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Rectal screening displays high negative predictive value for bloodstream infection with (ESBL-producing) Gram-negative bacteria in neonates with suspected sepsis in a low-resource setting neonatal care unit



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ABSTRACT

Objectives: We analysed the concordance of rectal swab isolates and blood culture for Gram-negative bacteria (GNB) isolates in neonates with a suspicion of neonatal sepsis admitted to a neonatal care unit in Haiti.

Methods: We matched pairs of blood and rectal samples taken on the date of suspected sepsis onset in the same neonate. We calculated the proportion of rectal isolates in concordance with the blood isolates by species and genus. We calculated the negative predictive value (NPV) for GNB and extended-spectrum β -lactamase (ESBL)-producing GNB for all rectal and blood isolate pairs in neonates with suspected sepsis. **Results:** We identified 238 blood and rectal samples pairs, with 238 blood isolate results and 309 rectal isolate results. The overall concordance in genus and species between blood and rectal isolates was 22.3% [95% confidence interval (CI) 17.4–28.0%] and 20.6% (95% CI 16.0–26.2%), respectively. The highest concordance between blood and rectal isolates was observed for samples with no bacterial growth (65%), followed by *Klebsiella pneumoniae* (18%) and *Klebsiella oxytoca* (12%). The NPV of detecting GNB bacterial isolates in rectal samples compared with those in blood samples was 81.6% and the NPV for ESBL-positive GNB was 92.6%.

Conclusions: The NPV of rectal swab GNB isolates was high in all patient groups and was even higher for ESBL-positive GNB. Clinicians can use the results from rectal swabs when taken simultaneously with blood samples during outbreaks to inform the (de-)escalation of antibiotic therapy in those neonates that have an ongoing sepsis profile.

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1. Introduction

Neonatal sepsis is one of the main causes of neonatal morbidity and mortality. It is estimated that approximately 3 million cases of neonatal sepsis occur globally per year, of which 11–19% result in

death [1]. Early detection and prompt empirical treatment of suspected neonatal sepsis with broad-spectrum antibiotics is common practice to avoid rapid progression to severe sepsis or septic shock [2]. The highest proportion of the burden of neonatal sepsis is carried by low- and middle-income countries [3]. The diagnosis of neonatal sepsis is based on clinical suspicion, since clinical signs and symptoms of neonatal sepsis are non-specific [4]. Worryingly, a recent study showed that nearly one-half of the bacteria responsible for neonatal infections are resistant to first-line (ampicillin or penicillin, and gentamicin) and second-line

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(third-generation cephalosporins) treatments recommended by the World Health Organization (WHO) [5,6]. Also, resistance to ampicillin and gentamicin has been reported to be as high as 71% in *Klebsiella* spp. and 50% in *Escherichia coli* in neonates [3]. Outbreaks of multidrug-resistant (MDR) bacteria are therefore increasingly reported from neonatal intensive care units (NICUs) in such settings [7,8].

Blood culture testing is considered the gold standard for the confirmation of bacteraemia in patients with sepsis. Blood cultures should be taken before antibiotics are administered in infants and young children [4] and can be used to tailor antibiotic treatment to neonates with suspected sepsis [9]. However, the positivity rate of blood cultures in the neonatal patient population is low and can be influenced by factors such as intrapartum antimicrobial administration, antibiotics administered before blood culture draw, low quantities of blood volume obtained from neonates for culture [10] or absence of bacteraemia. Two systematic reviews from Africa and Southeast Asia concluded that blood culture positivity in children was low, ranging from 8.2% [95% confidence interval (CI) 7.9–8.4%] to 6.6% (95% CI 6.3–6.9%) [11,12]. One recent study from South Africa showed a blood culture positivity rate in children below the age of 1 year with clinical signs and/or risk factors for severe bacterial infection of 15.7% (95% CI 15.2–16.2%) (of which 44.3% were due to pathogenic bacteria) [13].

