Sepsis in previously healthy neonates discharged home after delivery in Soweto, South Africa

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Background. There is a paucity of data on the aetiology of neonatal sepsis in sub-Saharan Africa.
Objectives. To investigate the incidence, aetiology and outcomes of physician-diagnosed sepsis in hospitalised neonates who had previously been discharged home after delivery in Soweto, South Africa.
Methods. A retrospective review using data abstracted from clinical and laboratory databases identified physician-diagnosed sepsis cases in neonates admitted to the general paediatric wards at Chris Hani Baragwanath Academic Hospital from January 2015 to September 2016. Neonates with physician-diagnosed sepsis were categorised into two groups based on putative pathogens recovered from blood and/or cerebrospinal fluid specimens: (*i*) culture-confirmed sepsis; and (*ii*) culture-negative sepsis.
Results. Of 1 826 neonatal admissions, 1 025 (56.2%) had physician-diagnosed sepsis: 166 (16.2%) with culture-confirmed sepsis and 859 (83.8%) with culture-negative neonatal sepsis. The commonest pathogens causing culture-confirmed neonatal sepsis were *Streptococcus viridans* (*n*=53; 26.5%), *S. agalactiae* (*n*=38; 19.0%), and *Staphylococcus aureus* (*n*=25; 12.5%). The case fatality rates for culture-confirmed sepsis and culture-negative sepsis were 10.8% (18/166) and 2.6% (22/859), respectively. The odds of death occurring during hospitalisation was 10-fold (95% confidence interval 3.7 - 26.9) higher in neonates with culture-confirmed sepsis compared with culture-negative sepsis.
Conclusions. In our setting, physician-diagnosed sepsis represents a huge disease burden in previously healthy neonates hospitalised from home. Most sepsis cases were attributed to *S. viridans*, *S. agalactiae* and *S. aureus*.

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Approximately 45% of all under-5 childhood deaths occur during the neonatal period (i.e. the first 28 days of life). In neonates, sepsis, complications of prematurity and asphyxia are the major underlying causes of death.[1] To reduce neonatal mortality, specific interventions are dependent on adequate characterisation of the causes of neonatal sepsis. Nevertheless, there are limited data on the aetiology of neonatal sepsis from sub-Saharan Africa, although neonatal deaths account for ~50% of all under-5 childhood deaths.[1,2]

In South Africa (SA), the number of neonatal infections caused by multidrug-resistant pathogens is increasing,[3] as in India.[4] At our institution, Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, sepsis due to drug-resistant hospital-acquired pathogens is the immediate cause of death in 63% of neonates born preterm who remain in hospital after delivery.[5] However, there are limited data on the aetiology of neonatal sepsis in healthy, mainly term neonates who are discharged home after delivery and are subsequently readmitted during the first month of life.

Objectives

We undertook a retrospective, descriptive study to characterise the prevalence and aetiology of sepsis in hospitalised neonates who had previously been discharged home after delivery.

Methods

Study design

A retrospective, descriptive study was undertaken of neonates (≤28 days of age) admitted to general paediatric wards at CHBAH from 1 January 2015 to 30 September 2016. Anonymised demographic information and the primary discharge diagnosis were abstracted from a paediatric database maintained by the Respiratory and Meningeal Pathogens Research Unit (RMPRU).[6] For all neonatal admissions, the relevant laboratory data, including the results of microbial cultures from submitted blood and cerebrospinal fluid (CSF), were obtained from the National Health Laboratory Service (NHLS) TrakCare system.

