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Underutilization and Quality Gaps in Blood Culture Processing in Public Hospitals of Peru

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Abstract. Correct processing of blood cultures may impact individual patient management, antibiotic stewardship, and scaling up of antimicrobial resistance surveillance. To assess the quality of blood culture processing, we conducted four assessments at 16 public hospitals across different regions of Peru. We assessed the following standardized quality indicators: 1) positivity and contamination rates, 2) compliance with recommended number of bottles/sets and volume of blood sampled, 3) blood culture utilization, and 4) possible barriers for compliance with recommendations. Suboptimal performance was found, with a median contamination rate of 4.2% (range 0–15.1%), with only one third of the participating hospitals meeting the target value of $< 3\%$; and a median positivity rate of 4.9% (range 1–8.1%), with only 6 out of the 15 surveilled hospitals meeting the target of 6–12%. None of the assessed hospitals met both targets. The median frequency of solitary blood cultures was 71.9% and only 8.9% ($N = 59$) of the surveyed adult bottles met the target blood volume of 8 – 12 mL, whereas 90.5% ($N = 602$) were underfilled. A high frequency of missed opportunities for ordering blood cultures was found (69.9%, 221/316) among patients with clinical indications for blood culture sampling. This multicenter study demonstrates important shortcomings in the quality of blood culture processing in public hospitals of Peru. It provides a national benchmark of blood culture utilization and quality indicators that can be used to monitor future quality improvement studies and diagnostic stewardship policies.

INTRODUCTION

Bloodstream infections represent an important global burden of disease, with mortality rates ranging from 12% to 56%, depending on the studied patient population and the causative pathogens.[1–3] Early administration of effective antimicrobial treatment is pivotal to reduce mortality.[4,5]

The current reference method to diagnose bloodstream infections is the blood culture.[6] To monitor the correct preanalytical (indications, sampling, and transport), analytical (laboratory work-up), and post-analytical (reporting) processing of blood cultures, standardized quality indicators can be assessed (Supplemental Figure 1). Standardized targets for these quality indicators have been proposed to maximize the detection of true pathogens (i.e., positivity rate) and minimize growth of contaminants that originate from accidental inoculation of skin or environmental bacteria (i.e., contamination rate), while reducing the turnaround time.[7–9]

The high clinical relevance and standardized quality indicators prioritize blood cultures for surveillance of antimicrobial resistance on a global level, as well as for diagnostic and antibiotic stewardship programs.[10–12] In contrast with culture of other body specimens (e.g., urine, stool, and respiratory tract specimens), there is good consensus and harmonization of clinical indications for blood culture ordering, such as suspicion of infective endocarditis, neutropenic fever, severe sepsis, or septic shock.[13,14] However, the compliance with these clinical indications has been assessed by a limited number of studies, mostly conducted in high-income countries and addressing the overutilization of blood cultures.[15,16] In contrast, in low-income and middle-income countries (LMIC), where underutilization of bacteriological diagnostics is frequent,[12,17] the compliance to these clinical indications and the frequency of missed opportunities for blood culture sampling have not yet been assessed.

Clinical microbiology laboratories in public hospitals in Peru face many of the challenges typical to the LMIC setting, including high work-load, high personnel turnover, limited training, and limited technical and infrastructural resources, including lack of laboratory information systems.[11] These limitations impact not only on the quality of blood culture processing and performance but also on the feasibility to conduct standardized quality assessments. Importantly, if these limitations are not identified and corrected, current national[18] and global plans[19] to scale up antimicrobial resistance surveillance and stewardship programs can be hindered.

Here, we present a multicenter study conducted in public hospitals across different regions of Peru, which aimed to assess and benchmark the quality of blood culture requesting, sampling, and processing among hospitalized patients who met clinical criteria for blood culture sampling.

MATERIALS AND METHODS

Selection of study sites. Peru is an upper middle-income country, geographically divided in 25 regions. The Peruvian

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health system is divided in a public and a private sector, with the public sector providing healthcare to approximately 90% of the Peruvian population.[20] This system is further fragmented into several subsystems with regional governance, with each region having at least one public tertiary hospital.

From May 2017 to July 2018, we conducted a screening of potentially participating hospitals by contacting at least one tertiary hospital per region. Hospitals meeting the following criteria were invited to the study: 1) presence of a functioning clinical microbiology laboratory, 2) performance of blood cultures on a regular basis, 3) at least three blood cultures positive for GLASS-priority pathogens in the last 3 months,[10] 4) presence of a physician (infectious diseases or internal medicine specialist) willing to collaborate, and 5) presence of a laboratory technician willing to collaborate. Depending on the availability of the collaborators, each hospital participated in one or more of the quality assessments.

Quality assessment of blood culture systems. We conducted four different quality assessments from July 2017 to December 2019, with the aim to evaluate the performance and key quality indicators of the blood culture systems available at the participating hospitals (Supplemental Figure 1). Definitions and targets of assessed quality indicators were standardized based on available international guidelines, such as the Clinical and Laboratory Standards Institute[8] (Supplemental Table 1).

