Affordable blood culture systems from China: *in vitro* evaluation for use in resource-limited settings

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Summary

Background Bloodstream infections (BSI) pose a significant threat due to high mortality rates and the challenges posed by antimicrobial resistance (AMR). In 2019, an estimated 4.95 million deaths were linked to bacterial AMR. The highest impact was seen in resource-limited settings (RLS). For diagnosis of BSI, performant continuously-monitoring blood culture systems (CMBCS) have been optimized. However, in RLS, the implementation of CMBCS is hindered by budget constraints and unsuitable environmental conditions. Manufacturers from growing economies are currently producing affordable *in vitro* diagnostics, which could fill the gap in capacity, but so far these are not established outside their domestic markets.

Methods This study evaluated the performance, usability, and interchangeability of Chinese CMBCS in a laboratory setting using simulated blood cultures with a panel of 20 BSI-associated strains. Four systems were selected for the assessment: Autobio BC60, Mindray TDR60, Scenker Labstar50, and DL-biotech DL-60.

Findings Overall, all evaluated CMBCS demonstrated good performance with high yield (96.7–100%) and specificity (97.5–100%), comparable to the reference system (bioMérieux 3D). In addition, when used as "manual" blood cultures in a conventional incubator with visual growth detection, performance was also satisfactory: yield was between 90 and 100% and specificity was 100% for all BCBs. Both the CMBCS and the BCBs were easy to use and lot-to-lot variability in BCBs was minimal. The interchangeability testing indicated that the BCBs from different brands (all except Scenker) were compatible with the various automates, further highlighting the potential for a harmonized "universal BCB."

Interpretation Based on this *in vitro* study, we recommend the use of these systems in settings with challenging environments and limited resources. The Autobio system performed best for automatic detection and DL-Biotech BCBs for manual cultures respectively (combination of performance, price, usability). The appropriateness for use in RLS should still be confirmed in a field study.

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Keywords: Blood cultures; Continuously-monitoring blood culture systems; Evaluation study; Resource-limited settings

Introduction

Bloodstream infections (BSI) are associated with high mortality and their treatment is compromised by antimicrobial resistance (AMR). A recent estimate based on mathematical models calculated that 4.95 million deaths worldwide were associated with bacterial AMR in 2019, 1.27 million of which were directly attributable to AMR. Resource-limited setting (RLS), which include low-income countries as well as remote, rural, and underserved areas in middle-income countries, are hit hardest, especially western sub-Saharan Africa.[1]

BSI diagnosis relies on blood cultures: culturing large volumes of patient blood to grow the causative microorganism, that is afterwards identified and tested

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Research in context

Evidence before this study

Chinese manufacturers of *in vitro* diagnostics have only recently started developing continuously monitoring blood culture systems and are not yet established outside their home country. So far, no evaluation studies were published in international peer-reviewed journals. We have searched PubMed using the terms "China", "automated blood culture systems" and neither of two retrieved studies evaluated Chinese blood culture systems to the currently marketed automated systems in high-resource settings. The search did not extend to local, Chinese, literature.

Added value of this study

Performant continuously-monitoring blood culture systems (CMBCS) have been optimized for diagnosis of bloodstream infection and are widely used in high-income countries. In resource-limited settings however, the implementation of CMBCS is hindered by budget constraints and unsuitable environmental conditions. Manufacturers from growing economies are currently producing affordable *in vitro* diagnostics, which could fill the gap in capacity, but so far these are not established outside their domestic markets and no evidence has been published about the performance of these system. Therefore, this data is not publicly available yet. The present independent *in vitro* study provides evidence on the performance and ease-of-use of these systems in an ideal laboratory setting. Based on this study, we recommend implementing these systems in settings with challenging environments and limited resources. In addition, the interchangeability testing indicated that the blood culture bottles from different brands (all except Scenker) were compatible with the various automates, further highlighting the potential for a harmonized "universal BCB."