Study population

The general paediatric wards at CHBAH serve the community of Soweto (a periurban township in Johannesburg) and surrounding communities. The live-birth cohort is ~30 000 births per annum, with ~70% of deliveries at CHBAH and ~30% at surrounding midwife-operated units.[7] Neonates born vaginally or via caesarean section at these health facilities are either admitted immediately after delivery (usually for complications related to prematurity, sepsis or asphyxia) or, if healthy, discharged home after a period of observation

(usually 6 - 72 hours). If these previously healthy neonates require subsequent hospitalisation for suspected infection, they are admitted to the general paediatric wards at CHBAH. There is also a low threshold for referring neonates who present directly to the primary healthcare clinics with suspected illness to CHBAH for further assessment. To be certain, the neonates analysed in this study were discharged home directly from the delivery suite, and not admitted to any hospital ward such as the neonatal wards or kangaroo mother care wards immediately after birth, before the current admission under review. We included healthy neonates delivered by caesarean section who stayed with their mothers in the postnatal wards until the mother was discharged home. At CHBAH, blood and CSF samples are routinely obtained from neonates admitted for suspected infection. HIV exposure and infection in neonates are determined by HIV enzyme-linked immunosorbent assay results in their mothers and neonatal HIV DNA polymerase chain reaction (PCR) results. The prevalence of HIV infection in pregnant women in this setting is ~30%.[8]

Study definitions and terms

Physicians at CHBAH use the following clinical symptoms and/or signs to diagnose sepsis in neonates: fever, hypothermia, poor feeding or not feeding, lethargy, apnoea, seizures, fast breathing, and chest in-drawing.[9] We stratified neonates with physician-diagnosed sepsis into two groups: (*i*) culture-confirmed neonatal sepsis; and (*ii*) culture-negative neonatal sepsis. Culture-confirmed neonatal sepsis was defined as culture of a putative pathogen from blood and/or CSF in neonates ≤28 days of age who were admitted directly from home following discharge from the healthcare facility where they were delivered. Neonates diagnosed with nosocomial infection were not included in the case definition above.

Isolates were regarded as pathogenic based on information summarised in *Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant*.[10,11] The following microbes were regarded as contaminant (i.e. clinically non-significant) isolates: *Bacillus* species, *Brevundimonas vesicularis*, coagulase-negative staphylococci, *Corynebacterium* species, *Micrococcus* species, *Ochrobactrum anthropi*, *Pseudomonas luteola*, *Pseudomonas stutzeri* and streptococcal species.[12,13] Polymicrobial infection was defined as the recovery of ≥2 pathogens from one or both of the following normally sterile sites: blood and/or CSF.[5]

HIV infection in neonates was based on an HIV-1 DNA PCR result, and neonates were considered to be HIV exposed but uninfected (HEU) if the neonate's DNA PCR result was negative and the mother was seropositive for HIV during pregnancy.

Statistical analysis

Descriptive statistical analyses were undertaken. Medians were compared using the Mann-Whitney *U*-test and categorical variables were compared using the χ^2 test or Fisher's exact test. The following variables were abstracted from the RMPRU database: gender, age, HIV status, length of stay, weight, length and final outcome. A multivariable regression analysis, using all the variables mentioned above, was done to compare clinical characteristics and outcomes between neonates with culture-confirmed sepsis and those with culture-negative sepsis. Statistical analyses were undertaken using Stata version 13.0 (StataCorp, USA).

Ethical considerations

Ethical permission for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M161115). A waiver for parental consent was granted for anonymised retrospective studies.

Results

During the study period, 10 249 children were admitted to general paediatric wards at CHBAH, including 1 826 neonates (17.8%). Of these neonates, 1 025 (56.1%) had physician-diagnosed sepsis: of these 166 (16.2%) had culture-confirmed sepsis and 859 (83.8%) had culture-negative sepsis (Table 1). Neonates diagnosed with culture-confirmed sepsis were younger (median (interquartile range (IQR)) age 11 (6 - 18) days v. 14 (8 - 20) days; p=0.007) and were hospitalised

Table 1. Comparison of clinical characteristics and outcomes in neonates with culture-confirmed sepsis and culture-negative sepsis who were admitted from home to Chris Hani Baragwanath Academic Hospital

