comorbidity (median CCI 3 vs 2, p=0.0001), and were less likely to be injecting drugs (4/302 (1%) vs 100/1549 (6%), *p*<0.0001).

Outcome

Both early mortality (death within 72 hours of first positive *S. aureus* blood culture) and overall mortality (death within 90 days) differed significantly between study centers (Figure 2(a)). Overall, 132 patients (7%) died within 72 hours (between-center range 4–14%, chi-squared *p*=0.03); and 563 (30%) patients died by day 90 (range 23–39%, chi-squared *p*=0.004).

Mortality also varied markedly depending on the dominant infective focus (Figure 2(b)). The highest mortality occurred in patients with pneumonia (87 cases, 54% mortality), followed by unknown focus (172 cases, 46%), and endocarditis (41 cases, 31%). Lowest mortality occurred in patients with peripheral venous catheter (27 cases, 18%) and osteoarticular infections (51 cases, 19%). Overall the median duration of hospitalization was 18 days (IQR 9–31 days) following first positive *S. aureus* blood culture; this varied significantly (*p*<0.0001) between centers (range 12–21 days).

Predictors of Survival at 90 days

The association between demographic and clinical factors and overall mortality by 90 days is shown in Table 2. Besides pneumonia and "unknown" infective focus, crude (unadjusted) mortality was associated with older age, not using injecting drugs, nosocomial or healthcare-

associated acquisition, higher comorbidity, and more severe disease. There was significant variation in crude 90-day mortality across centers (range 23-39%, p=0.004; Table 1 and Figure 3).

In multivariable models (Table 2), all these factors except injecting drug use remained significantly associated with mortality. There was strong evidence of interactions between age and CCI (p=0.0006) and SOFA and CCI (p=0.0003) (Supplementary Figure 1), such that the substantially increased risk associated with greater values of each of them was attenuated (i.e. reached a threshold) if patients had high values of all of them. Increases in SOFA score had a particularly marked effect on mortality risk in patients without comorbidities (Supplementary Figure 1(b)): increasing SOFA score changed risk much less in those with substantial comorbidities. The multivariable model confirms that patients with pneumonia (hazard ratio, HR=2.28, 95% CI 1.58–3.29, $p<0.0001$), unknown infective focus (HR=2.36, 95% CI 1.70–3.27, $p<0.0001$) had significantly higher mortality than those with central lines or another dominant focus (Table 2).

The crude mortality risk estimates relative to center-1 and the adjusted estimates (adjusted for clinical and demographic factors and interactions between them) were substantially different, both quantitatively and qualitatively (Figure 3). Among five centers (centers 2,4,7,8,9) with crude relative-risk point estimates substantially lower than the reference, adjustment brought three back to near 1 but hardly affected two, one of which remained statistically significantly less than center 1. Conversely, for two centers (3 and 10) which had crude relative-risk point estimates near 1, adjustment revealed significantly higher mortality risks. When deaths within the first three days were excluded to account for differences in the early management of infection or late clinical presentation of patients, the mortality effect in center 10 was reduced, but remained significant (Supplementary Table 1).

The Cox model estimates an overall "average" association with mortality that is proportional for each factor over time from the first positive blood culture (similar to the "average" produced from a logistic model), whereas Figure 2(b) suggests that the mortality associated with infective foci may vary differently. Thus, we estimated how mortality risk varied over time from the first positive blood culture drawn according to dominant infective focus (and SOFA score) using multivariable flexible parametric models (Figure 4). The overall higher mortality risk identified in patients with pneumonia and unknown infective focus was driven by very high mortality within the first weeks, which dropped to approach that of other deep foci by day 42; over the longer-term, all deep foci had similar mortality. In contrast long-term mortality risk was much lower for superficial foci (peripheral lines), and intermediate for those with central lines and skin and soft tissue infections. There was also evidence, as might be expected, that the impact of higher baseline SOFA scores decreased with time from positive blood culture (p=0.0001; Supplementary Figure 2). However, these additional improvements to the model were small in magnitude and did not alter the center effects (Figure 3). Models allowing both focus and center effects to vary over time (rather than focus and SOFA score) suggested that differences between centers were greatest early in the disease course (Supplementary Figure 3).