Implications of all the available evidence

The study emphasizes the importance of selecting cost-effective and useable blood culture systems for resource-limited settings. The evaluated Chinese systems show promise in improving BSI diagnosis and management in resource-limited settings, contributing to efforts to combat antimicrobial resistance and enhance patient care. However, challenges related to pricing, accessibility, and environmental adaptability still need to be addressed in real-life for successful implementation.

for susceptibility to antimicrobials. This information is instrumental to treat the patient correctly and to ensure that the initial empiric antimicrobial treatment covers the infection cause. Besides their clear clinical relevance, blood cultures also play a fundamental role in AMR surveillance and antimicrobial stewardship, both essential components of the World Health Organization action plan to contain AMR.[2,3]

Blood culture diagnostic sensitivity is low due to the low bacterial concentration in the blood.[4,5] Nevertheless, highly performing continuously-monitoring blood culture systems (CMBCS) are widely used in high-income countries. These CMBCS have a dual working mechanism. Firstly, they provide the ideal conditions (constant temperature while agitating) for microorganisms to grow in the blood culture bottle (BCB) broth. Secondly, they continuously evaluate growth based on a change in the colorimetric or fluorescent CO_2-sensor in the BCB.

In RLS, budgetary, logistic, and infrastructure barriers hamper wide scale CMBCS implementation. Here, "manual" blood cultures are more frequently used. BCBs with sampled blood are incubated in a conventional incubator at 35–37 °C and regularly taken out of the incubator for visual inspection of growth signs, *e.g.,* turbidity, gas production, or bacterial deposit.[4,6] Although this is a valid method for low-throughput laboratories, it is time consuming and becomes less time efficient in proportion to an increasing number of samples. In addition, it is a very subjective technique that requires good training and user expertise to be implemented correctly.

Drawbacks of CMBCS include cost and robustness, as they are not adapted to hot, dusty and/or humid conditions typical of RLS, and they require regular preventative maintenance which may not be available in more remote locations. Both aspects make these systems rarely used in RLS, outside of research centres or central hospitals.[4] Notwithstanding, the global market for blood cultures is growing,[7] both in low- and middle-income countries (LMIC) and high-income countries. It was estimated that the global blood culture test market generated $3900 million in 2019, and is projected to double by 2027, growing at a compound annual growth rate of 9.3% from 2020 to 2027.[8] Some of the key players here will be manufacturers from growing economies that are producing affordable *in vitro* diagnostics but so far are not established outside their domestic markets. Usability, performance, and acceptability of devices produced by these relatively unknown manufacturers will be important for implementation. Great efforts have been made to increase access to blood culture systems in LMICs in the past few years, but resources and capacity are still lacking.[9]

When using either CMBCS or manual blood cultures, in our opinion, preference should be given to quality-assured commercially available products over BCBs made in-house (in a non-controlled environment).[4] However, access to these is often a problem in LMICs: diagnostics products are frequently more expensive when purchased in an LMIC and availability is limited overall.[10–12] BCBs (or other laboratory consumables) being out-of-stock is not uncommon. A

generic CMBCS that is not BCB-specific and thus could be used with different brands of BCBs ("interchangeability") would be an asset for these settings, offering a solution in case of low supply. Therefore, harmonization of CMBCS and BCBs is of immense value and should be part of the target product profile (TPP) for blood cultures.

In this diagnostic comparative study, we screened the Chinese blood culture market for CMBCS for potential use in RLS. We selected four CMBCS and their accompanying paediatric BCBs and evaluated their performance (yield and time-to-positivity) using simulated blood cultures in a laboratory reference setting. In addition, we evaluated their usability and the interchangeability of CMBCS and BCBs of the different brands.

Methods

Selection of CMBCS

The first manufacturer/CMBCS selection was done by a web search using Google search, in English, entering the keywords "blood culture" OR "blood culture system*", AND "automated" AND "China", OR "Chin*" AND "manufacturer". After establishing contact, relevant information was collected using a questionnaire based on a previously published TPP.[13] Minimal and optimal criteria were defined and each criterium was scored (3 = satisfies optimal criteria with strong evidence, 0 = no evidence to support claim). The criteria were defined as: distribution and maintenance capacity in sub-Saharan Africa, operating conditions, reliability of technology, manufacturing expertise and capacity, quality systems and regulatory strength. The final selected CMBCS were procured, shipped, and installed at the Institute of Tropical Medicine (ITM) laboratory. With future use in district hospital laboratories in mind, we purchased the CMBCS with a capacity of 50–60 BCBs. We evaluated paediatric BCBs only, because of practical reasons (lower amount of blood needed) and because paediatric BSI are common in RLS. Furthermore, the composition of paediatric and adult BCBs is comparable,[14] so results are generalisable.

Performance testing

Testing was done at ITM between July and December 2022 using simulated blood cultures consisting of defibrinated horse blood spiked with selected strains (bacteria and yeast, see Table 1). Performance of the CMBCS under evaluation was compared with a reference system, the BacT/ALERT 3D CMBCS (bioMérieux, Marcy-l'Étoile, France). Testing was always done in triplicate, using three different lots of BCBs, with inclusion of blank samples.