The gastrointestinal tract of hospitalised infants has been shown to serve as a reservoir of bloodstream infections (BSIs) caused by *Candida* spp., *Klebsiella* spp., *E. coli* and *Pseudomonas* spp. [14]. Also, 20% of episodes of late-onset sepsis (LOS) in neonates are caused by infections with Gram-negative bacteria (GNB) [14]. It has also been shown that intestinal overgrowth is a predisposing factor for sepsis development in the neonatal population [15,16]. Das et al. showed that there is an association between intestinal colonisation and sepsis [16]. Neonates with intestinal colonisation of GNB had a higher incidence of clinical sepsis than those without GNB colonisation [16]. A meta-analysis by Folgari et al. in 2018 showed an association between GNB colonisation and a confirmed BSI with GNB in neonates, but it did not conclude that routine rectal screening in NICUs was recommended owing to limited evidence [17]. The lack of evidence around the added value of rectal screening for GNB colonisation in neonates admitted to NICUs was also confirmed in another meta-analysis from 2017 [18].

Between 2011 and 2018, Médecins Sans Frontières (MSF) managed the 'Centre de Référence pour les Urgences Obstétricales' (CRUO) in Port-au-Prince, Haiti, an emergency obstetric hospital and associated neonatal care unit (NCU). In July 2014, the hospital identified an increase in sepsis cases, and healthcare-associated transmission of extended-spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae* was suspected [8]. In subsequent years,

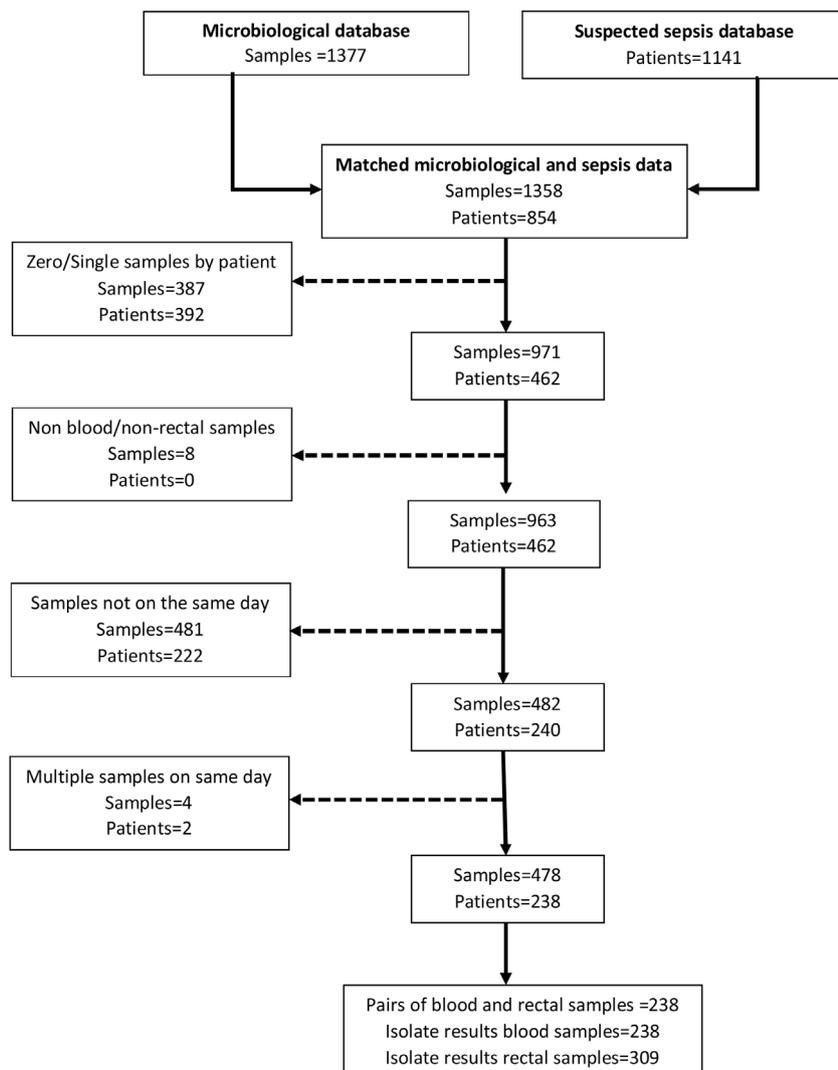


Fig. 1. Flow chart of study data.

repeated outbreaks of other MDR-GNB also occurred (unpublished data). As a response to this outbreak, CRUO started routine blood cultures on neonates who presented with suspected clinical sepsis. As an enhanced surveillance measure and to strengthen infection prevention and control measures, we also took simultaneous rectal swabs from all neonates with suspected sepsis to better understand colonisation with MDR-GNB. This strategy of enhanced surveillance allowed us to isolate all neonates identified with MDR-GNB [8].

