



## Narrative review

## How to: accreditation of blood cultures' proceedings. A clinical microbiology approach for adding value to patient care

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## ARTICLE INFO

## Article history:

Received 12 November 2017

Received in revised form

8 January 2018

Accepted 11 January 2018

Available online 2 February 2018

Editor: L. Leibovici

## Keywords:

Accreditation

Best practices

Blood culture

ISO 15189 standards

Key performance indicator

Method verification

Test method monitoring

## ABSTRACT

**Background:** Quality assurance and quality management are driving forces for controlling blood culture best practices but should not be disconnected from the end-point target, i.e. patient value.

**Aims:** This article is intended to help microbiologists implement blood culture accreditation that is actually beneficial to patient management.

**Sources:** Experience from a nationwide taskforce for promoting quality assurance and competence in clinical microbiology laboratories, guidelines on blood culture.

**Content:** Experience in blood culture accreditation according to International standard ISO 15189 standards is provided in this review, with a particular focus on critical points that are specific to blood culture (e.g. excluding strain identification or antimicrobial susceptibility testing). Blood culture test method verification is based on risk analysis, and evaluation of the test method's performance is based on the literature review and suppliers' data. In addition, blood culture performance relies largely on the quality of its pre-analytical phase, and the test method should be monitored based on key performance indicators such as the volume of blood cultured, the contamination rate and time to transportation. Other critical key indicators include the rate of false-positive signals, the rate of positive blood cultures, the ecology associated with positive results, and the timely communication of the results to the ward during the post-analytical phase. Finally, a critical analysis of quality controls and of the tools needed to improve blood culture monitoring in the future is provided.

**Implication:** Appropriate quality assurance should focus on patient value rather than technical details to provide an appropriate clinical service. **B. Lamy, Clin Microbiol Infect 2018;24:956**

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## Introduction

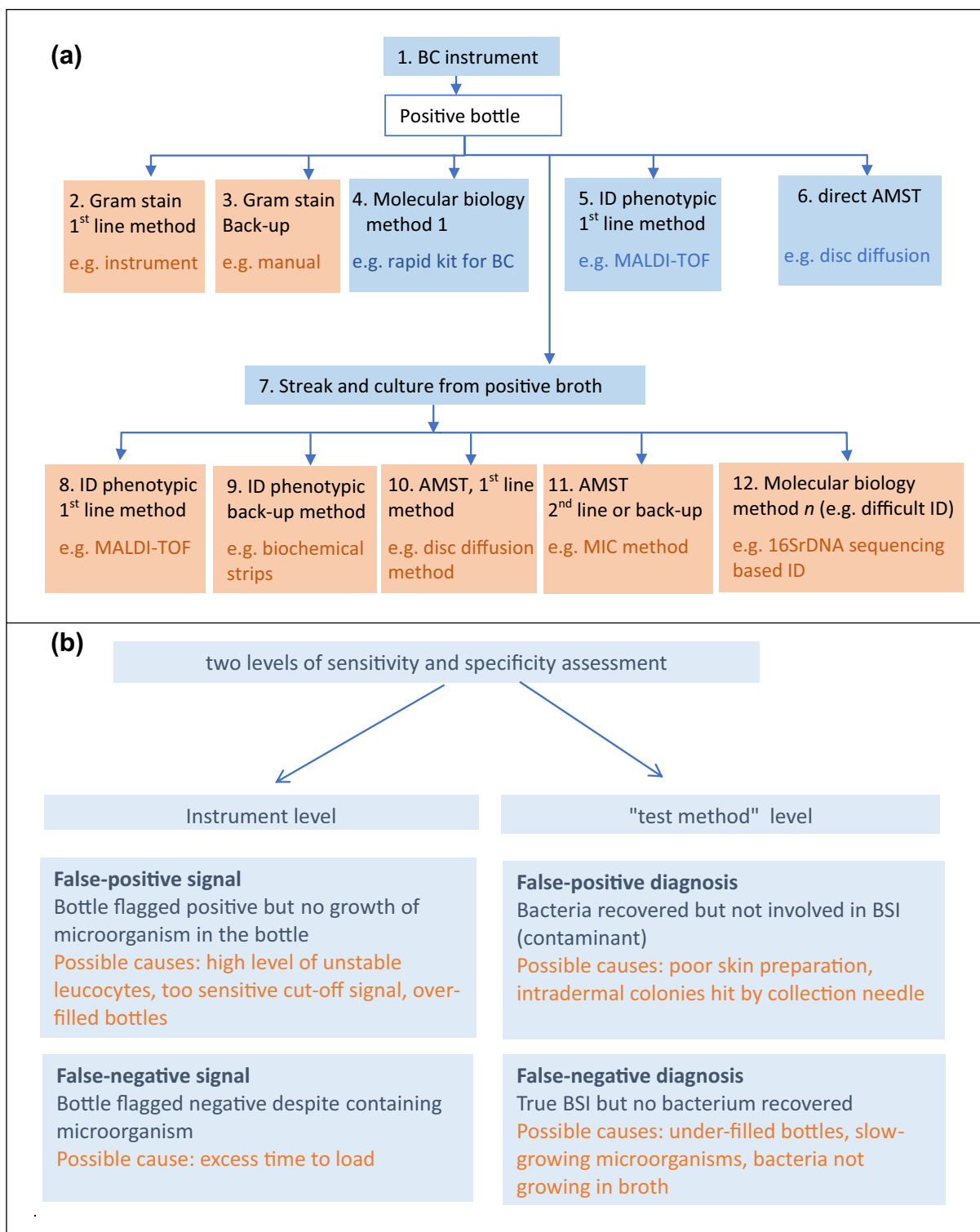
Given today's high standards for quality and competence, a test method must be shown to be fit for purpose such that a facility's customers can have confidence in the results produced. Quality management systems in medical laboratories are specified by

international standard ISO 15189. Objective evidence must be provided of this confidence, which is achieved through method validation, quality and technical requirements, quality management and a process of continual quality improvement; these factors are clear driving forces for controlling blood culture best practices.