Assessment 1: Aggregated quality indicators. As part of a hospital-based antimicrobial resistance surveillance study conducted in Peru between July 2017 and July 2019 (manuscript under preparation), we collected on a monthly basis summary data from the sentinel hospital microbiology laboratories. These data included the total number of blood culture bottles processed (both adult and pediatric bottles), bottles with any growth and bottles with growth of coagulase negative *Staphylococcus* (CoNS), as well as the number of patients with a blood culture sampled. This information was collected by a designated laboratory personnel through manual review of the blood culture laboratory notebook, and completed in a standardized form that was sent to the study coordinator monthly for 6–12 months. Using this aggregated information, we calculated the contamination rate and the positivity rate, and assessed the proportion of hospitals that met the established targets for these quality indicators (Supplemental Table 1). Additionally, during 1 month of the study, we collected individual blood culture data to calculate the ratio of bottles processed per sampled adult patients and the proportion of solitary blood cultures (Supplemental Table 1).

Assessment 2: Sampling and transportation indicators. Between September 2019 and December 2019, a cross-sectional study was conducted at the microbiology laboratories of the participating hospitals to assess two quality indicators: 1) sampled volume of all adult blood culture bottles processed, and 2) needle-to-incubator time of all sampled and submitted bottles (Supplemental Table 1).

During the 3-week period, the weight of all inoculated adult bottles before being placed into the incubator was measured using a calibrated analytic scale (0.001 JA-P series, JA303P model). To calculate the blood volume sampled, the weight of the bottle before inoculation was subtracted from the weight of the inoculated bottle, and the weight difference was divided by 1.06 g/mL (to correct for the density of blood) to obtain the volume of blood.[21] For the sites that used commercial blood culture bottles, the average weight of the empty bottles was calculated by weighting 5% of the total bottles estimated to be processed during the 3 weeks of the study. For the single site that used in-house bottles, the weight before inoculation was measured for each bottle apart. In addition, laboratory staff registered on a standardized paper form the time of sample collection recorded on the laboratory request forms and the time of placement of blood culture bottles into the incubator. This allowed us to calculate the needle-to-incubator time.

Assessment 3: Clinical survey on missed opportunities for blood culture utilization. Between September 2019 and December 2019, a point-prevalence study was conducted at the hospital wards of the participating hospitals, to determine the frequency of blood culture utilization and missed opportunities for blood culture sampling among hospitalized patients who were started on antibiotics within the previous 7 days.

Survey content. A standardized data collection paper form was prepared (Supplemental Form 1). Data to be collected included start date of antibiotics, type of antibiotic therapy (pathogen-directed, based on antimicrobial susceptibility results; or empiric otherwise), date of blood culture ordering, date of blood culture sampling, and clinical indications for blood culture sampling during the 2 days before initiation of antibiotic treatment. The following clinical indications for blood culture sampling were assessed.[7,13,14]

1. Sepsis or septic shock: For adults, it was defined as the presence of fever (axillary temperature $\geq$ 38°C) OR hypothermia (axillary T $\leq$ 36°C) AND one of the following signs of severity: hypotension (systolic blood pressure $\leq$ 100 mm Hg), confusion (Glasgow coma scale $<$ 15), or increased respiratory rate ($\geq$ 22 per minute). For pediatric and neonate patients, the diagnosis of sepsis was counted only if explicitly written in the chart.
2. Suspicion of one of the following severe localized infections: Catheter-related bloodstream infection, infectious arthritis, infectious osteomyelitis, infectious endocarditis, or other endovascular infections, intra-abdominal infections, meningitis, severe pneumonia, severe skin and soft tissue infections.
3. Suspicion of other systemic conditions: Neutropenic fever, fever of unknown origin, severe malaria, and typhoid fever
4. Neonatal sepsis or severe localized infection.

A missed opportunity was defined as the absence of a blood culture sampled and submitted to the microbiology laboratory when at least one clinical indication for blood culture sampling was recorded in the patient's medical chart.

Survey validation. The data collection form was initially reviewed by three local infectious diseases experts. Before the start of the study, the tool was tested by collecting data of five hospitalized patients at one public hospital (data not included in the analysis). Questions detected to be confusing or ambiguous were discussed and modified after consensus was reached between the two principal investigators (F. C. and C. G.).

Survey implementation. The survey was conducted by a team of local physicians led by a local infectious disease specialist at each site. Before the initiation of the study, this

team received a face-to-face training session on how to fill the survey forms by collecting information from the patient charts. During the first day of survey, the study coordinator was on site to answer any questions of the team. During the rest of the study, a streamline communication was set up between the local team and the coordinator (via WhatsApp®), to allow real-time consultation of questions regarding the completion of the survey forms. The survey was conducted only on weekdays and during regular hours (8 AM to 8 PM) and collected information from patients' clinical (paper) charts. At each hospital, one ward was covered per day. An initial ward census was performed at 8 AM and only clinical charts of patients who were hospitalized at that time *and* had an ongoing antibiotic treatment started within the previous 7 days, were included.