There is limited evidence around the potential value of identification of bacterial rectal colonisation in neonates in guiding empirical treatment for neonatal sepsis. Data from the MDR-GNB surveillance in CRUO therefore presented us with a unique opportunity to further explore the relationship between colonisation, BSI and suspected clinical sepsis in this vulnerable patient group in a low-resource context. We aimed to analyse the concordance of rectal swab isolates and blood culture GNB isolates in neonates with suspicion of neonatal sepsis in Haiti.

2. Materials and methods

2.1. Study setting

CRUO was a container hospital that opened in 2011 to improve access to healthcare for women with complicated pregnancies and their offspring in Port-au-Prince. The hospital contained 162 beds, of which 56 beds were part of the NCU. The hospital closed in July 2018. Due to the clinical profile of women delivering in CRUO (e.g. high prevalence of pre-eclampsia and eclampsia) and their neonates (e.g. premature, low birthweight), a large proportion of neonates admitted in CRUO received prophylactic antibiotic treatment (with first-line treatment) immediately after birth.

2.2. Study population

We included data for all neonates diagnosed with suspected neonatal sepsis after admission to CRUO between October 2014 and July 2018 and for whom simultaneous (within 24 h of each other) blood and rectal samples were taken for culture on the date of onset of their suspected sepsis. A clinical suspicion of neonatal sepsis was defined as a neonate in the NCU who presented with one or more of the following clinical signs: prolonged capillary refill; certain skin changes (redness, sclerema); distended abdomen with/without haemorrhagic, brownish or bilious gastric aspirates; tachypnoea; tachycardia; persistent jaundice; unstable temperature; signs of disseminated intravascular coagulation (bleeding from catheter sites, bloody secretions from nose and mouth, petechiae); reduced muscle tone; and lethargy, apathy or irritability. Early-onset sepsis (EOS) was defined as clinical sepsis with a date of onset within 48 h after birth. Late-onset sepsis (LOS) was defined as the onset of clinical sepsis after 48 h of life.

All clinical and epidemiological data were collected in the routine Health Information System for MSF.

2.3. Microbiological diagnostics

After sample collection, blood samples were stored in an incubator at 37 °C and rectal samples were stored in a refrigerator until the time of their transport to the laboratory. Samples were sent on the day of collection to the Clinical Bacteriology Laboratory of the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) and were plated on MacConkey, Columbia CNA agar and chocolate agar with Polyvitex plates and incubated for 24 h at 37 °C. Isolates were identified using the VITEK® 2 g-negative card, and antimicrobial susceptibility testing was performed using the VITEK® 2 AST-N233 card. Presence of ESBLs

was established through the double-disk synergy test (Comité de l'Antibiogramme de la Société Française Microbiologie (CA-SFM) 2013 recommendations [19]) using Mueller–Hinton agar with antibiotic-impregnated disks (3 cm distance between disks) for β -lactamase detection or confirmation. Amoxicillin/clavulanic acid was placed in the middle of the agar, surrounded by disks for third- and fourth-generation cephalosporins (ceftazidime, cefotaxime, ceftriaxone and cefepime) [8].

All microbiological data were collected in a specified Excel-based database.