Method validation is challenging in clinical microbiology because living microorganisms represent an extra source of uncontrollable variation that can affect results and because test methods are the sum of sequential and conditional sub-processes. For instance, blood culture can comprise 6 to 12 sub-processes for validation (Fig. 1a). One frequent pitfall is that accreditation can focus excessively on

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**Fig. 1.** Complex test method in clinical microbiology and consequences for performance analysis according to ISO 15189 standards. Example of blood culture. (a) The entire process is composed of several simple processes (sub-processes) for which either the output element of the process  $n - 1$  is the input element of the next process  $n$  (sequential process) or an input element is that of one of several processes. Some sub-processes are conditional, meaning that they are implemented according to the result of the previous output element. Depending on the laboratory organization in place, the entire process may include 6 to 12 sub-processes for validation, including back-up methods (e.g. Gram staining or identification phenotypic method, first-line method and back-up method). Several ID methods (e.g. ID phenotypic method and molecular biology blood culture kit) can coexist in the process, depending on the strategies in place. Red: sub-processes shared with other microbial test methods; blue: sub-processes specific to blood culture test method. (b) Example of consequences induced by the complex structure of the process. In the performance analysis, two levels of assessment should be distinguished and considered, the instrument level and the diagnosis level. Abbreviations: ID, identification; AMST: antimicrobial susceptibility testing.

technical details rather than on patient value, which results in an inappropriate clinical service, i.e. quality being disconnected from the end-point target of improved patient care. Indeed, the opportunity costs associated with an overemphasis on the technical aspects of a process, with the associated marginal gains, are incurred at the expense of other (pivotal) aspects of the process (e.g. pre- and post-analysis). With the deliberate aims of combating this danger and promoting an approach that is helpful to patient care, several initiatives have been developed. One such initiative is the French Society for Microbiology's national Committee for Quality in Microbiology (QUAMIC), which guides laboratories in appropriate method verification achievement, preventing excessive controls and promoting improved patient care [1,2]. Here, some of these experiences are discussed through the example of blood culture test method validation, with a particular focus on critical points that are specific to blood culture (e.g. excluding strain identification or antimicrobial susceptibility testing). This article is not intended to be an inventory of all the determinants and recommendations that are available elsewhere [3–8] but instead aims to help microbiologists to implement blood culture accreditation such that it is actually beneficial to patient management.

### Overview of the blood culture process, requirements and pitfalls

Aimed to diagnose bloodstream infection, blood culture should be processed and reported in a timely fashion because effective antimicrobial therapy critically influences the outcomes of patients with sepsis [9–12]. A sufficient volume of blood inoculated at bedside (optimally 40–60 mL distributed in four to six bottles) is critical for bacterial detection [3,4,8,13]. Culture-positive bottles follow sub-processes outlined in Fig. 1a. The combined effect of under-filled blood culture bottles and a high rate of solitary blood cultures (only two bottles collected during a sepsis event in adult patients) results in an insufficient volume of blood cultured, with an increased risk of false-negative results [8]. False-positive results are mostly caused by sample contamination during blood collection. Furthermore, automatic microbial growth detection from bottles is associated with a false-positive signal in patients with very high levels of leucocytes and/or with over-filled bottles [14–16]. False-negative signals can occur when a bottle is flagged negative despite containing bacteria (e.g. due to the pre-incubation temperature and excess time from blood collection to loading the instrument [17–20] or to slow-growing microorganisms or microorganisms that cannot grow in the blood culture broth). Such events result in two levels of performance analysis (episode, instrument) that should be considered in method verification (Fig. 1b).

### Method accreditation versus method validation

The scope of accreditation for a test method includes three phases (pre-analysis, analysis, and post-analysis), and control of the entire process is reached by quality management that includes procedures, personnel qualification and monitoring of key indicators. Method validation is more strictly centred on the analysis phase (Fig. 2). Blood culture represents a particular process with very few equivalents in laboratory tests because the entire volume of a specimen is taken for analysis, and this sample volume critically determines disease detection. Consequently, it is difficult to separate the pre-analytical and the analytical phases for method validation.

### Blood culture test method verification

The question of how to achieve method validation of blood culture can be greatly clarified by considering that a test method is