Characteristics	Culture-confirmed sepsis (*N*=166)	Culture-negative sepsis (*N*=859)	Adjusted OR (95% CI)	*p*-value
Male gender, *n* (%)	100 (60.2)	467 (54.4)	0.65 (0.42 - 1.01)	0.056
Age (days), median (IQR)	11 (6 - 18)	14 (8 - 20)	0.96 (0.93 - 0.99)	0.007
HIV status, *n* (%)			0.88 (0.64 - 1.22)	0.446
Infected	0	7 (0.8)		
Exposed	52 (31.3)	239 (27.8)		
Unexposed	97 (58.4)	539 (62.8)		
Unknown	17 (10.2)	74 (8.6)		
Length of stay (days), median (IQR)	7 (4 - 13)	5 (3 - 8)	1.09 (1.06 - 1.13)	<0.001
Weight (g), median (IQR)	*n*=148	*n*=54	0.93 (0.71 - 1.22)	0.598
	3 000 (2 700 - 3 500)	3 300 (2 900 - 3 700)		
Length (cm), median (IQR)	*n*=111	*n*=594	0.99 (0.99 - 1.01)	0.753
	50 (48 - 53)	50 (48 - 53)		
Final outcome, *n* (%)*			10.02 (3.73 - 26.89)	<0.001
Death	18 (10.8)	22 (2.6)		
Discharged home	140 (84.3)	804 (93.6)		
Transfer to other hospital	7 (4.2)	33 (3.8)		
Refused treatment	1 (0.6)	0		

OR = odds ratio; CI = confidence interval; IQR = interquartile range.
*Death was compared with a composite outcome comprising discharge home, transfer to other hospital and refused hospital treatment.

for a longer time (7 (4 - 13) days v. 5 (3 - 8) days; $p<0.001$) than those with culture-negative sepsis (Table 1).

A total of 200 putative pathogens were isolated from 166 neonates with culture-confirmed sepsis. This included identification of a single pathogen from either blood or CSF in 135 neonates (81.3%) and from both blood and CSF in 14 (8.4%) (Table 2). Polymicrobial sepsis occurred in 10.2% of culture-confirmed cases, which included ≥2 pathogens isolated from either blood or CSF in 16 neonates (9.6%), and ≥2 pathogens from both blood and CSF in 1 neonate (0.6%). Overall, the commonest pathogens from culture-confirmed sepsis cases were *Streptococcus viridans* (*n*=53; 26.5%), *S. agalactiae* (*n*=38; 19.0%), *Staphylococcus aureus* (*n*=25; 12.5%) and *Escherichia coli* (*n*=20; 10.0%) (Fig. 1). *Klebsiella pneumoniae* (*n*=7; 3.5%), *Acinetobacter baumannii* (*n*=3; 1.5%) and methicillin-resistant *S. aureus* (*n*=1; 0.5%) accounted for 5.5% of all isolates. The commonest putative pathogens isolated from blood were *S. viridans* (*n*=46; 34.1%), *S. aureus* (*n*=24; 17.8%) and *S. agalactiae* (*n*=22; 16.3%). On CSF, *S. agalactiae* (*n*=16; 24.6%), *Enterococcus faecium*

Table 2. Site and nature of pathogen recovery from neonates admitted from home to Chris Hani Baragwanath Academic Hospital

Single v. multiple pathogens	Blood, *n* pathogens	CSF, *n* pathogens
A single pathogen isolated from either blood or CSF (*n*=135 neonates)	98	37
A single pathogen isolated from both blood and CSF (*n*=14 neonates)	14	14
≥2 pathogens isolated from either blood or CSF (*n*=16 neonates)	22	12
≥2 pathogens isolated from both blood and CSF (*n*=1 neonate)	1	2
Total	135	65

CSF = cerebrospinal fluid.