2.4. Data management

We merged the data from the Health Information System ($n = 1141$ neonates) with the microbiological database ($n = 1377$ samples) for the data analysis (Fig. 1). Prior to merging the databases, we removed any observations from the two databases that were for neonates who had been re-admitted for treatment or microbiological results that were likely to be contaminants [20]. In line with local protocols, we made the following assumptions: (i) rectal and blood samples taken on the day of onset of their suspected sepsis were taken at the same time; (ii) rectal and blood samples were taken at the time that sepsis was diagnosed; and (iii) rectal and blood samples were taken before administration of antibiotic treatment. We removed all observations in the merged data set that could not be matched (i.e. single blood or rectal sample, or samples from the same patient that were not taken in the same moment), that were not from blood or rectal swabs (i.e. pus, etc.) and for patients for whom multiple blood samples were taken on the same day (potentially due to a data quality issue). We focused the analysis on GNB and therefore excluded all microbiological results for Gram-positive bacterial isolates. In total, 238 matched samples from 238 patients were included for analysis, with 238 bacterial isolate results from blood samples and 309 isolate results from rectal swabs.

2.5. Data analysis

We described the patient profile for which we had bacterial isolate information available. For each individual patient (for whom matched blood and rectal samples were available), we calculated the time between the date of onset of sepsis and the date of treatment with first-line antibiotic therapy (ampicillin and gentamicin), second-line therapy (amikacin and ceftazidime) and third-line therapy (meropenem). Thus, we could distinguish which antibiotic therapy patients were receiving after their sepsis was diagnosed. We compared the difference in isolate results between neonates who received the different lines of antibiotic therapy to explore whether second- or third-line treatment was associated with higher rates of colonisation or blood culture positivity with MDR bacteria.

We calculated the proportion and 95% CI of rectal isolates in concordance with the blood isolates for each species and genus. CIs were calculated using Wilson's method [21]. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for GNB and ESBL-producing GNB for all rectal and blood isolate pairs in all suspected neonates with sepsis. For example, for the NPV, we calculated the proportion of true negatives (rectal isolate and blood isolate were not GNB) amongst all non-GNB isolates in the rectal samples. We also explored these four parameters in neonates who were diagnosed with EOS and LOS, and compared neonates who had only received first-line antibiotics and only second-line antibiotics at the time of sepsis diagnosis. Concordance was reached when the species or the genus identified in a blood isolate was the same in a rectal isolate. If there were multiple rectal isolates per patient, concordance occurred if

any rectal isolate corresponded with the blood isolate. We used McNemar's test to compare the concordance between results of the rectal and blood isolates for each patient.

All data cleaning and data analysis was conducted using Stata Statistical Software: Release 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Overall results

We were able to match clinical and microbiological data from 854 patients with a total of 1358 samples (blood and rectal) who were admitted to CRUO between January 2015 and June 2018 and who displayed symptoms of suspected sepsis during their admission period (Fig. 1). Following cleaning procedures, we included data from 238 neonates in the final analysis (Fig. 1). Most neonates were male ($n = 126$; 52.9%), their mean \pm standard deviation (S.D.) birthweight was 1704.8 ± 654.1 g [median 1525 g, interquartile range (IQR) 1225–2027 g] and the mean \pm S.D. gestational age was 33.4 ± 4.0 weeks (median 33 weeks, IQR 30–36 weeks). Of the 238 neonates, 36 (15.1%) had EOS. We had information on the type of antibiotic treatment received for 181 neonates (76.1%). The majority of neonates had received both first- and second-line treatment (132/181; 72.9%) at the time of their suspected sepsis onset.

A total of 238 pairs of blood and rectal swabs from neonates with suspected sepsis were retained for this analysis for a total of 547 isolate results (blood = 238, rectal = 309). For 171 matched blood and rectal sample pairs, no isolate or a single isolate was identified in either sample. For 67 blood and rectal pairs, multiple colonies of differing species were identified in the rectal swabs. Amongst the blood and rectal pairs, 163 (68.5%) isolated GNB only in the rectal sample, 31 pairs (13.0%) had no growth in either samples, 7 pairs (2.9%) isolated GNB only in blood and in 37 pairs (15.5%) GNB were isolated both in rectal and blood samples. The median duration between birth of the neonate and positive identification of GNB in their rectal samples was 6 days (IQR 4–9 days) and for GNB in their blood samples was 5 days (IQR = 3.5–7 days).