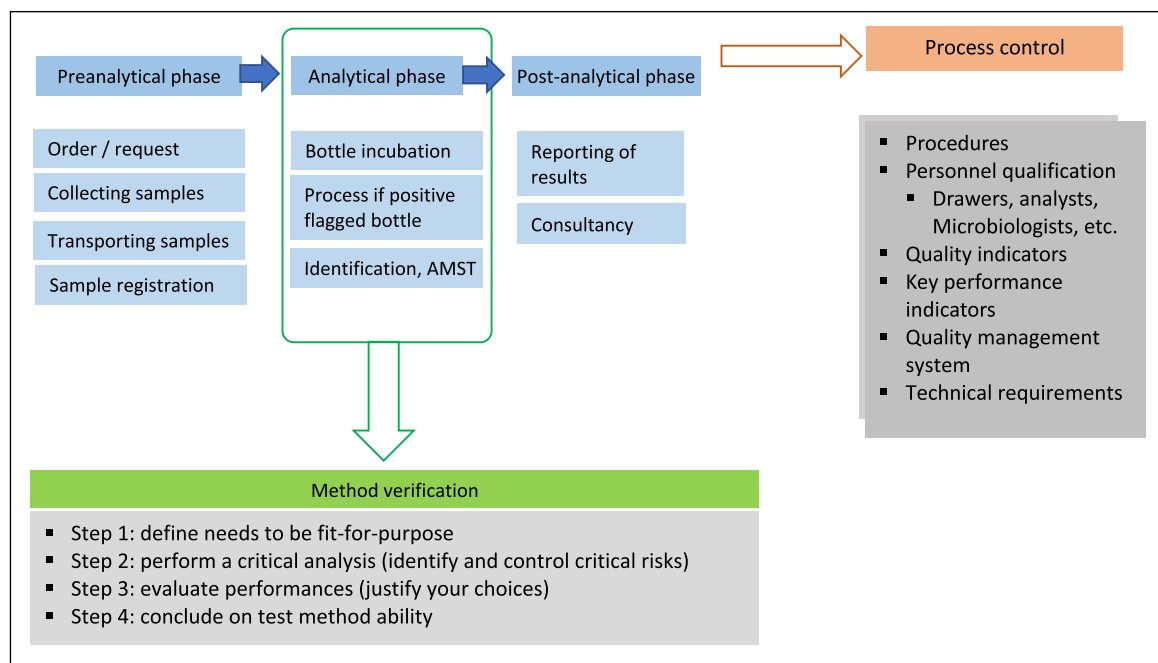
a complex process involving several simple processes (Fig. 1). Validation includes validating every sub-process used to report negative or positive results. Because blood culture has been extensively assessed and is currently the reference standard for diagnosing bloodstream infection, test method validation is limited to 'verification', provided that the user respects general and supplier guidelines. The laboratory still needs to confirm its ability to apply the method, but the workload is considerably lower compared with that associated with the validation of a method that has been developed in-house. When users practice a sub-process that differs from guidelines and for which the level of evidence in the literature does not ensure enough confidence for safe patient management, this particular sub-process should be validated and not only verified until enough evidence is available. Direct antimicrobial susceptibility testing from broth of positive bottles instead of antimicrobial susceptibility testing from colony is such an example at the time of this review's publication. As a qualitative method, blood culture verification is limited to the following:

- A critical analysis of the test method to identify the critical steps and define ways to control these steps. Several methods exist for analysing the causes and consequences, but the easiest and most versatile is certainly the 5-M Method. This method, based on the Ishikawa diagram, is highly versatile. The causes that emerge during analysis are grouped into the following categories: machine, method, manpower, materials and medium. Then, methods of control are described and implemented.
- An evaluation of the test method's performance for justifying the choices made locally, primarily based on the literature and supplier data to document sensitivity, specificity, ruggedness and stability. Based on these data, users should conclude that filled bottles should be maintained at room temperature to reduce the risk of false-negative results, that collecting more than three paired bottles over a 24-h period is not necessary and that collecting up to three paired bottles could be performed on one occasion and not over a 24-h period [3,4,8,18–20].
- On-site verifications are limited to equipment performance records when instruments are furnished. When replacing the machine used, instrument comparison is not necessary because no result comparison is performed for an individual patient. Follow-up is mostly based on indicator records.

Laboratories should rely on their quality management system to obtain a high degree of confidence that analytical aspects of the process are working well, and to monitor improvements in quality when required. The objective is to prevent errors, to maintain the lowest rate of non-conformities and to help define methods for improvement. For instance, competence assessment is pivotal in clinical microbiology. Such assessment requires job description, training, confirmation and a re-assessment routine before performance of tasks. Compliance with manufacturers' instructions and indicator records, which serve as an internal quality control, internal quality assurance and external quality assessment, are also beneficial for the categories of manpower, methods and machine. Finally, performing non-conformity assessments, internal audits and management reviews is useful for obtaining a high degree of confidence that analytical aspects are under control.

### How to monitor the blood culture process? The value of key-performance-indicator-based internal quality assurance

It is often asked whether incubator temperature should be externally verified, as temperature is a critical factor for bacterial growth. This verification is not recommended [1,2] because there is no reliable means for achieving this objective without risking the



**Fig. 2.** Test method and how to control it according to ISO 15189. Overview of the three-phase process (pre-analytical, analytical, post-analytical) and scopes and control means of the test method validation (limited to analytical phase) and of the test method accreditation (extended to the whole process). Abbreviations: QC, quality control.

disturbance of the stability of the instrument temperature, and it is widely accepted that metrology control stops where the instruments starts. Instead, verification of proper functioning of temperature alarms, thorough and regular maintenance by suppliers, and regular survey of the positive bottle rate are preferable. This latest approach is valuable, as a steady rate reflects the proper functioning of the instrument in its entirety.