Frozen reference strains were prepared and spiked into horse blood ("the inoculum"), as described before.[6] All BCBs were inoculated using 2 ml of the same inoculum and incubated in the CMBCS under evaluation (Fig. 1). Three BCBs of one lot only for each brand were incubated in a conventional incubator as "manual blood cultures" for twice-daily visual inspection for growth signs.[6,15] In addition, the colour change of the chromogenic indicator at the bottom of the BCB was evaluated. Three reference BCBs of one lot (BacT/ALERT PF Plus, bioMérieux), inoculated with 2 ml of the same inoculum, were incubated in the reference CMBCS (bioMérieux). As a negative control, one blank (horse blood only) was added for each lot and each brand (1 BCB/strain/brand/lot) in both the CMBCS and the conventional incubator.

Time-to-positivity (TTP) was either given by the CMBCS or corresponded to the first time of the twice-daily visual inspection when at least one growth sign was observed. If growth signs were detected after 5 (CMBCS) or 7 (manual system) days, or if growth was detected in blank samples, the findings were confirmed by subculturing a drop of the blood culture broth overnight on Columbia agar plates with sheep blood (Becton Dickinson and Company (BD), Franklin Lakes, NJ, USA) at 35–37 °C, with or without CO_2 (depending on the species spiked). *In vitro* performance was evaluated in terms of microbial yield ("yield"), TTP and lot-to-lot variability.

	Species	Reference	CFU in inoculum (2 ml of blood)
Enterobacterales	*Escherichia coli*	ATCC[a] 25922	4.4
	Salmonella Typhimurium	ATCC 14028	18.0
	Salmonella Typhi	21602/3[b]	4.2
	Klebsiella pneumoniae	ATCC 700603	6.4
	Enterobacter cloacae	ATCC 13047	17.1
Staphylococcus/Enterococcus	*Staphylococcus aureus*	ATCC 25923	13.6
	Staphylococcus epidermidis	ATCC 14990	6.7
	Enterococcus faecalis	ATCC 29212	11.8
Streptococcus	*Streptococcus pneumoniae*	ATCC 49619	13.3
	Streptococcus anginosus	ATCC 33397	38.9
	Streptococcus pyogenes	ATCC 19615	10.7
	Streptococcus suis	ATCC 43765	21.8
Non-fermenting Gram-negatives	*Pseudomonas aeruginosa*	ATCC 27853	23.3
	Burkholderia cepacia	ATCC 25416	15.8
	Acinetobacter baumannii	ATCC 19606	41.3
Fastidious	*Haemophilus influenzae*	ATCC 49247	4.7
	Neisseria subflava	ATCC 49275	25.8
Yeasts	*Candida albicans*	ATCC 66027	7.1
	Cryptococcus neoformans	ATCC 14116	22.0
	Candida tropicalis	ATCC 750	15.3

All blood culture bottles within one run were filled using the same inoculum and are thus considered to contain a similar concentration of microorganisms. [a]ATCC = American Type Culture Collection. [b]Clinical isolate.

Table 1: **Study set-up information per run: details on the evaluation panel, with information on the calculated number of CFU that were added to the 2 ml of horse blood in the blood culture bottle (aiming at 1–50 CFU per ml).**