We isolated seven different species of GNB in blood samples and 23 different species of GNB from rectal samples during the study period (Table 1). The majority of blood samples showed no growth (81.5%) (Table 1). The most common bacterial isolates from blood samples were *Klebsiella oxytoca* (8.4%) and *K. pneumoniae* (7.1%). In rectal samples, 12.9% showed no growth and the most commonly isolated bacteria included *K. pneumoniae* (25.6%), *E. coli* (15.5%), *K. oxytoca* (14.2%) and *Enterobacter cloacae* (7.4%) (Table 1). Moreover, 14.3% of bacteria isolated from blood and 38.2% of bacteria isolated from rectal samples were ESBL-producing bacteria (Table 1).

Of the identified GNB isolates in blood samples, 34 (14.2%) were ESBL-positive. In rectal samples there were 118 ESBL-producing GNB isolates identified (38.2%). No other MDR isolates (apart from the ESBL-positive isolates) were identified according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [22].

3.2. Sensitivity, specificity, positive predictive value and negative predictive value of rectal isolates

In all neonates for whom we had data, the overall sensitivity, specificity, PPV and NPV of detecting GNB bacterial isolates in rectal samples compared with those in blood samples was 84.1%, 16.0%, 18.5% and 81.6%, respectively. For ESBL-positive GNB

Table 1
Bacterial isolates in blood and rectal samples.

Species	Overall				ESBL-producing ^a			
	Blood		Rectal		Blood		Rectal	
	n	%	n	%	n	%	n	%
No growth	194	81.5	40	12.9				
<i>Klebsiella oxytoca</i>	20	8.4	44	14.2	19	95.0	30	68.2
<i>Klebsiella pneumoniae</i>	17	7.1	79	25.6	14	82.4	45	57.0
<i>Enterobacter cloacae</i>	3	1.3	23	7.4			11	47.8
<i>Aeromonas hydrophila</i>	1	0.4	4	1.3				
<i>Escherichia coli</i>	1	0.4	48	15.5			12	25.0
<i>Enterobacter aerogenes</i>	1	0.4	5	1.6	1	100	2	40.0
<i>Stenotrophomonas maltophilia</i>	1	0.4	2	0.6				
<i>Citrobacter freundii</i>			18	5.8			10	55.6
<i>Pseudomonas aeruginosa</i>			11	3.6				
<i>Klebsiella</i> spp.			8	2.6			4	50.0
<i>Acinetobacter baumannii</i>			7	2.3				
<i>Acinetobacter junii</i>			1	0.3				
<i>Acinetobacter lwoffii</i>			1	0.3				
<i>Pantoea</i> spp.			6	1.9				
<i>Proteus mirabilis</i>			3	1.0				
<i>Citrobacter farmeri</i>			2	0.6			1	50.0
<i>Citrobacter koseri</i>			1	0.3				
<i>Pseudomonas fluorescens</i>			1	0.3				
<i>Pseudomonas mendocina</i>			1	0.3				
<i>Pseudomonas stutzeri</i>			1	0.3				
<i>Raoultella ornithinolytica</i>			1	0.3			1	100
<i>Serratia odorifera</i>			1	0.3			1	100
Others			1	0.3			1	100
Total	238		309		34		118	

ESBL, extended-spectrum β -lactamase.

^a Percentage of total number of isolates of that species.

isolates, the sensitivity was reduced, but the specificity, NPV and PPV increased (Table 2).

The sensitivity for a positive GNB in a rectal sample remained high for neonates with EOS, LOS and those receiving only first- or second-line antibiotics (>80% for all categories). For all these categories of neonates, the specificity and PPV remained low. The NPV for each of these subgroups was between 76.0% and 100%. In the group of neonates who only ever received second-line antibiotics, we were unable to calculate the NPV owing to zero results in the false negative and true negative parts of the two by two table (Table 2).

There was a statistically significant difference in the proportion of discordant blood and rectal isolates all groups, except in the subgroup analysis for neonates who only received second-line antibiotics ($P = 0.06$). This latter finding is likely due to the limited number of samples that were eligible for this subgroup analysis (Table 2).