Verifying that the analytic process is under control is typically achieved in clinical laboratories using quality controls (QCs), i.e. materials that mimic patient specimens and that contain a known amount of measurand. The QC approach is traditionally poorly developed in clinical microbiology because of basic issues associated with providing robust QC. Concerning blood culture, the issue is highlighted by the fact that bottle positivity depends strongly on the bacterial density in blood, which is generally very low (median 1 CFU/mL [8]) and that QC materials are virtually impossible to prepare. Despite this important unresolved limitation, certain local accreditation committees and suppliers have suggested or may suggest that ISO 15189 standards for medical laboratories can be met by regularly (e.g. monthly) spiking bottles with reference strains (e.g. *Escherichia coli* 15,000 CFU/mL [21]) to verify proper bacterial growth, positive bottle detection and time to detection. This approach is inconsistent because this condition is far from routine practice, because it is performed with easy-to-grow strains and because some of the information can consistently be verified in a different manner, at no extra cost. In addition, a credible purpose for such a QC is difficult to determine. If the goal is to verify broth fertility, the QC is indeed superfluous given the more thorough tests performed by suppliers on every batch before product release. It is acknowledged that commercially prepared blood culture media are exempt from end-user control [22]. If the goal is to identify malfunctions in cell detectors, a regular QC will not efficiently address the issue given the total number of positions in an instrument. Such QC practices constitute a costly false security and are not recommended [1,2]. Key performance indicator (KPI) -based monitoring should be preferred.

Although QC materials are difficult to produce in clinical microbiology, borrowing from blood science methodologies can

prove useful for reaching higher degrees of confidence. An original approach that suits microbiology well consists in monitoring the method with KPI and run charts well-known in blood science. KPI-based monitoring provides information similar to that of a QC, but rather than being based on imperfect QC materials, such monitoring uses data extracted from routine processes and is based on parameters that critically affect blood culture performance, so better reflecting the routine process quality. A good KPI monitors the quality of a critical part of a process and is designed to be helpful in identifying the real causes when data are unacceptable. KPIs are longitudinally monitored, e.g. according to a Levey–Jennings chart using an acceptable range based on a literature review and/or a risk analysis. KPIs out of range should lead to process changes. Several KPIs have been proposed and are in use: for the pre-analysis phase, the volume of blood cultured, the rate of contamination and the time required for the bottle to be loaded; for the analysis phase, the rate of the instrument false-positive signal, the annual positive blood culture ecology, and the rate of positive bottles; and for the post-analysis phase, the frequency of positive results promptly communicated to wards (Table 1). These KPIs, with the exception of the ecology indicator, can be monitored either continuously or occasionally (via regular audits), either throughout the entire institution or in part of it, according to local decisions. Such an approach monitors processes more efficiently than using QC materials [1,2]. Fig. 3 shows an example of how to monitor quality with a KPI run chart.

#### One example: monitoring the volume of blood cultured

It is notoriously difficult to judge, in clinical situations, the volume of blood that is drawn, particularly under pressure. The volume of blood cultured should be monitored both by the volume of blood per bottle and the number of bottles because these two indicators reflect the total volume, the end-point that determines blood culture sensitivity [8]. If one or both do not fall within the acceptable range (Table 1), causes of the quality defect should be identified, solution(s) implemented and issue resolution verified. Accurately identifying the real cause(s) influences the choice of

solutions, which is critical for reaching efficient improvement, as shown in Fig. 4. For instance, under-filled bottles require educated phlebotomy/nurse teams, while high-frequency solitary blood culture requires actions pertaining to blood culture ordering [8,23,24]. Note that monitoring limited to the volume of blood per bottle will not permit the detection of improper ordering and will hamper successful improvement. Recording both the volume of blood per bottle and the number of filled bottles is therefore advised. Once the real cause is identified, solution(s) to be implemented should be cautiously discussed because some are more effective and/or more robust than others [25]. From a similar baseline situation, two hospitals chose different strategies for improving blood volume, but the strategy adopted by Hospital 2 was more effective (Fig. 4).

Instrumentation developments can aid in volume monitoring despite certain limitations. The Bactec FX instrument (Becton-Dickinson Microbiology Systems, Sparks, MD, USA) estimates the volume of blood based on red blood cell metabolism, but this estimation is less accurate in the case of anaemia or impaired red blood cell metabolism, and data are disappointingly not released at the individual bottle level [26]. The Virtuo blood culture system (bioMérieux, Marcy l'Étoile, France) automatically estimates the volume of each bottle using photometric detection of the liquid level in the bottle, but access to data analysis may incur an extra cost.

#### Other indicators and remaining questions

Similar initiatives should be undertaken with other KPIs (Table 1). Concerning the contamination rate, monitoring is more

tedious because clinical data collection is necessary to appropriately analyse data. Additionally, despite an extensive literature on this topic [6,7,27], a practical standard definition for contamination and what threshold should be used remains challenging. The threshold of 3% is often reported [6,7,28], although we should not be satisfied with a 3% rate, and the extent of blood culture contamination can be obscured by the definition of contamination [29]. Efforts should be undertaken to clarify and standardize these points in a manner that allows for future consistent inter-laboratory comparisons. Contamination rates can be diminished by revised procedures and techniques (e.g. skin preparation, sampling site and a decrease in the number of samples through the single-sampling strategy, similar to the recently described diversion technique) and educational programmes [6–8,29–38].