Assessment 4: Local guidelines and practices. A standardize survey was applied to the responsible personnel of clinical microbiology laboratory, to address the availability of local guidelines and sampling practices. A questionnaire of 12 questions (Supplemental Form 2) was applied via phone call, to determine whether the hospital had 1) guidelines that detailed clinical indications for blood culture sampling, 2) guidelines or Standard Operating Procedures (SOP) for blood culture sampling and handling, and 3) a designated team for blood culture sampling; and to evaluate their perceptions regarding 1) the causes for sampling solitary blood cultures and inadequate blood volume, 2) frequency and reasons for shortage of blood culture supplies.

DATA MANAGEMENT AND ANALYSIS

Standardized paper forms were completed by our hospital collaborators using study codes to identify bottles (Assessment 2) and patients (Assessment 3), or to collect aggregated data (Assessment 1). No identifiable information was collected, to ensure the confidentiality of the patients. Completed paper forms were sent monthly to our research laboratory in Lima, where central data entry was conducted into an Excel database, where data analysis was also performed.

ETHICAL CONSIDERATIONS

Approval from UPCH IRB (UPCH-IRB: 100495, 103801) and the Ethics Committee of the 16 participating hospitals was obtained prior to the start of the study at each hospital.

RESULTS

Hospitals and laboratories characteristics. From a total of 23 tertiary hospitals screened, seven hospitals did not meet one or more of the selection criteria, the other 16 hospitals from 13 different regions were included in the study (Supplemental Figure 3). Fifteen hospitals participated in the Assessments 1 and 4, eight in the Assessment 2 and seven in the Assessment 3. Six of them participated in all four quality assessments (Supplemental Figure 2, Table 1). As the participating hospitals were referral hospitals for their region, they were all located in urban areas and served a large patient population. The number of hospital beds ranged from 110 to 640, and all hospitals had intensive care unit (ICU) and pediatric wards. Among the 16 hospitals, 14 had an automated blood culture system in place and 11 had automated identification and susceptibility testing (Table 1). None of the hospitals used anaerobic blood culture bottles.

Aggregated quality indicators. A total of 34,079 blood culture bottles and 22,914 patients were surveilled at the 15 participating hospitals during the Assessment 1. The median blood culture positivity rate was 4.9%, ranging across hospitals from 1.0% to 8.1%, with six hospitals meeting the target value of 6–12%. The median contamination rate was 4.2%, ranging from 0% to 15.1%, with five hospitals meeting the target value of less than 3%. Overall, five hospitals did not reach the target for any of both indicators, 10 hospitals met the target for only one indicator, and none met the target for both indicators. In addition, the median number of bottles submitted per adult sampled patient was 1.4, ranging from 1.0 to 2.5. Any of the hospitals met the target of at least four bottles (two sets). Accordingly, a high proportion of solitary blood culture among adult patients was observed (median 71.9%, ranging between 0% and 100%) (Table 1).

Sampling and transport indicators. A total of 1,261 blood culture bottles were processed at eight participating hospital microbiology laboratories during a 3-week period. Of these, 690 (54.7%) were adult bottles, 564 (44.7%) were pediatric or neonatal bottles, and 7 (0.6%) had no data regarding the type of bottle. Incorrect use of pediatric bottles was found in one hospital, where 33.1% (53/160) of the pediatric bottles had been used for sampling adult patients. Incorrect use of adult bottles for sampling neonatal or pediatric patients was found only in three cases. Assessment of inoculated blood volume was done for adult bottles correctly used to sample adult patients ($N = 687$). From these, 22 bottles (3.2%) were excluded from the analysis, because they had errors on the registration of the weight. Among the 665 included bottles, the median blood volume was 4.1 mL (interquartile range [IQR]: 2.7–5.8 mL), with only 59 (8.9%) bottles meeting the target volume of 8–12 mL, and 602 (90.5%) bottles underfilled (Figure 1).

Three out of eight hospitals did not register the time of blood culture sampling on a routinely basis. Therefore, the needle-to-incubator time was calculated for five hospitals and for a total of 559 sampled bottles. The median needle-to-incubator time was 1 hour and 10 minutes (IQR: 25 minutes to 3 hours and 45 minutes). The target of transport within 2 hours was met for 100% of the bottles in three hospitals, whereas in the other two hospitals this target was met in 89.3% (67/75) and 38.8% (137/353) of the submitted bottles (Figure 2). For these two hospitals, most bottles with a too long needle-to-incubator time were sampled during night shifts, between 10 PM and 9 AM, when the microbiology laboratory was closed.

Missed opportunities for blood culture utilization. From a total of 1,168 censed hospitalized patients, 676 (57.9%) were receiving antibiotic treatment at the time of the survey, and 362 (31.0%) had been started on antibiotic treatment within the previous 7 days. Of these, 342 (94.5%) were receiving empiric antibiotic treatment and 20 (5.5%) were receiving pathogen-directed antibiotic treatment based on grown cultures from different specimens, among whom only 4 patients had grown blood cultures.