Discussion

We have previously noted striking differences in SAB case-fatality rates between hospitals (3). To investigate the reasons for these differences requires a substantial unbiased patient cohort that supports adjustment for multiple confounding patient and disease factors. Therefore, we conducted a large, international, observational cohort study of SAB to determine whether differences in survival between treatment centers are most likely explained by patient factors and type of infection, or whether they persist after adjustment

suggesting that they might be due to clinical interventions, and therefore be regarded as a measure of institutional quality.

To summarize all measures related to the management of infection, we introduced "center" as a factor in the analysis. We confirmed the previously observed marked differences in crude 90-day mortality. However, center effects were generally smaller than the effects of pneumonia as the infective focus and an "unknown" infective focus. When adjusting for confounders in a Cox regression model, center effects changed markedly compared to crude estimates. Thus, variations in case-mix may outweigh the effect of infection management on a hospital level. We therefore conclude that hospital-wide crude mortality is not suitable as an indicator of organizational quality of care.

There is little doubt that quality of care influences outcome on the individual patient level in patients with SAB and it has been shown that achievement of quality measure indicators can improve outcome (10). However, as shown here, the crude mortality rate is strongly influenced by other factors. In a complex and heterogenous disease like SAB, the link between a quality intervention and outcome may be weak. For example, taking follow-up blood cultures may be vital in some patients to detect infective endocarditis, but less important in other patients with peripheral venous catheter infection. Likewise, early antibiotic therapy may be more effective in patients with severe comorbidities than in patients without comorbidities (19).

From clinical experience, we expected that the risk of death could vary over time for different infective foci. Indeed, several different dynamics could be identified using flexible parametric models that account for this (Figure 4). For example, mortality in patients with pneumonia and unknown foci was greatest shortly after SAB onset, converging to a similar long-term mortality risk as other deep foci. In contrast, patients with endocarditis had a lower initial mortality risk, potentially reflecting the time it takes for *S. aureus* to destroy the heart

valves and/or cause clinically relevant foci at distant sites. Superficial foci, such as line infections, had a substantially lower ongoing mortality risk than deep-seated foci. This difference confirms the clinical observation that deep-seated infection is a more serious disease entity and may reflect unaddressed reservoirs of infection or sequelae of SAB. In the case of "unknown focus", however, we cannot rule out that early mortality is driven by a lack of time for correctly diagnosing the underlying focus in severely ill patients.

This study was designed to remedy limitations of our previous post-hoc analysis, for example by including data on comorbidities and illness acuity (3). The strengths of the study are its size, the comprehensive, prospective collection of data from consecutive patients including details of comorbidity, severity of disease, and clinical course, with very little missing data. We also included hospitals from different healthcare systems that should increase the likelihood of observing the impact of different hospital care delivery models on outcome from an infectious disease.

Nevertheless, limitations remain. Important risk factors or confounders may have been missed. For example, we have not assessed the impact of pathogen factors beyond methicillin resistance. Previous studies have reported decreased (20) or similar (21) survival rates in patients infected with MRSA. Although, in the univariable analysis MRSA was associated with a higher mortality, the effect was lost when adjusting for confounders. This may be explained by the fact that patients with MRSA were older, had more severe comorbidity, and a higher severity of disease. Previous studies which have attempted to determine the impact of pathogen factors on outcome of SAB indicate that effects are variable between different clonal lineages and multi-locus sequence types. However, the effects are likely to be small in comparison to patient and management factors (4,22).

Furthermore, if there were differences in the detection of SAB between hospitals (e.g. by different policies governing when to take blood cultures) or if patients present themselves at

later disease stages (e.g. due to differences in healthcare systems), this could have introduced a bias into the analysis if it were related to factors other than those we already adjusted for. We are not aware of such differences but cannot exclude them. Lastly, whilst centers included all patients treated for SAB, we cannot exclude the possibility that patients on end-of-life pathways were managed differently in different hospitals in terms of active antibiotic treatment. Finally, the need to perform detailed prospective assessment of patients resulted in our study being performed in large, tertiary teaching centers with specialist infectious diseases teams. It is possible that these centers all have similarly high standards of management for *S. aureus* infection, which may limit generalizability of our results. To further explore which measures and interventions can reduce the mortality of SAB, a detailed study should be performed on multiple hospitals from the same healthcare system across different levels of care.