In other respects, time to results is critical, particularly in the case of sepsis, because the delay negatively affects the positive blood culture rate [20,39–41], time to effective antimicrobial therapy and patient survival [9,42]. Monitoring time to bottle load is advised. This procedure involves monitoring the time required for transportation and time to load once bottles are received. These should be minimized as far as possible. Several societies recommend time to transportation <2 h [4], which is the target for which all must strive. However, even a threshold of 4 h, as tolerated elsewhere [43], may be difficult to reach in many current routines [39,40]. Efforts should focus on this point, with the caveat that transportation is not always under the responsibility of microbiologists. Time to results should be assessed regularly (e.g. annually). Controlling time to results implies considering incorporating advanced rapid test methods but also revising

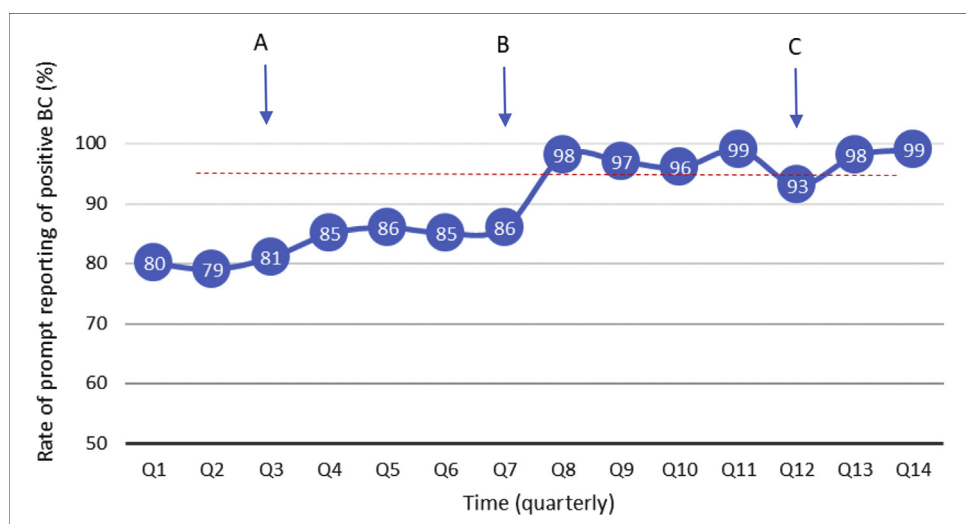
**Table 1**  
Examples of monitoring key performance indicators useful for verifying that the blood culture process is under control; only indicators specific to the blood culture process are listed [1,2]

Phase	Indicator	Comment	Acceptable range	Importance of the indicator	Monitoring frequency (example)
Pre-analytical	Volume of blood per bottle	- Poor volume negatively impacts on BC sensitivity [8] - Estimated from the bottle weight or fluid level after collection	8–10 mL [5,8] possible KPI: 80% in the range 8–10 mL	Critical	Regular <sup>a</sup>
	Rate of solitary blood cultures <sup>b</sup> per sample period (24 h)	Solitary BC negatively impacts on BC sensitivity (adult patients and children >13 kg), appropriate number of bottles per sample period should be four to eight [3,4,8,50]	As low as possible Target <10%	Critical	Regular <sup>a</sup>
	Time to bottle load	Delayed bottle loading negatively impacts on BC yield [17–20]	As low as possible	High	Regular <sup>a</sup>
	Rate of contamination	Contamination negatively impacts on BC specificity [6,7]	As low as possible Suggested KPI <3%	Critical	Regular <sup>a</sup>
Analytical	Rate of positive bottles per instrument (or per module if instrument makes it possible)	Designed to survey that the instrument (or one module) has no default in detecting positive bottle; checks the proper functioning of the instrument in its entirety	Depends on laboratory recruitment. To be defined locally. Should be steady or, when variable, mostly related to seasonal variation	Moderate	Quarterly
	Rate of false-positive signal	False-positive signals negatively impact on BC incubating (critical step) and can reflect a process default that need to be remedied (e.g. anaerobic/aerobic bottle inversion at bottle entry, over-filled bottles)	As low as possible. Hampered by no recent evaluation of currently commercialized media	Moderate. Decision to follow this KPI depends on the risk analysis performed locally	Regular <sup>a</sup>
	Rate of species recovered (ecology)	Overall knowledge of the ecology of the institution. Investigation is required in case of marked reduction of a bacterial group	NA Should be steady or, if variable, mostly with seasonal variations, recruitment being equal	High	Annual
Post-analytical	Rate of appropriate and prompt reporting of positive results to clinicians	Delayed or absence of reporting negatively impacts patient care	As low as possible	Critical	Regular <sup>a</sup>

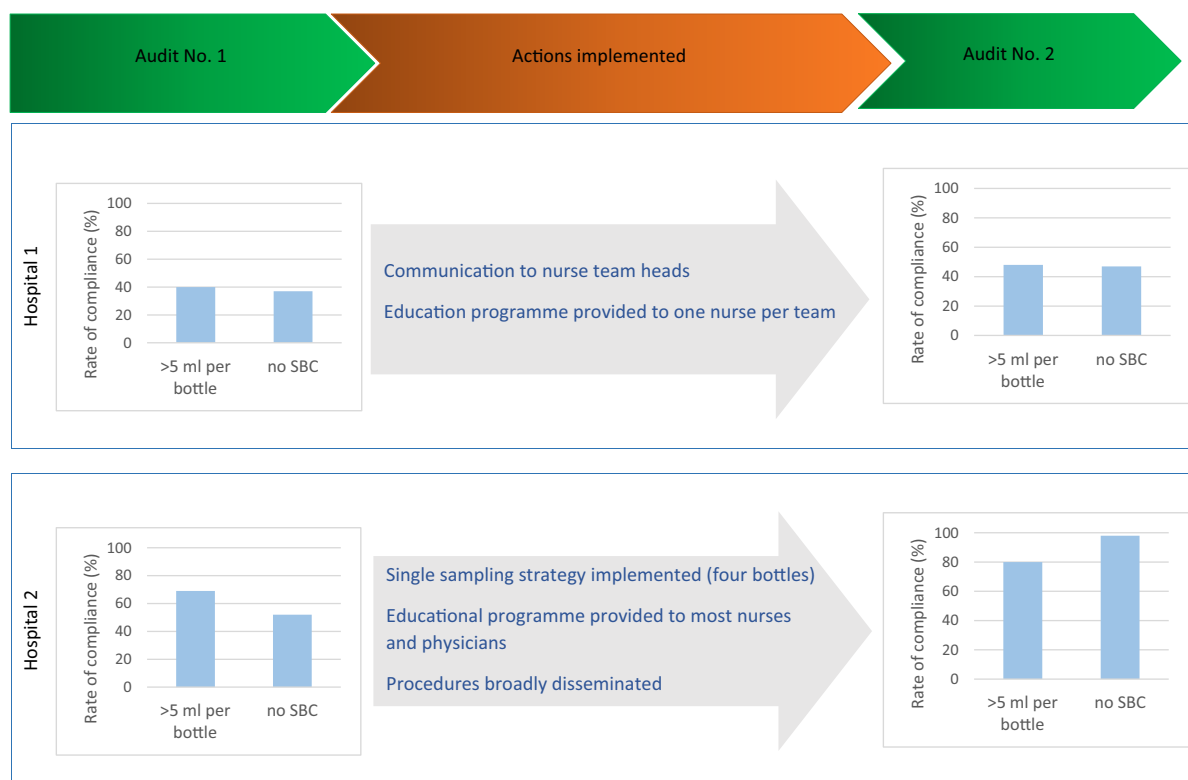
Abbreviations: BC, blood culture; KPI, key performance indicator.