From the 362 included patients, 51 (14.1%) were neonates, 62 (17.1%) were pediatric, and 249 (68.8%) were adult patients. A total of 316 patients (87.3%) showed at least one clinical indication for blood culture sampling, but

TABLE 1
Characteristics and microbiology resources and aggregated quality indicators of blood culture processing at participating hospitals in Peru (Assessment 1)

Hospital	Region	BC system	Identification and AST method	Total beds	ICU beds	Months of follow-up	Bottles processed	Patients sampled	Positivity rate	Contamination rate	Ratio pediatric to adult patients	No. bottles submitted per adult patient	Frequency of solitary blood cultures among adult patients
H1	Coast	BACTEC	MicroScan	448	38	11	6,322	5,347	6.0%	7.6%	1:1.4	2.5	31.8%
H2	Coast	BacT/ALERT	MicroScan	640	7	6	2,366	1,435	5.2%	10.9%	1:3.7	1.0	100.0%
H3	Coast	Bt240	Phoenix	388	31	12	12,460	5,981	8.1%	7.9%	–	–	–
H4	Coast	BacT/ALERT	Vitek-2	133	12	12	374	212	2.9%	3.7%	1:12.0	1.2	83.3%
H5	Coast	BC120	Manual	191	22	8	1,187	843	1.3%	2.4%	–	–	–
H6	Coast	BACTEC	MicroScan	220	6	12	2,050	1,446	6.3%	15.1%	–	–	–
H7	Coast	BacT/ALERT	MicroScan	298	20	12	3,285	3,160	4.0%	12.2%	1:1.0	1.2	88.2%
H8	Coast	BACTEC Plus	MicroScan	154	5	7	396	245	3.3%	5.8%	1:5.4	1.5	60.5%
H9	Coast	BacT/ALERT	Manual	176	13	4	311	311	1.0%	0.0%	–	–	–
H10	Coast	BacT/ALERT	Vitek-2	297	6	6	664	550	7.8%	4.2%	1:1.2	1.6	38.6%
H11	Coast	BacT/ALERT	MicroScan	110	11	6	737	348	6.1%	3.0%	1:6.5	2.5	8.0%
H12	Andes	BacT/ALERT	Manual	218	5	12	1,180	971	4.9%	1.9%	1:1.9	1.1	85.1%
H13	Andes	BacT/ALERT	Vitek-2	221	10	–	–	–	–	–	–	–	–
H14	Jungle	Manual (Hemotest bottles)	Vitek-2	283	35	12	1,553	1,004	4.3%	1.0%	1:6.5	2.0	0.0%
H15	Jungle	BACTEC	Manual	113	6	8	510	416	4.9%	0.0%	–	–	–
H16	Jungle	Manual (In-house bottles)	Manual	175	10	9	684	645	7.0%	6.4%	1:2.3	1.0	100.0%
Total				**4,065**	**237**	**137**	**34,079**	**22,914**	**4.9%**	**4.2%**	–	**1.4**	**71.9%**

AST = antimicrobial susceptibility testing; ICU = intensive care unit. Data express numbers unless otherwise stated. BACTEC (Becton Dickinson), BacT/ALERT (bioMérieux), Hemotest (Labifarma), DL-Bt-240 (DL), BC120 (Zhuhai DL Biothech), MicroScan (Beckman Coulter), Vitek-2 (bioMérieux), Phoenix Becton Dickinson.

only 95 of them (30.1%) had one or more blood cultures sampled, finding a total of 221 (69.9%) missed opportunities for blood culture utilization. The frequency of missed opportunities for blood culture utilization varied depending on hospital ward and the clinical indication, with surgical wards having the highest frequency of missed opportunities (90.9%) and ICU the lowest (32.7%) (Table 2). The date of blood culture sampling was documented in the patients' files only in 51 (53.7%) patients, of whom one third (N = 18, 35.3%) had the blood culture sampled 1 or more days after initiation of the antibiotic treatment.

Local guidelines and practices. None of the surveyed hospitals had local guidelines with the clinical indications that should prompt blood culture ordering. Conversely, 13 out of 15 laboratories did have guidelines or SOP for blood culture sampling. However, none of these SOP were aligned with Clinical & Laboratory Standards Institute guidelines, recommending to sample one to two bottles (in two hospitals), two to three bottles from different venipuncture sites (in eight hospitals), or one blood culture set (two bottles) from one venipuncture site (in three hospitals). Reference to the optimal volume per bottle was detailed in 11 of these SOP, with 6 recommending 10 mL per bottle, 5 recommending 5–10 mL and 3 recommending 5 mL.

All hospitals had a dedicated phlebotomy team; these teams were responsible for collecting any blood sample, including blood cultures. In 6 out of 15 hospitals these teams were only available during regular hours, which results in other hospital staff sampling blood cultures (in four hospitals) or no blood culture ordering (in two hospitals) during nonregular hours or weekends. Importantly, in 14 out of 16 hospitals drawing a set of blood culture (two paired bottles) is not done by default, even if stated in their laboratory SOP. It requires that the ordering physician completes two separate request forms or specifically requests the need for two or more bottles. As to barriers to comply with the recommended blood volume, the surveyed personnel identified having a difficult venous access or a large number of additional blood tests collected from the same venipuncture, as the most frequent barriers. Limited availability of blood culture bottles or other supplies was infrequent in all surveyed hospitals (Supplemental Table 2).