Using a large prospective cohort, we have identified substantial differences between study centers in mortality following SAB. However, adjustment for patient factors at baseline including age, burden of comorbid diseases, infective focus, mode of acquisition, and disease severity did markedly change the effect of "center" on mortality. Therefore, crude mortality is not a valid quality of care outcome measure and should not be used to guide hospital reimbursement.

Declaration of interests

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Authors´ contributions

KN: data collection and data management, data analysis, data interpretation, manuscript preparation and manuscript review. HS, SR, WVK, MS, HBK, RT, CHL, JE, LEL, LM, GT: study design, data collection, data interpretation, manuscript review. NCG, KHS, HG, EN: data collection, manuscript review. ASW: data analysis, data interpretation, manuscript preparation and manuscript review. GT: study design, data collection, data management, data interpretation, and manuscript review. ML and AJK: study design, data collection, data management, data analysis, data interpretation, manuscript preparation and manuscript review. All authors have read and approved the final draft submitted.

References

1. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler, V. G., Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603–61. doi:10.1128/CMR.00134-14
2. Kern WV. Management of *Staphylococcus aureus* bacteremia and endocarditis: progresses and challenges. Curr Opin Infect Dis. 2010;23(4):346–58. doi:10.1097/QCO.0b013e32833bcc8a
3. Kaasch AJ, et al. Staphylococcus aureus bloodstream infection: a pooled analysis of five prospective, observational studies. J Infect. 2014;68(3):242–51. doi:10.1016/j.jinf.2013.10.015
4. Recker M, et al. Clonal differences in Staphylococcus aureus bacteraemia-associated mortality. Nat Microbiol. 2017. doi:10.1038/s41564-017-0001-x
5. Hos NJ, et al. Amino acid alterations in fibronectin binding protein A (FnBPA) and bacterial genotype are associated with cardiac device related infection in Staphylococcus aureus bacteraemia. J Infect. 2014. doi:10.1016/j.jinf.2014.09.005
6. Thwaites GE, et al. Clinical management of *Staphylococcus aureus* bacteraemia. Lancet Infect Dis. 2011;11(3):208–22. doi:10.1016/S1473-3099(10)70285-1
7. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin Microbiol Rev. 2012;25(2):362–86. doi:10.1128/CMR.05022-11
8. Rieg S, et al. Mortality of *S. aureus* bacteremia and infectious diseases specialist consultation--a study of 521 patients in Germany. J Infect. 2009;59(4):232–9. doi:10.1016/j.jinf.2009.07.015
9. Vogel M, et al. Infectious disease consultation for Staphylococcus aureus bacteremia - A systematic review and meta-analysis. J Infect. 2016;72(1):19–28. doi:10.1016/j.jinf.2015.09.037
10. Lopez-Cortes LE, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of Staphylococcus aureus bacteremia. Clin Infect Dis. 2013;57(9):1225–33. doi:10.1093/cid/cit499
11. Measures Inventory [Internet]. Available from: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityMeasures/CMS-Measures-Inventory.html
12. NHS Digital. NHS Digital Indicator Portal [Internet]. Available from: https://indicators.hscic.gov.uk
13. Thwaites GE, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2017. doi:10.1016/S0140-6736(17)32456-X
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
15. Vincent JL, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.

16. Friedman ND, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002;137(10):791–7.
17. Smit J, et al. Onset of symptoms, diagnostic confirmation, and occurrence of multiple infective foci in patients with Staphylococcus aureus bloodstream infection: A look into the order of events and potential clinical implications. Infection. 2018. doi:10.1007/s15010-018-1165-x
18. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175–97. doi:10.1002/sim.1203
19. Kaasch AJ, et al. Delay in the administration of appropriate antimicrobial therapy in *Staphylococcus aureus* bloodstream infection: a prospective multicenter hospital-based cohort study. Infection. 2013;41(5):979–85. doi:10.1007/s15010-013-0428-9
20. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis. 2003;36(1):53–9. doi:10.1086/345476
21. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive Staphylococcus aureus bacteraemia: an observational cohort study. Lancet Infect Dis. 2014;14(10):967–75. doi:10.1016/S1473-3099(14)70876-X
22. Rieg S, et al. Microarray-Based Genotyping and Clinical Outcomes of Staphylococcus aureus Bloodstream Infection: An Exploratory Study. PloS one. 2013;8(8):e71259. doi:10.1371/journal.pone.0071259