<sup>a</sup> To be defined in each laboratory.

<sup>b</sup> Solitary BC: one or two bottle per episode.



**Fig. 3.** Run chart of the rate prompt reporting of positive blood culture (Gram stain result) to clinicians. Prompt reporting was defined in this example as reporting Gram stain result by phone within 1 h after Gram reading completion. Data of the audits were extracted from the laboratory system that traces time of result reporting. The acceptable range adopted (95%–100%) results from risk analysis and was implemented in Q2. Before Q3, procedure in positive blood culture reporting did not address single positive bottle with Gram-positive cocci grape-like clustering. 'A' marks a change in practice that was implemented in Q3, with a clear procedure specifying that Gram stain result of every positive blood culture should be reported to clinician and a short educational training was provided to staff. 'B': following disappointing results observed in Q4–Q7, risk analysis revealed that results were poorly reported during week-end periods when fewer operators are available. Workflow organization during week-end was revised in Q7 and reminders of procedure were provided to staff. This led to the acceptable range being reached. 'C': Risk analysis showed that the lowered rate observed in Q12 (out of range) resulted from a new employee who did not properly report results. Action provided was education to this employee with a re-assessment routine, showing that the situation normalized.



**Fig. 4.** Example of improvement of the quality of the volume of blood cultured in two hospitals based on key indicator monitoring. From relatively similar baseline situations (data from audit 1), two institutions adopted different strategies that resulted in different levels of efficiency, as demonstrated by the results from audit 2. The limited communication implemented by Hospital 1 should be addressed. By contrast, the single-sampling strategy (six bottles in one sampling) adopted by Hospital 2 involved a striking decrease in solitary blood cultures. The results from audit 2 show that further actions should differ between the two hospitals: Hospital 2 should focus on bottle filling only, while Hospital 1 should include actions pertaining to both bottle filling and number of sets (order).



organizational aspects to save time [42,44]. This is certainly an under-investigated area that requires attention with individualized approaches [45].

### What types of tools do we need and where should we go?

Most of the suggested KPIs can be monitored in every laboratory, although some may be tedious to collect, and few information technology systems currently enable a relevant, convenient and fully automated analysis. Some efforts in this area should be made by blood culture instrument manufacturers, information technology systems and local information technology service departments to improve smooth monitoring and to provide help for efficient actions [25]. Additionally, such indicators, when standardized, can be used for inter-laboratory comparisons. Analysing data at the population level (laboratories) can improve visibility and monitoring efficiency. Determining whether a result of 'moderate performance' is indeed a 'very good' or a 'poor' outlier result compared with those of the paired group is insightful. Such programmes for blood culture key indicators are currently not available in many European countries, although they have been implemented for decades in the USA [23,46–48]. These types of programmes should be promoted, given the power of this approach [49].

### Conclusion

The main questions raised by the accreditation of blood culture and improved awareness of critical steps of the process lead to improved blood culture, bloodstream infection diagnosis and patient care practices. ISO 15189 accreditation is therefore a good policy for laboratories for receiving credit for their performance, but caution calls for the inappropriate escalation of quality measures that would lead to false security and be counterproductive to patient management to be addressed. Every quality assurance initiative must be implemented with the basic requirement of achieving an actual contribution to patient care. It is essential to maintain perspective and to keep in mind that patient care is the goal of any change. Some issues remain unresolved from a practical point of view despite rather clear knowledge and calls for developments to assist microbiologists and healthcare workers.

### Transparency declaration

The authors declare no conflict of interest.

### Funding

This work received no funding.

### Personal contribution

BL, AF, CC, CH and PL conceived and designed the approach; PL coordinated discussions and working group QUAMIC; BL drafted the paper; CH, PL, CC and AF helped to draft the manuscript; and PL, CC, CH and AF critically revised the manuscript. All authors read and approved the final manuscript.

### Acknowledgements

The manuscript was revised for English language by American Journal Experts (AJE). The content of this article was presented at the ESCMID postgraduate education course in Nice on 28 March 2017 entitled *Improving the diagnosis of bloodstream infections—advancing technology for better care* (organising groups: ESGBIS, ESGB, ESGEM, ESGMD, ESGS, EFISG). The authors wish to

thank the QUAMIC study group from the French Society for Microbiology (SFM) for fruitful discussions.