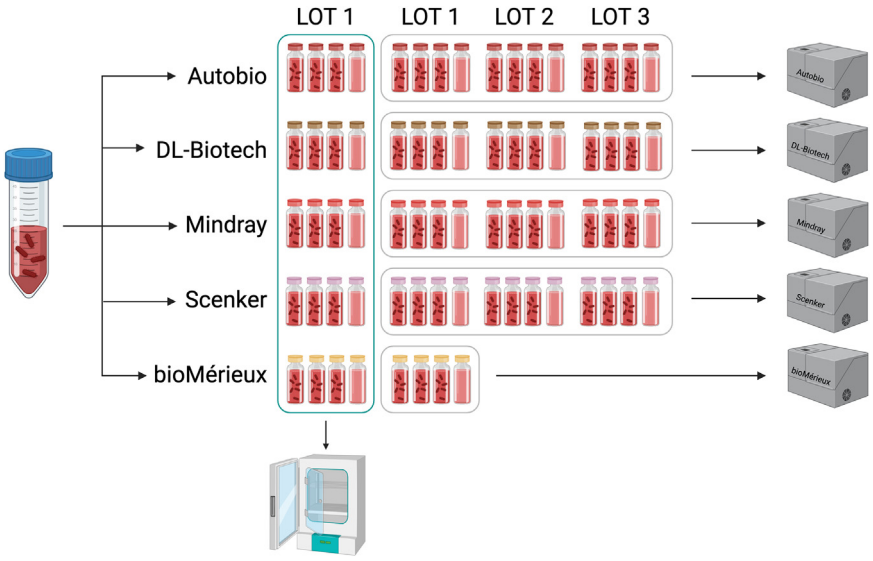

Fig. 1: Set-up of 1 run: 2 ml of spiked horse blood was added to 3 BCBs of 3 lots of each manufacturer under evaluation. In addition, 1 blank (non-spiked blood) BCB was for each lot/manufacturer. 9 spiked replicates (3 replicates of 3 lots) and 3 blanks were incubated in their associated automate for continuous growth monitoring (in purple). 3 spiked replicates of lot 1 of each manufacturer and 1 blank were incubated in a conventional incubator for twice-daily visual evaluation (in turquoise). For the reference (bioMérieux) 1 lot was used. Figure created with Biorender.com.

Interchangeability of blood culture systems and blood culture bottles

BCBs from all brands were incubated in CMBCS from all brands to evaluate the interchangeability of bottles and automates. Interchangeability was assessed by evaluating the physical fit of the BCBs in the CMBCS, recognition of the barcodes and correctness of the TTP given by the automate. For each brand, 3 replicate BCBs inoculated with *Escherichia coli* spiked in horse blood were incubated in all "fitting" CMBCS. In addition, 3 blank BCBs from all brands were incubated in all fitting CMBCS as negative control.

Usability testing

We used a predefined questionnaire[6] to assess the ease of use of all BCBs and CMBCS. The questionnaire was completed by all laboratory staff involved in the performance study.

Statistics

To determine the yield, the percentage of bottles with detected growth was calculated per brand. Spiked BCBs with failed growth detection were considered false negatives (FN). In addition, the percentage of blank bottles with detected growth (false positives (FP)) was calculated per brand. For the analysis of TTP, the spiked BCBs with failed growth detection (FN) were imputed as 120 h (the maximum detection time). For the comparison of TTP between the different brands, a linear mixed model was fitted with log transformed TTP as the outcome in function of brand and strain with a random intercept for lot. Lot was nested within the brand, as every brand has its own BCBs, and the random effect was coded accordingly. Strain was included in the model as a fixed effect as the normality assumption was violated for certain strains, but estimates were not considered for interpretation. To obtain estimates for lot-to-lot variability, separate linear mixed models with log-transformed TTP as the outcome were fitted per brand with strain as fixed effect and a random intercept for lot. A linear model was fitted for the reference BCB in function of strain as only one lot was used. All analyses, except lot-to-lot variability, were repeated for the manual set-up, whereby only linear models were used instead of linear mixed models as only one lot was used. For the interchangeability and usability study, only descriptive results are given. All analyses were conducted in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Role of funders

The Funders participated in the study design and writing of the manuscript, but had no role in data collection, data analyses and interpretation of the data.

Results

Selection of manufacturers

Four CMCBS with the lowest BCB capacity were selected based on the predefined set of criteria outlined in the methods section: the Autobio BC60, Mindray TDR60, Scenker Labstar50, and DL-biotech DL-60 CMCBS (priced between $5000 and $12,000) and associated paediatric BCBs (priced between $1.5 and $3.5 per bottle). More details can be found in Table 2.