DISCUSSION

Blood culture is a critical diagnostic tool for the management of bloodstream infections. Blood culture results contribute to two of the five strategic objectives of the Global Action Plan on Antimicrobial Resistance: 1) to strengthen global surveillance of antimicrobial resistance and 2) to optimize the use of antimicrobial agents through antibiotic and diagnostic stewardship.[19] Therefore, optimal processing of blood culture is needed for scaling up efforts to contain antimicrobial resistance.

This multicenter study demonstrates important shortcomings in the quality and performance of blood culture processing in public hospitals across different regions of Peru. Similar shortcomings have been described in hospitals of other LMIC.[7] By characterizing these shortcomings, this study provides a national benchmark of blood culture utilization and quality indicators and provides a starting point for proposing and implementing targeted interventions to

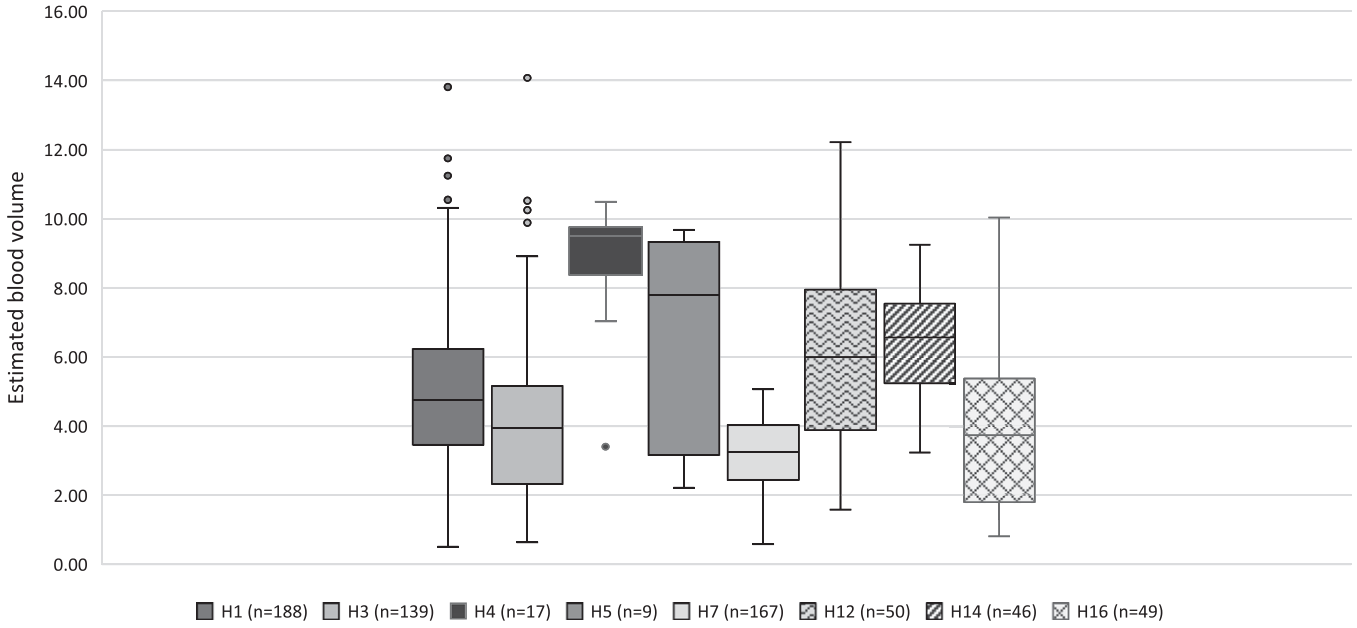

FIGURE 1. Box-plot distribution of the blood volume inoculated to surveyed bottles in eight participating hospitals. The boxes represent the interquartile range, with the lower and upper ends representing the first and third quartiles, respectively. The horizontal line within the boxes represent the median, and the lower and upper whiskers represent the minimum and maximum, whereas the dots above and below the whiskers represent the outliers. Dotted lines represent the target volume from 8 to 12 mL.