3.3. Concordance by species and genus

Overall, the concordance in species between blood and rectal isolates was 20.6% (95% CI 16.0–26.2%) (Table 3). This concordance for all samples based on genus was slightly higher 22.3% (95% CI 17.4–28.0%). Concordance between rectal and blood samples was slightly higher in neonates with EOS compared with those with LOS (Table 3). When grouping neonates who only received first-line antibiotics and only received second-line antibiotics, the concordance was similar in these groups of neonates (~20%) (Table 3). The highest concordance occurred in rectal and blood samples that had no growth (65%). The concordance was highest in samples with no growth ($n = 32$; 65%) followed by samples that isolated *K. pneumoniae* ($n = 9$; 18%) and samples that isolated *K. oxytoca* ($n = 6$; 12%). There was one pair of rectal and blood samples that displayed concordance for *E. coli* and *E. cloacae*.

Table 2

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of rectal and blood isolate pairs by bacterial groups in neonates with suspected sepsis.

Patient group	Bacteria type	Positive blood samples		Positive rectal samples		Sensitivity		Specificity		PPV		NPV		McNemar's test (P-value) 95% CI
		n (%)	N	n (%)	N	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Overall sepsis	GNB	44 (18.5)	238	268 (86.7)	309	84.1	69.9–93.4	16.0	11.1–21.9	18.5	13.4–24.6	81.6	65.7–92.3	<0.001
	ESBL + GNB	34 (14.3)	238	118 (38.2)	309	70.6	52.5–84.9	61.3	54.2–68.0	23.3	15.5–32.7	92.6	86.8–96.4	<0.001
EOS	GNB	6 (16.7)	36	29 (67.4)	43	83.3	35.9–99.6	40.0	22.7–59.4	21.7	7.5–43.7	92.3	64.0–99.8	<0.001
LOS	GNB	38 (18.8)	202	240 (90.2)	266	84.2	68.7–94.0	11.6	7.1–17.5	18.1	12.7–24.6	76.0	54.9–90.6	<0.001
Only first-line antibiotics	GNB	3 (10.3)	29	36 (92.3)	39	100	29.2–100	11.5	2.5–30.2	11.5	2.5–30.2	100	29.2–100	<0.001
Only second-line antibiotics	GNB	4 (44.4)	9	14 (100)	14	100	39.8–100	0.0	0.0–52.2	44.4	13.7–78.8	Undef.	0.06	0.06

CI, confidence interval; GNB, Gram-negative bacteria; ESBL, extended-spectrum β -lactamase; EOS, early-onset sepsis; LOS, late-onset sepsis.**Table 3**

Concordance between Gram-negative bacteria isolates from blood and rectal sample pairs according to species and genus group.

Patient group	N	Species			Genus		
		Concordant pairs	Concordance (%)	95% CI	Concordant pairs	Concordance (%)	95% CI
All suspected sepsis	238	49	20.6	16.0–26.2	53	22.3	17.4–28.0
All EOS	36	14	38.8	24.8–55.1	14	38.8	24.8–55.1
All LOS	202	35	17.3	12.7–23.1	39	19.3	14.5–25.3
First-line antibiotic recipients	50	10	20.0	11.2–33.0	10	20.0	11.2–33.0
Second-line antibiotic recipients	130	28	21.5	15.3–29.4	32	24.6	18.0–32.7
Third-line antibiotic recipients	2	1	50.0 [~]	9.5–90.5	1	50.0	9.5–90.5

CI, confidence interval; EOS, early-onset sepsis; LOS, late-onset sepsis.

4. Discussion

The results from this study suggest that the concordance between rectal GNB isolates and blood GNB isolates in neonates with suspected sepsis is very low. As a consequence, the PPV for GNB isolates from rectal swabs for predicting confirmed BSIs (and the implicated bacterial pathogen) is low in neonates in this low-resource setting of Port-au-Prince, Haiti. The low concordance and PPV applies both to neonates with suspected EOS and LOS and is not dependent on the MDR profile of the isolated bacteria.

Our findings are in line with those from a recent meta-analysis where it was shown that only 7.9% of diagnosed BSIs were concordant with gut or rectal colonisation results [17]. However, they contrast with findings from the USA where Smith et al. found that 98% of BSIs caused by GNB were preceded by gastrointestinal colonisation of the same species from weekly surveillance rectal swabs [14]. It is unlikely that surveillance and microbiological diagnostics in low-resources settings such as Haiti would achieve similar results as in the USA as the yield on blood cultures from neonates are likely to be lower.