Brand	Autobio BC60	Mindray TDR60	Scenker Labstar50	DL-Biotech DL-60
Automate				
Capacity	60 bottles	60 bottles	50 bottles	60 bottles
Dimensions (W x D x H) + weight	49 x 41 × 39 cm 53 kg	60 x 52,5 x 75,5 cm 106 kg	67 x 64 × 68 cm 98 kg	54 x 37,6 x 36,1 cm 23,5 kg
Power consumption	300 VA	500 VA	450 VA	460 VA
Agitation	Continuous rocking	Continuous rocking	Continuous rotating	Continuous rocking
Detection	CO_2 Sensor + colorimetry	CO_2 Sensor + colorimetry	CO_2 Sensor + colorimetry	CO_2 Sensor + colorimetry
Normal operating conditions	10–30 °C; ≤85% humidity; 85 kPA—106 KPa atmospheric pressure	1–30 °C; 10–90% humidity; 76 KPa—106 KPa atmospheric pressure	10–30 °C; ≤85% humidity; 86 KPa—106 KPa atmospheric pressure	10–30 °C; ≤80% humidity; 76 KPa—106 KPa atmospheric pressure
Price	$5000	$12,000	$5200	$9500
Blood culture bottles				
Storage	2–25 °C	2–30 °C, avoid light	4–30 °C dry, avoid light	Room temperature (<30 °C)
Shelf-life	12 months	12 months	12 months	12 months
Sample volume	1–5 ml	1–3 ml	2–10 ml	1–3 ml
Broth composition	Tryptone 1% w/v; Gelatin Peptone 1% w/v; Yeast Extract 0.45% w/v; Glucose 0.3% w/v; Sodium Polyanethol Sulfonate 0.025% w/v; Resin 0.5% w/v; and other amino acids as components	Tryptone; Beef extract powder; Yeast extract; Glucose; Growth factor; Heart infusion; Anticoagulants; Adsorption resin	Pure water 25 ml; Peptone 2.22%; Yeast powder 0.22%; Brain heart infusion 0.34%; Glucose 0.05%; Sucrose 0.08%; Sodium polyanethol sulfonate (SPS) 0.03%; 1.6 g Macroporous adsorbent resin	Columbia broth powder 35 g; peptone 10 g; potassium dihydrogen phosphate 1.5 g; glucose 5 g; mannitol 2 g; sodium citrate 3 g; resin 4 g
Broth volume	20 ml	25 ml	25 ml	25 ml
Price/bottle	$1.9	$3.5	$1.5	$1.8

Table 2: **Details of selected blood culture systems for evaluation study.**

CMBCS

For each CMBCS under evaluation, a total of 180 spiked samples (3 replicates of 3 different BCB lots, spiked with 20 different species) and 80 blank samples was tested. The yield of the CMBCS was 96.7% (170/180) for Autobio, 98.3% (177/180) for Mindray, and 100% (180/180) for DL-biotech, Scenker, and the reference system. *C. neoformans* was false negative in 6 replicates of the Autobio system, and *S. suis* was false negative in 3 replicates of the Mindray system (with growth/no growth of subculture, specified in Table 3). The specificity of all systems was 100% (80/80), except for Autobio which was the only CMBCS with false positive results and a specificity of 97.5% (78/80).

The results obtained from the linear mixed model comparing TTP between the different brands can be interpreted as the mean difference in log time-to-positivity between that particular brand and the reference automate (BacT/ALERT). Autobio was associated with a significantly shorter log TTP (–0.08, 95% CI –0.13 to 0.03; p = 0.001 (linear mixed model)) and Mindray (+0.08, 95% CI 0.03–0.13; p = 0.003 (linear mixed model)) was associated with a significantly longer log TTP than the reference.

Manual system

To test the "manual" BCBs, we included a total of 60 spiked samples and 20 blank samples. When used as "manual" BCB, yield was 100% (60/60) for DL-Biotech and Mindray, equal to the reference. Autobio and Scenker had a lower yield of 95% (57/60) and 90% (54/60) respectively, with confirmed growth on subculture, for *C. neoformans* and *A. baumannii* (Scenker only) (Table 4). Specificity of all brands was 100% (20/20).

The estimates obtained from the linear model can be interpreted as the mean difference in log TTP between that particular brand and the reference CMBCS (bioMérieux). DL-Biotech was associated with a significantly shorter TTP than the reference (–0.13, 95% CI –0.24 to 0.01; p = 0.029 (linear mixed model)).

Changes in the colour indicator and turbidity were the first signs of growth most frequently reported. For all brands under evaluation, the indicator colour change was much more visually distinguishable compared to the reference (especially for non-Enterobacterales, but more difficult to evaluate for the fastidious organisms and yeasts) (Fig. 2).

Lot-to-lot variability blood culture bottles CMBCS

Lot-to-lot variability for TTP across all blood culture bottles was very small, and within-lot variability was larger (Table 5). Similar results per brand were obtained, Mindray has the largest lot-to-lot and within-lot variability.