### References

- [1] Hémoculture et accreditation. In: Courcol R, Laudat P, editors. QUAMIC, Paris: Société française de microbiologie Ed; 2017. p. 85–96.
- [2] Hémoculture – SH Form 43. In: Courcol R, Laudat P, editors. QUAMIC, Paris: Société française de microbiologie Ed; 2017. p. 97–136.
- [3] Lamy B, Seifert H. Microbial diagnosis: septicemia. In: Cornaglia G, Courcol R, Herrmann JL, Kahlmeter G, Peigue-Lafeuille H, Vila J, editors. European manual of clinical microbiology: SFM/ESCMID. Paris: Société française de microbiologie Ed; 2012. p. 101–10.
- [4] Baron EJ, Miller JM, Weinstein MP, Richter SS, Gilligan PH, Thomson Jr RB, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). Clin Infect Dis 2013;57:e22–121.
- [5] Willems E, Smismans A, Cartuyvels R, Coppens G, Van Vaerenbergh K, Van den Abeele AM, et al., Bilulu Study Group. The preanalytical optimization of blood cultures: a review and the clinical importance of benchmarking in 5 Belgian hospitals. Diagn Microbiol Infect Dis 2012;73:1–8.
- [6] Snyder SR, Favoretto AM, Baetz RA, Derzon JH, Madison BM, Mass D, et al. Effectiveness of practices to reduce blood culture contamination: a laboratory medicine best practices systematic review and meta-analysis. Clin Biochem 2012;45:999–1011.
- [7] Garcia RA, Spitzer ED, Beaudry J, Beck C, Diblasi R, Gilleen-Blabac M, et al. Multidisciplinary team review of best practices for collection and handling of blood cultures to determine effective interventions for increasing the yield of true-positive bacteremias, reducing contamination, and eliminating false-positive central line-associated bloodstream infections. Am J Infect Control 2015;43:1222–37.
- [8] Lamy B, Dargère S, Arendrup MC, Parienti JJ, Tattévin P. How to optimize the use of blood cultures for the diagnosis of bloodstream infections? A state-of-the-art. Front Microbiol 2016;7:697.
- [9] Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med 2017;45:623–9.
- [10] Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376:2235–44.
- [11] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.
- [12] Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749–55.
- [13] Bouza E, Sousa D, Rodriguez-Creixems M, Lechuz JG, Munoz P. Is the volume of blood cultured still a significant factor in the diagnosis of bloodstream infections? J Clin Microbiol 2007;45:2765–9.
- [14] Meessen NEL, Jacobs JA. Blood volume in BACTECPLUS/F culture bottles sampled using the direct-draw technique. Clin Microbiol Infect 1998;4:471–2.
- [15] Alfa M, Sanche S, Roman S, Fiola Y, Lenton P, Harding G. Continuous quality improvement for introduction of automated blood culture instrument. J Clin Microbiol 1995;33:1185–91.
- [16] Reimer LG, Wilson ML, Weinstein MP. Update on detection of bacteremia and fungemia. Clin Microbiol Rev 1997;10:444–65.
- [17] Chapin K, Lauderdale TL. Comparison of Bactec 9240 and Difco ESP blood culture systems for detection of organisms from vials whose entry was delayed. J Clin Microbiol 1996;34:543–9.
- [18] Sautter RL, Bills AR, Lang DL, Ruschell G, Heiter BJ, Bourbeau PP. Effects of delayed-entry conditions on the recovery of microorganisms from BacT/ALERT and BACTEC blood culture bottles. J Clin Microbiol 2006;44:1245–9.
- [19] Seegmüller I, Eschenbach U, Kamereck K, Miethke T. Sensitivity of the BacT/ALERT Famedium for detection of *Pseudomonas aeruginosa* in pre-incubated blood cultures and its temperature-dependence. J Med Microbiol 2004;53:869–74.
- [20] Venturelli C, Righi E, Borsari L, Aggazzotti G, Busani S, Mussini C, et al. Impact of pre-analytical time on the recovery of pathogens from blood cultures: results from a large retrospective survey. PLoS One 2017;12:e0169466.
- [21] SHGTA06. Guide technique d'accréditation: contrôle de qualité en biologie médicale. Available at: <http://www.cofrac.fr/documentation/SH-GTA-06>.
- [22] CLSI/NCCLS quality control for commercially prepared microbiological culture media M22. 3rd ed. Wayne, PA: Clinical and Laboratory Standard Institutes Ed; 2004.
- [23] Novis DA, Dale JC, Schiffman RB, Ruby SG, Walsh MK. Solitary blood cultures: a College of American Pathologists Q-probes study of 132,778 blood culture sets in 333 small hospitals. Arch Pathol Lab Med 2001;125:1290–4.
- [24] Vitrat-Hinckey V, Francois P, Labarere J, Recule C, Stahl JP, Pavese P. Appropriateness of blood culture testing parameters in routine practice. Results from a cross-sectional study. Eur J Clin Microbiol Infect Dis 2011;30:533–9.