The management and diagnosis of neonatal sepsis is a challenge for numerous reasons. Neonatal sepsis is very non-specific in its clinical presentation and multiple conditions will mimic the signs and symptoms of sepsis [10,23]. Furthermore, use of blood culture for the diagnosis of confirmed BSIs has several limitations. These include the low positivity rate in neonatal blood cultures [10] and the time required to receive the final microbiological results (not considering the additional delay from microbiological laboratories not working on weekends in low-resource settings). A combination of factors means that clinicians have little reliable information to aid them in deciding to (de)-escalate antibiotic therapy in neonates with suspected (ongoing) sepsis. Our study showed that the NPV of rectal swab isolates was >75% in all patient groups included in the

study and 92.6% for ESBL-positive GNB. This finding suggests that in a context where simultaneous rectal swabs are being taken for surveillance purposes (i.e. during a context of repeated outbreaks of MDR-GNB), clinicians can use the results from rectal swabs (that arrive sooner than blood culture results) together with other clinical parameters to decide not to escalate antibiotic therapy in those neonates that have an ongoing sepsis profile. Thus, enhanced rectal swab surveillance can improve the antibiotic choice. It should be noted that most neonates will become colonised with GNB within 1 week after their birth, thus the true added value of rectal swab surveillance for antibiotic stewardship might be reduced after this period. A recent study in Spain showed that neonatal colonisation with ESBL-producing Enterobacteriaceae was associated with maternal vaginal colonisation with the same organism [24]. Use of vaginal colonisation surveillance in the identification and early treatment of neonatal sepsis could also be further investigated in low- and middle-resource countries.

The main limitation of this study is that it is based on opportunistic analysis of surveillance and clinical microbiological analyses. The data collection was therefore not established with the intention of conducting this study, thus the sample size is small. Also, it should be noted that the data used for the study were collected in a low-resource setting, which might have contributed to suboptimal biological sample collection, transport and reporting. Moreover, true concordance for bacterial isolates can only be established through molecular typing (such as whole-genome sequencing), thus our results only provide a suggestion to explore this in more detail with more advanced methods. Finally, the proportion of *K. oxytoca* isolates producing ESBL was higher than expected in this context. It is possible that this is due to the overproduction of K1 β -lactamase by these isolates [25], however we were unable to confirm this with additional laboratory testing.

In conclusion, rectal screening swabs during outbreaks in NCUs might contribute to improved de-escalation practices in antibiotic treatment, particularly for ESBL-positive GNB. We recommend that these findings are validated in a prospective manner in other neonatal care settings with larger sample sizes. This will allow to evaluate the more practical implications of such surveillance (delay in results etc.) and would allow for accurate documentation of the clinical impact of using rectal swab surveillance to inform antibiotic treatment in neonates.

Availability of data and materials

MSF has a managed access system for data sharing. Data are available on request in accordance with MSF's data sharing policy. Requests for access to data should be made to data.sharing@msf.org. For more information, please see: 1. MSF's Data Sharing Policy: <http://fieldresearch.msf.org/msf/handle/10.144/306,501>; and 2. MSF's Data Sharing Policy PLoS Medicine article: <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001562>.

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Conflict of interests

None declared.

Ethical approval

This study was approved by the National Bioethical Committee of the Ministry of Public Health and Population of Haiti. The study was exempt from approval of the MSF Ethical Review Board as it pertained to routinely collected data. All analysed data were de-identified.