Interchangeability of blood culture systems and blood culture bottles

Testing was done with all CMBCS and BCBs, except for Scenker, due to the slightly different physical format of their BCBs. Scanning BCB barcodes of other brands was

	Growth (n/N)	Yield (%)	Organism causing (false) negative results	Lot, Replicate of (false) negative results	Specificity	Linear mixed model with log TTP as the dependent variable (random intercept for lot)		
						Estimates	CI	p
bioMérieux (reference)	60/60	100%			100%			
Autobio	174/180	96.7%	*C. neoformans*[6]	Lot 1: 1/3 replicates[a] Lot 2: 2/3 replicates[b] Lot 3: 3/3 replicates[c]	97.5%	−0.08	−0.13 to −0.03	0.001
DL-Biotech	180/180	100%			100%	0.01	−0.04 to 0.07	0.581
Mindray	177/180	98.3%	*S. suis*[3]	Lot 3: 3/3 replicates[d]	100%	0.08	0.03 to 0.13	0.003
Scenker	180/180	100%			100%	−0.04	−0.09 to 0.01	0.153

Table 3 does not display the intercept, nor the fixed effects for the strains as they are not of interest here. [a]Growth of subculture. [b]One with growth of subculture, one with no growth of subculture. [c]One with growth of subculture, two with no growth of subculture. [d]Three with no growth of subculture.

Table 3: **Yield and TTP analysis for CMBCS.**

not always possible. In the Mindray system, there was no barcode detection when other brands were scanned, which resulted in the BCB being recorded as 'unknown.' Because of this "mismatch", no digital information about the BCB was saved, but information on the TTP was available while the BCB was still in the automate. In the DL-Biotech system, barcode scanning was not possible; the barcode had to be entered manually in the 'extra code' window.

Overall, all BCBs were "accepted" by the systems and TTP of the different BCBs was comparable within each automate (Table 6). The only failed BCBs were the Autobio BCBs in the Mindray system; no TTP was detected (TTP 120 h = no detection), no barcode or ID was registered, and the status was recorded as 'anon.' After 5 days (120 h), the BCBs were removed from the automate and were visually evaluated as positive, based on the clear colour change of the indicator. The negative controls were consistently negative.

Usability testing of blood culture systems and blood culture bottles

The questionnaire was completed by four end users (Supplemental Table S4). All CMBCS and BCBs scored high for usability, except for the Scenker CMBCS (difficult and non-intuitive in use) and Mindray BCBs (lack of vacuum in bottles). For manual use, the colour change of the chromogenic growth indicator was easy to evaluate, as was the broth turbidity for all BCBs.

Discussion

We evaluated the performance and ease-of-use of four selected Chinese CMBCS in an *in vitro* reference setting with simulated blood cultures. Our study demonstrates that, in general, all CMBCS under evaluation performed well. This study was done with future implementation in RLS in mind. This results in the following considerations for this next phase.

When selecting a CMBCS for RLS, the price of equipment and consumables is an important factor to consider. Pricing of the CMBCS ranged from $5000 (Autobio) to $12,000 (Mindray) which is still substantially more economical compared to the established brands and below the maximum in the published TPP.[13] The same was true for the BCBs, that ranged from $1.5 (Scenker) to $3.5 (Mindray). Of note, we have received these price offers directly from the company, as a European customer, and are not aware of the prices for distribution in LMIC which regrettably tend to be much higher.[16]

	Growth (n/N)	Yield (%)	Organism causing (false) negative results	Replicates causing (false) negative results	Specificity	Linear model with log TTP as the dependent variable		
						Estimates	CI	p
bioMérieux (reference)	60/60	100%			100%			
Autobio	57/60	95.0%	*C. neoformans*[3]	3/3[a]	100%	−0.03	−0.14 to 0.08	0.601
DL-Biotech	60/60	100%			100%	−0.13	−0.24 to −0.01	0.029
Mindray	60/60	100%			100%	0.02	−0.09 to 0.13	0.737
Scenker	54/60	90.0%	*A. baumannii*[3] *C. neoformans*[3]	3/3[b] 3/3[a]	100%	0.11	−0.00 to 0.22	0.059

Table 4 does not display the intercept, nor the fixed effects for the strains as they are not of interest here. Results should be interpreted with caution as the log TTP was not normally distributed nor continuous due to the inspection method used. However, we assumed the same data generation method as for the automatic detection. [a]Growth of subcultures. [b]No growth of subcultures.