- [25] Kim B, Choi J, Kim K, Jang S, Shin TG, Kim WY, et al. Bacteremia prediction model for community-acquired pneumonia: external validation in a multicenter retrospective cohort. *Acad Emerg Med* 2017;24:1226–34.
- [26] Chang J, Park JS, Park S, Choi B, Yoon NS, Sung H, et al. Impact of monitoring blood volume in the BD BACTECTM FX blood culture system: virtual volume versus actual volume. *Diagn Microbiol Infect Dis* 2015;81:89–93.
- [27] Dargère S, Cormier H, Verdon R. Contaminants in blood cultures: importance, implications, interpretation and prevention. *Clin Microbiol Infect* 2018;24:964–9.
- [28] Patton RG. Blood culture contamination definitions can obscure the extent of blood culture contamination: a new standard for satisfactory institution performance is needed. *Infect Control Hosp Epidemiol* 2016;37:736–8.
- [29] Lamy B, Roy P, Carret G, Flandrois JP, Delignette-Muller ML. What is the relevance of obtaining multiple blood samples for culture? A comprehensive model to optimize the strategy for diagnosing bacteremia. *Clin Infect Dis* 2002;35:842–50.
- [30] Alahmadi YM, McElnay JC, Kearney MP, Aldeyab MA, Magee FA, Hanley J, et al. Tackling the problem of blood culture contamination in the intensive care unit using an educational intervention. *Epidemiol Infect* 2015;143:1964–71.
- [31] Self WH, Mickanin J, Grijalva CG, Grant FH, Henderson MC, Corley G, et al. Reducing blood culture contamination in community hospital emergency departments: a multicenter evaluation of a quality improvement intervention. *Acad Emerg Med* 2014;21:274–82.
- [32] Park WB, Myung SJ, Oh MD, Lee J, Kim NJ, Kim EC, et al. Educational intervention as an effective step for reducing blood culture contamination: a prospective cohort study. *J Hosp Infect* 2015;91:111–6.
- [33] Denno J, Gannon M. Practical steps to lower blood culture contamination rates in the emergency department. *J Emerg Nurs* 2013;39:459–64.
- [34] Patton RG, Schmitt T. Innovation for reducing blood culture contamination: initial specimen diversion technique. *J Clin Microbiol* 2010;48:4501–3.
- [35] Binkhamis K, Forward K. Effect of the initial specimen diversion technique on blood culture contamination rates. *J Clin Microbiol* 2014;52:980–1.
- [36] Rupp ME, Cavalieri RJ, Marolf C, Lyden E. Reduction in blood culture contamination through use of initial specimen diversion device. *Clin Infect Dis* 2017;65:201–5.
- [37] van Ingen J, Hilt N, Bosboom R. Education of phlebotomy teams improves blood volume in blood culture bottles. *J Clin Microbiol* 2013;51:1020–1.
- [38] Dargère S, Parienti JJ, Roupie E, Gancel PE, Wiel E, Smaiti N, et al. Unique blood culture for diagnosis of bloodstream infections in emergency departments: a prospective multicentre study. *Clin Microbiol Infect* 2014;20:O920–7.
- [39] Saito T, Iinuma Y, Takakura S, Nagao M, Matsushima A, Shirano S, et al. Delayed insertion of blood culture bottles into automated continuously monitoring blood culture systems increases the time from blood sample collection to the detection of microorganisms in bacteremic patients. *J Infect Chemother* 2009;15:49–53.
- [40] Morton B, Nagaraja S, Collins A, Pennington SH, Blakey JD. A retrospective evaluation of critical care blood culture yield—do support services contribute to the “weekend effect”? *PLoS One* 2015;10:e0141361.
- [41] Ronnberg C, Mildh M, Ullberg M, Ozenci V. Transport time for blood culture bottles: underlying factors and its consequences. *Diagn Microbiol Infect Dis* 2013;76:286–90.
- [42] Kerremans JJ, van der Bij AK, Goessens W, Verbrugh HA, Vos MC. Immediate incubation of blood cultures outside routine laboratory hours of operation accelerates antibiotic switching. *J Clin Microbiol* 2009;47:3520–3.
- [43] Isenberg HD. Aerobic bacteriology, blood cultures, general detection and interpretation. In: York MK, Henry M, Gilligan P, editors. *Clinical microbiology procedures handbook*. Washington, D.C.: American Society of Microbiology Press; 2010. Section 3.4.1.
- [44] Salazar E, Divatia M, Cernoch PL, Olsen RJ, Long SW, Land GA, et al. Improving positive blood culture removal time significantly decreases total processing time. *Arch Pathol Lab Med* 2015;139:199–203.
- [45] Banerjee R, Ozenci V, Patel R. Individualized approaches are needed for optimized blood cultures. *Clin Infect Dis* 2016;63:1332–9.
- [46] Schiffman RB, Strand CL, Braun E, Louis-Charles A, Spark RP, Fried ML. Solitary blood cultures as a quality assurance indicator. *Qual Assur Util Rev* 1991;6:132–7.
- [47] Schiffman RB, Bachner P, Howanitz PJ. Blood culture quality improvement: a College of American Pathologists Q-Probes study involving 909 institutions and 289 572 blood culture sets. *Arch Pathol Lab Med* 1996;120:999–1002.
- [48] Schiffman RB, Strand CL, Meier FA, Howanitz PJ. Blood culture contamination: a College of American Pathologists Q-Probes study involving 640 institutions and 497 134 specimens from adult patients. *Arch Pathol Lab Med* 1998;122:216–21.
- [49] Augustin JC, Carlier V. Lessons from the organization of a proficiency testing program in food microbiology by interlaboratory comparison: analytical methods in use, impact of methods on bacterial counts and measurement uncertainty of bacterial counts. *Food Microbiol* 2006;23:1–38.
- [50] Kellogg JA, Manzella JP, Bankert DA. Frequency of low-level bacteremia in children from birth to fifteen years of age. *J Clin Microbiol* 2000;38:2181–5.