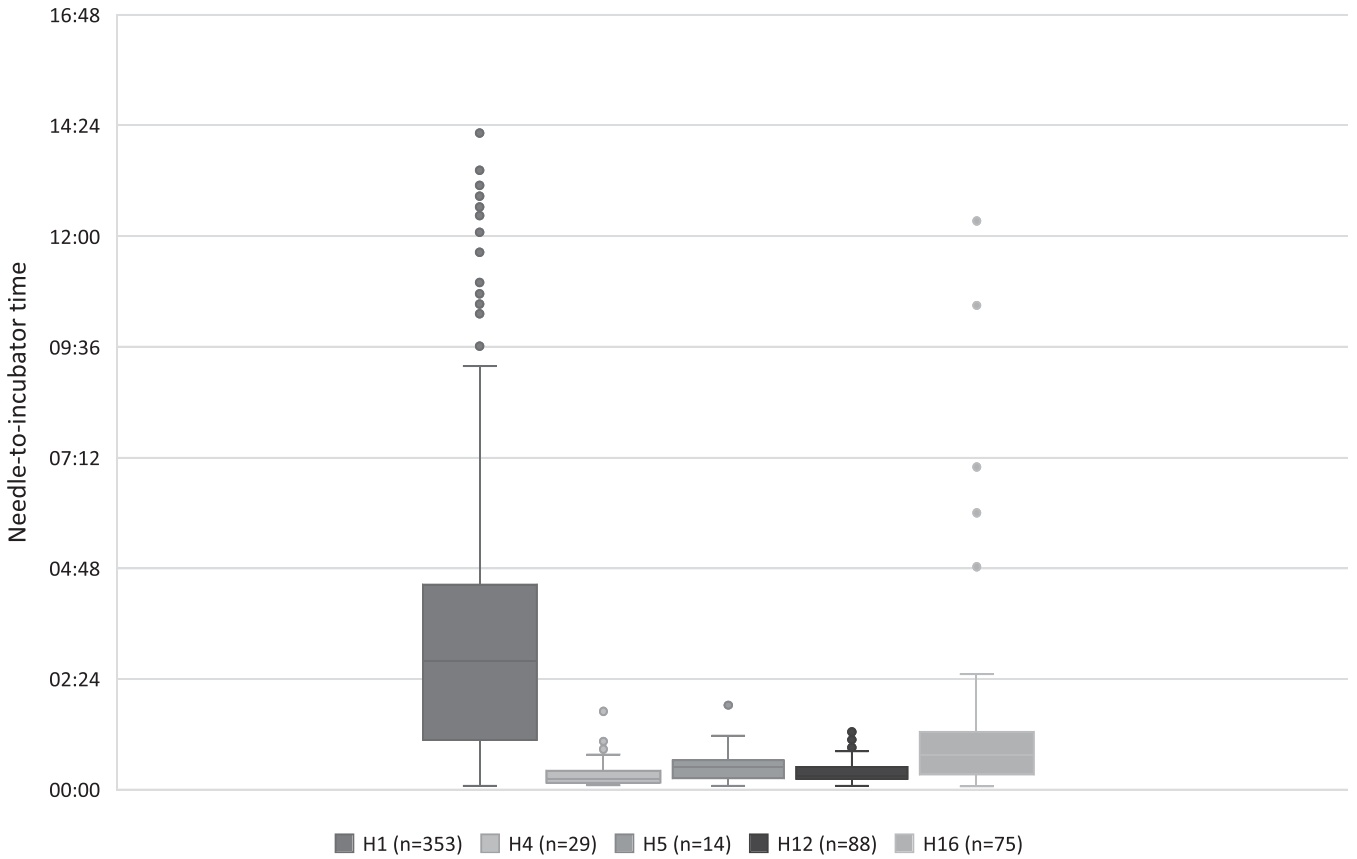

FIGURE 2. Distribution of the needle-to-incubator time assessed in five hospitals in Peru. The boxes represent the interquartile range, with the lower and upper ends representing the first and third quartiles, respectively. The horizontal line within the boxes represent the median, and the lower and upper whiskers represent the minimum and maximum, whereas the dots above and below the whiskers represent the outliers. Dotted line represents the target of 2 hours or less for transport time.

TABLE 2
Blood culture utilization among hospitalized adult, pediatric and neonatal patients with clinical indications for blood culture sampling in 10 hospitals in Peru (Assessment 3).

		Total		Adults		Pediatric		Neonates	
	Clinical indications	*N*	Missed opportunities	*N*	Missed opportunities	*N*	Missed opportunities	*N*	Missed opportunities
All	Included patients	**362**	–	**249**	–	**62**	–	**51**	–
	Any clinical indication	316	221 (69.9%)	207	161 (77.8%)	58	41 (70.7%)	51	19 (37.3%)
	Sepsis or septic shock	36	22 (61.1%)	31	21 (67.7%)	5	1 (20%)	–	–
	Severe localized infection	257	202 (74.3%)	203	157 (77.3%)	54	40 (74.1%)	–	–
	Systemic condition	6	2 (33.3%)	4	2 (50%)	0	0 (0%)	–	–
Medical wards	Included patients	**174**	–	**101**	–	**36**	–	**37**	–
	Any clinical indication	154	104 (67.5%)	85	61 (71.8%)	32	24 (75%)	37	19 (51.4%)
	Sepsis or septic shock	20	13 (65.0%)	19	13 (68.4%)	1	0 (0%)	–	–
	Severe localized infection	128	88 (68.8%)	83	59 (71.1%)	31	24 (77.4%)	–	–
	Systemic condition	4	1 (25.0%)	3	1 (33.3%)	1	0 (0%)	–	–
Surgical wards	Included patients	**134**	–	**117**	–	**17**	–	**0**	–
	Any clinical indication	110	100 (90.9%)	93	85 (91.4%)	17	15 (88.2%)	0	0 (0%)
	Sepsis or septic shock	3	3 (100%)	3	3 (100%)	0	0 (0%)	–	–
	Severe localized infection	108	99 (91.7%)	92	84 (91.3%)	16	15 (93.8%)	–	–
	Systemic condition	2	1 (50.0%)	1	1 (100%)	1	0 (0%)	–	–
ICU	Included patients	**54**	–	**31**	–	**9**	–	**14**	–
	Any clinical indication	52	17 (32.7%)	29	15 (51.7%)	9	2 (22.2%)	14	0 (0%)
	Sepsis or septic shock	13	6 (46.2%)	9	5 (55.6%)	4	1 (25%)	–	–
	Severe localized infection	36	15 (41.7%)	28	14 (50%)	7	1 (14.3%)	–	–
	Systemic condition	0	0 (0%)	0	0 (0%)	0	0 (0%)	–	–