Table 4: **Yield and TTP analysis for manual blood cultures.**

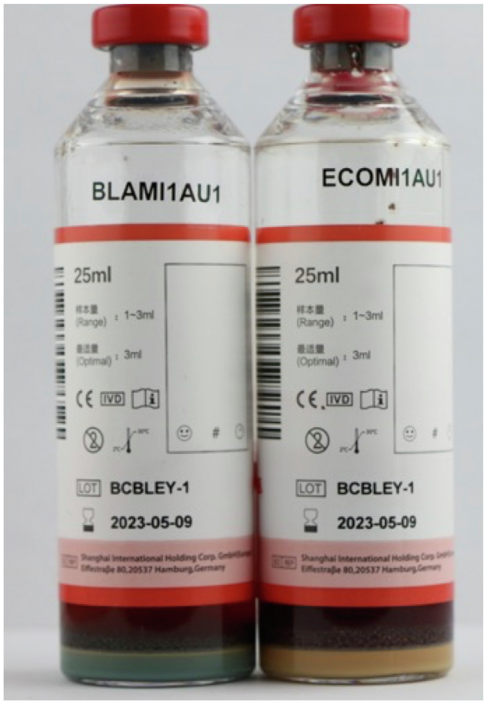

Fig. 2: Illustration of difference in colour indicator of not grown (left: purple) and grown (right: yellow) blood culture bottle.

When looking at performance of the four selected CMBCS, the Autobio system had the shortest log TTP, also compared to the reference system, although yield and specificity were less than 100% (3 false negatives and 3 true negatives of *C. neoformans*). The Mindray system had a longer log TTP and non-perfect yield, due to one lot of BCBs failing for one species (no growth of *S. suis* in 1/3 lots). The Scenker and DL-Biotech automatic systems both had a yield and specificity of 100%. For these two systems, there was not enough evidence to claim that the log TTP differed significantly from the reference. The reference CMBCS used in this study was the bioMérieux system. The differences in TTP with another established player, BD, have been studied before[17–20] and were consistently small (*i.e.* up to a few hours difference). It is important to note that TTP may not have a major impact on the "actionable result" ((change in) treatment of the patient) if there is no 24-h service in the laboratory, which is often the case in RLS and even more in smaller health centres and laboratories.[3,13]

	Between lot variability (standard deviation)	Within lot variability (standard deviation) i.e. residual error
Overall	0.000	0.175
Reference	Not done	0.023
Autobio	0.007	0.036
DL-Biotech	0.005	0.054
Mindray	0.036	0.153
Scenker	0.003	0.023

Table 5: **Lot-to-lot and within-lot variability of all CMBCS under evaluation (estimates are on the log scale).**

Blood culture bottles	CMBCS			
	bioMérieux	Autobio	Mindray	DL-Biotech
bioMérieux	12:24	10:33	12:10	12:19
Autobio	12:58	10:52	120:00	13:00
Mindray	14:10	11:43	13:00	12:51
DL-Biotech	12:58	10:07	11:28	12:15

Table 6: **Average TTP (hh:mm) of triplicate measurements of interchangeability study.**

In this study, we tested 3 different consumable (BCB) lots. We reported very small lot-to-lot variability in the TTP, which is an indicator of the manufacturing quality of the consumable including the raw materials. In addition, availability of the equipment and, even more important, accessibility of these consumables is crucial. During market scouting, brands were selected that had already established an African office or distributor. To anticipate possible future stock ruptures, we tested whether different brands of BCBs could be used with the CMBCS under evaluation. Low stock volumes and difficulties in getting consumables delivered on time is often a problem in RLS. Therefore, it would be very convenient if, during stock-outs, another brand could be used to ensure patient care. Our pilot data, done with a limited number of spiked and blank samples, demonstrate that—at least for Autobio, DL-Biotech, Mindray, and the reference (bioMérieux)—all BCBs gave a comparable TTP in all four systems (except for Autobio in Mindray, which did not register a TTP). This positive result was unexpected since the chromogenic indicators of the BCBs under evaluation have different baseline colours (grey to purple) compared to the reference (brown). This finding gives some insight into the working mechanism of the automate, which probably measures a baseline colour and evaluates colour change for growth detection (and not the specific colour by itself). In addition, it reinforces the idea of stimulating manufacturers to develop a harmonised "universal BCB" that can be used with multiple CMBCS, by adding it to the TPP.

To implement blood cultures in RLS, a good, intuitive, user-friendly system with approachable regional technical support is necessary. In this regard, all systems, except for the Scenker system, scored highly on usability, which was comparable or even better than the reference system. Autobio and DL-Biotech have an intuitive CMBCS that is simple to operate, while Mindray has a slightly more complicated but seemingly more robust system. We tested the smallest CMBCS, for

60 BCBs. All were modular, with a possibility to add extra incubation units to the same main system if blood culture demand increases. The Scenker system had incubation space for only 50 BCBs, was not modular, was very big and heavy, and had a less attractive design that was the most complicated to use. Scenker did have a newer model for 60 BCBs available at the time of contact but was not willing to provide this model for our evaluation study.