References

- [1] Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. *Lancet Respir Med* 2018;6:223–30.
- [2] Folgori L, Bielicki J. Future challenges in pediatric and neonatal sepsis: emerging pathogens and antimicrobial resistance. *J Pediatr Intensive Care* 2019;8:17–24.
- [3] Zaidi AKM, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005;365:1175–88.
- [4] Plunkett A, Tong J. Sepsis in children. *BMJ* 2015;350:h3017.
- [5] Folgori L, Ellis SJ, Bielicki JA, Heath PT, Sharland M, Balasegaram M. Tackling antimicrobial resistance in neonatal sepsis. *Lancet Glob Health* 2017;5:e1066–8.
- [6] Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics—systematic review and meta-analysis. *Arch Dis Child* 2013;98:146–54.
- [7] Stapleton PJM, Murphy M, McCallion N, Brennan M, Cunney R, Drew RJ. Outbreaks of extended spectrum β -lactamase-producing Enterobacteriaceae in neonatal intensive care units: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F72–8.
- [8] Lenglet A, Faniyan O, Hopman J. A nosocomial outbreak of clinical sepsis in a neonatal care unit (NCU) in Port-au-Prince Haiti, July 2014–September 2015. *PLoS Curr* 2018;10;. doi:<http://dx.doi.org/10.1371/currents.outbreaks.58723332ec0de952adef9a9b6905932>.
- [9] Thaver D, Zaidi AKM. Burden of neonatal infections in developing countries. *Pediatr Infect Dis J* 2009;28(Suppl):S3–9.
- [10] Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. *Pediatr Clin North Am* 2013;60:367–89.
- [11] Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:417–32.
- [12] Deen J, von Seidlein L, Andersen F, Elle N, White NJ, Lubell Y. Community-acquired bacterial bloodstream infections in developing countries in South and Southeast Asia: a systematic review. *Lancet Infect Dis* 2012;12:480–7.
- [13] Lochan H, Pillay V, Bamford C, Nuttall J, Eley B. Bloodstream infections at a tertiary level paediatric hospital in South Africa. *BMC Infect Dis* 2017;17:750.
- [14] Smith A, Saiman L, Zhou J, Della-Latta P, Jia H, Graham PL. Concordance of gastrointestinal tract colonization and subsequent bloodstream infections with Gram-negative bacilli in very low birthweight infants in the neonatal intensive care unit. *Pediatr Infect Dis J* 2010;29:831–5.
- [15] Basu S. Neonatal sepsis: the gut connection. *Eur J Clin Microbiol Infect Dis* 2015;34:215–22.
- [16] Das P, Singh AK, Pal T, Dasgupta S, Ramamurthy T, Basu S. Colonization of the gut with Gram-negative bacilli, its association with neonatal sepsis and its clinical relevance in a developing country. *J Med Microbiol* 2011;60:1651–60.
- [17] Folgori L, Tersigni C, Hsia Y, Kortsalioudaki C, Heath P, Sharland M, et al. The relationship between Gram-negative colonization and bloodstream infections in neonates: a systematic review and meta-analysis. *Clin Microbiol Infect* 2018;24:251–7.
- [18] Harder T, Seidel J, Eckmanns T, Weiss B, Haller S. Predicting late-onset sepsis by routine neonatal screening for colonisation by Gram-negative bacteria in neonates at intensive care units: a protocol for a systematic review. *BMJ Open* 2017;7:e014986.
- [19] Comité de l'Antibiogramme de la Société Française Microbiologie (CA-SFM). 2013.
- [20] Hossain B, Islam MS, Rahman A, Marzan M, Rafiqullah I, Connor NE, et al. Understanding bacterial isolates in blood culture and approaches used to define bacteria as contaminants: a literature review. *Pediatr Infect Dis J* 2016;35(5 Suppl 1):S45–51.
- [21] Brown LD, Cai TT, Das Gupta A. Interval estimation for a binomial proportion. *Stat Sci* 2001;16:101–17.
- [22] European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. EUCAST. 2019.
- [23] Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. *J Trop Pediatr* 2015;61:1–13.
- [24] Jiménez-Rámila C, López-Cerero L, Aguilar Martín MV, Vera Martín C, Serrano L, Pascual A, et al. Vagino-rectal colonization and maternal–neonatal transmission of Enterobacteriaceae producing extended-spectrum β -lactamases or carbapenemases: a cross-sectional study. *J Hosp Infect* 2019;101:167–74.
- [25] Potz NAC, Colman M, Warner M, Reynolds R, Livermore DM. False-positive extended-spectrum β -lactamase tests for *Klebsiella oxytoca* strains hyper-producing K1 β -lactamase. *J Antimicrob Chemother* 2004;53:545–7.