ICU = intensive care unit.

improve blood culture processing in Peru. Moreover, by including hospitals from different regions and from the two main public health systems (ESSALUD and MINSA), this study provides results that are generalizable to the biggest proportion of hospitals in Peru and possibly across other Latin America countries with similar conditions.

In this study, the median positivity rate among all surveilled blood culture bottles was 4.9%, with more than half of the surveilled hospitals having positivity rates below the target of 6–12%. This finding contrasts with the results of a study conducted in 15 hospitals in Colombia, that showed positivity rates ranging from 9.7% to 12.2%.[22] Other studies conducted at other LMIC outside Latin America have reported positivity rates as high as 28%.[23] Positivity rates lower than the target have been proposed to reflect an overutilization of blood cultures.[9] However, the small number of blood culture bottles processed and the high frequency of missed opportunities for blood culture sampling presently found in most participating hospitals does not support this assumption as the reason for the low positivity rates in this setting. Of note, the positivity rate would have been higher if it had been calculated per set (pair) of blood culture bottles or per suspected bloodstream infection rather than per bottle as was done now;[24] however, as over 70% of the adult patients in the present study only had a solitary (single) blood culture bottle sampled, the difference might be minimal.

A more plausible explanation for the low positivity rate found in several hospitals in this study is that the processed blood cultures had a low detection sensitivity because of the suboptimal pre-analytical or analytical processing. In that sense, most of the hospitals had automated blood culture systems that should minimize the problems within the analytical phase. In contrast, we found important underperformance on pre-analytical quality indicators that can have a direct impact on the detection sensitivity of blood cultures. For instance, 90.8% of the surveilled adult bottles were underfilled, with an inoculated blood volume below 8 mL. In addition, the median number of bottles submitted per adult sampled patient was 1.4, ranging from 1.0 to 2.5, far below the target of 4. This finding likely reflects a common practice of ordering less than two sets of blood cultures (i.e., four bottles) per sampled patient, and frequent submission of solitary cultures. Because the sensitivity of blood cultures depends on the blood volume sampled, it is recommended that at least two blood culture sets of 20–30 mL of blood each are sampled over 24 hours to have a detection sensitivity above 80%.[8,25] We could extrapolate from the results obtained in this study that less than a quarter of the recommended volume is routinely sampled from patients with suspicion of bloodstream infections in hospitals in Peru, and therefore the sensitivity of blood cultures processed in these hospitals may be very low. Importantly, there are two national laboratory manuals (one general and one for bacteriological procedures for nosocomial infections) that provide guidelines regarding blood culture sampling and handling. However, these guidelines recommend to obtain two to three blood culture bottles from two to three different venipuncture sites, with a recommended volume of 5–30 mL[26,27] (Supplemental Table 3). Similarly, while most of the laboratories had their own manual, none recommended to obtain two to three blood culture sets, as per international guidelines.[8] Actualization and harmonization of these national and local manuals are needed, along with training to laboratory and ward personnel and implementation of a quality assurance system that monitors the compliance with the recommended number of blood culture sets and blood volume.

An additional factor that can further decrease the sensitivity of blood cultures is the initiation of antibiotics prior to the collection of the blood culture.[28] Although we were able to assess this indicator only in half of the patients that had a blood culture sampled, due to lack of documentation of the date and time of blood culture sampling, we found that one third of the blood cultures were sampled one or more days after initiation of the antibiotic treatment.

These findings highlight the need to introduce in hospitals in Peru the use of a standardize request form for blood cultures that captures information such as day of hospitalization, data on antibiotic use, number of bottles ordered and sampled, pre and post inoculation weight and time of sampling. Moreover, hospital staff should be trained on the importance of the correct completion of this form and active reinforcement could be provided by including this information in the report of the blood culture results. Finally, periodic assessment of quality indicators using this information should be conducted and results should be presented to hospital staff and compared within and among institutions.

Contamination of blood cultures can have an important impact on patient care and healthcare costs. Contaminants can lead to misdiagnosis of infection and unneeded administration of antimicrobial treatment, which can be associated with side effects, longer hospital stays, and healthcare costs.[29] In addition, work up of false-positive cultures results in unnecessary resource utilization in the hospital and laboratory.[30] Blood culture contamination could also lead to false-negative blood cultures by preventing growth of the true pathogens. In this study, the median contamination rate was 4.2%, ranging from 0% to 15.1%, with only one third of the participating hospitals meeting the target value of less than 3%. Moreover, half of the hospitals had a contamination rate higher that the positivity rate, even 2-fold or 3-fold higher in some cases.