Another important factor to consider is the quality of the consumable. A proper BCB vacuum is instrumental in direct sampling, which is the recommended practice and decreases the risk of contamination.[4] All brands performed well in this regard, except for Mindray. In RLS, commercially available blood culture bottles, such as the BacT/ALERT blood culture bottles, normally used in combination with a CMBCS, are occasionally used as "manual cultures"[4] and visual inspection of the BCB may be a contingency practice in case of equipment failure. BCBs are incubated in a conventional incubator and evaluated for visual signs of growth twice daily. Therefore, it is important that the broth is clearly visible (to check turbidity), and that the label does not obscure the growth signs. Further, the colour indicator is also evaluated visually, thus a distinct colour change improves visual growth detection. The colour indicator—normally monitored by the CMBCS—is very important in this practice since it provides a more "objective" criterion for growth. To this end, we report that off-label manual use of the Chinese BCBs was satisfactory. In terms of TTP, DL-Biotech performed better than the reference, and its yield was 100%. There was no statistically significant difference in TTP between the other brands and the reference, but the yields of Autobio and Scenker were not perfect, 95% and 90% respectively. Changes in colour indicator and turbidity were most frequently the first growth signs reported.

Usability of the BCBs for manual cultures was very high. We have previously experienced that the large labels on BacT/ALERT bottles can impede broth inspection,[21] which may result in missed detections or delays in the detection of microbial growth. In contrast, most of the BCBs under evaluation had smaller labels (Fig. 3), which makes growth evaluation in the broth easier. The colour indicator, if present in the manual BCBs, is crucial for detecting the first signs of growth. When growth occurred, the chromogenic indicator changed from grey/purple to yellow. This change was easier to distinguish than the reference BCBs colour change (that change from brown to yellow) and was especially clear in the Enterobacterales. Nevertheless, the fastidious organisms and yeasts were more challenging to evaluate due to the variability in their growth patterns.

Our study was unique in the evaluation of the performance and usability of four blood culture systems from China for potential use in RLS. Although a large number of spiked samples was tested, there are still some limitations to take into account when interpreting the results. As this was an *in vitro* study in a reference setting, conditions were ideal, with well-trained and experienced laboratory technicians, which differs from real-life settings. Ideally, we would like to have exposed the blood culture systems to high temperature and humidity, and dust, but this was not possible in this project. In addition, we used defibrinated horse blood that, although demonstrated to be comparable to human blood,[6] might still slightly impact the results. We have not tested the antimicrobial neutralizing resins in the BCBs and would expect a different effect on microbial growth in the presence of antimicrobials. In addition, we only tested one reference strain per species, and no clinical strains or clinical samples (in which the bacterial load varies) but tested a large panel of RLS BSI-associated species. In addition, we did not test for possible false-positive causes. However, this *in vitro* study set-up has advantages over a clinical study. It enabled us to include a large sample size and to spike the BCBs with a high variety of relevant predefined

Fig. 3: Illustration of the labels and transparent space on the BCBs under evaluation, front and back, compared to reference (on the left).

microorganisms, which would be very time-consuming and less efficient when done in a clinical setting. In addition, it required less budget and avoided logistic hurdles.[3] To conclude, based on this *in vitro* study, we would recommend the use of these systems in settings with challenging environments and limited resources, after further confirmatory testing in a clinical setting. All 4 systems had satisfactory to good performance and ease-of-use. Assets were the interchangeability of the BCB in all, but Scenker, systems. The Autobio system appears to perform best for automatic detection and DL-Biotech BCBs for manual cultures (combination of performance, price, usability) (individual scores in Supplemental Table S4). These should be further evaluated in a field study for appropriateness for use in RLS.

Contributors

Study conceptualisation: LH, TV, AN, CFE, BG, JJ.
Study design: LH, TV, BG, JJ.
Literature search: LH, AN.
Data collection and analysis: TV, LH, EG.
Data interpretation and presentation: LH, EG.
Figures: LH, TV.
Writing–original draft: LH, EG.
Writing–review and editing: LH, TV, AN, CFE, BG, CFR, PD, JJ.
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All authors have read and approved the final version of the manuscript. TV and LH accessed and verified the data. LH was responsible for the decision to submit the manuscript.

Data sharing statement

The dataset is available from figshare, https://doi.org/10.6084/m9.figshare.24926490.v1.

Declaration of interests

PJD has received consulting fees from FIND. The other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105004.

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