Similar findings have been reported in other LMIC, with a contamination rate of 10.4% in a national hospital in Nigeria,[31] and contamination rates ranging from 1% to 17% in 16 hospitals from Turkey.[32] However, our results contrast with those reported from multicenter studies conducted in middle-income countries in Latin America, such as Chile[33] and Colombia,[22] which have reported low contamination rates (0.7% and 1.6%, respectively), meeting the recommended international guidelines. Further studies are needed to address the causes of the elevated contamination rates found in this study. Assessment of compliance with adequate skin disinfection techniques and barriers for adequate implementation of these techniques could provide needed information to propose cost-effective strategies that help minimize contamination and therefore unnecessary resource utilization in public hospitals in Peru.

Other important finding of our study is that it demonstrates underutilization of blood cultures across different hospitals and different hospitalization wards. A striking high frequency of missed opportunities for blood culture sampling was found, especially in surgical wards, where only 9% of patients presenting a clinical indication for blood culture did have a blood culture sampled. Additional studies are needed to understand the factors driving this underutilization. These may include lack of local guidelines or dissemination of guidelines, or operational gaps, such as lack of microbiology personnel during weekends and nonregular hours. It may also include clinicians' perception that blood cultures are not useful, given the low sensitivity and low specificity (high contamination) that this diagnostic tool currently has in their hospitals. Financial barriers are less likely, because blood cultures at public hospitals are mostly covered by the Integral Health Insurance and laboratory personnel report adequate supply for blood culture processing. To our knowledge, there are no previous studies addressing the frequency of missed opportunities using a point prevalence approach as currently done. Our results could serve as an initial benchmark for future national and regional studies.

One limitation of our study is that during the surveillance study conducted as Assessment 1, we collected aggregated data from the microbiology laboratories of the participating hospitals. This was done to simplify the monthly data collection that our collaborators had to conduct by reviewing the laboratory paper notebooks. This approach was done considering the work overload and limited human resources that public microbiology laboratories have in Peru. Because of this simplification, we lost the capacity to have more detailed information that could allow us to calculate the positivity and contamination rates per blood culture set or per patient, or to stratify the results by pediatric and adult patients. After this same strategy of simplification of data collection, we used the growth of CoNS as a proxy of contamination. For the purposes of this study, no other microorganisms, such as *Bacillus* spp. and *Corynebacterium* spp. and *Micrococcus* spp., were counted as contaminants, because of the limitations of some of the laboratories to achieve identification of these pathogens. This approach, could have resulted in a slight underestimation of contamination, as most participating hospitals reported recovering less than 10 of these isolates per year, which would result in less than 0.2% increase of the contamination rate; whereas only one hospital reported recovering 15–20 of these isolates per year, which would result in an increase of 0.8% of its contamination rate (Supplemental Table 4). However, it is important to also consider that some of the CoNS might have been true pathogens causing a bloodstream infection. Unfortunately, because of the common practice to sample only one bottle per patient, most of the participating laboratories did not have the capacity to distinguish contamination from true bloodstream infection when a CoNS is recovered. Previous studies have reported that 12–25% of patients with blood cultures positive for CoNS have true bacteremia, identifying as risk factors the presence of intravascular catheters or prosthetic devices, and prematurity among neonates.[34,35] In that sense, because the number of ICU beds (pediatric and adult ICU) in the included hospitals is small (Table 1), the number of patients at risk of true CoNS bacteremia might be in the low range. Assuming that up to 25% of the blood cultures with growth of CoNS in this study could be true pathogens, the median contamination rate could decrease from 4.2% down to 3.2%, remaining still above the target.

Other limitation of our study is that not all the included hospitals participated in all four assessments, and that the duration of the surveillance study varied from 6 to 12 months between the different hospitals. This variability reflects the complexity of our health system and the variability that exist between regions, with personnel facing different degrees of workload and turnover. Although it is critical that countries work on resolving these limitations, it is also critical to implement quality monitoring systems adapted to the reality of working laboratories and hospitals. This study could be viewed as a map road on how to implement a quality monitoring system adapted to these limitations.

Importantly, if the identified quality shortcomings are not corrected, current national[18] and global plans[19] to scale up antimicrobial resistance surveillance and stewardship programs could be hindered. Therefore, this study contributes

to inform policy makers on the need to establish a nationwide quality assurance system for clinical microbiology laboratories that include the monitoring of specific quality indicators for blood cultures. Our results could guide future studies oriented to implement and assess the impact of one or more bundle interventions in optimizing the quality and performance of blood culture systems processed in Peru.

CONCLUSION

Through four different quality assessments, we determined that blood culture processing in public hospitals in Peru do not meet the targets of standardized performance and quality indicators, highlighting the urgent need to address critical barriers to the optimal processing of blood cultures and to implement bundle interventions to optimize this important diagnostic and surveillance tool.

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