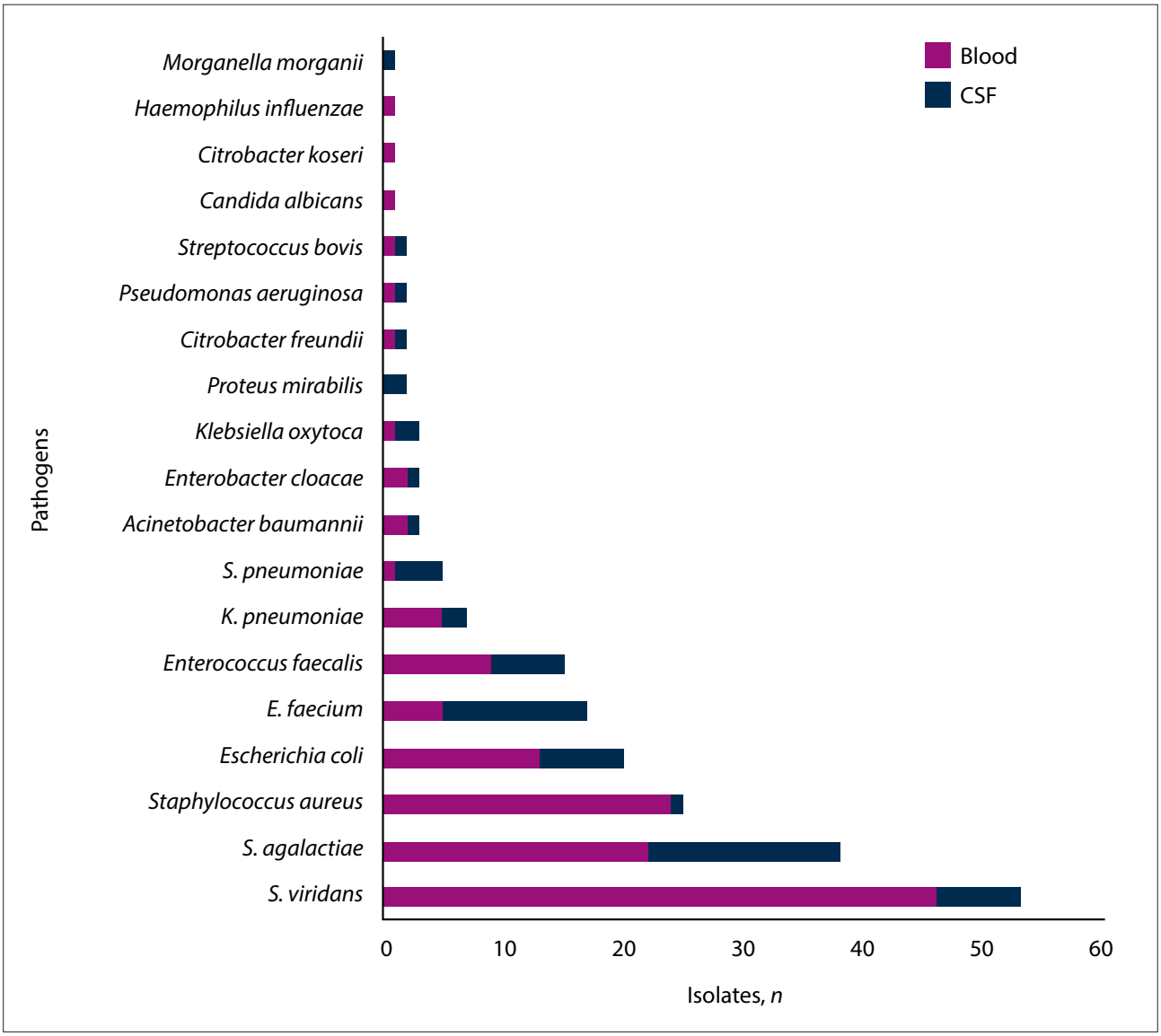

Fig. 1. Aetiology of neonatal sepsis, stratified by culture site, in neonates admitted from home to the general paediatric wards at Chris Hani Baragwanath Academic Hospital from 1 January 2015 to 30 September 2016. (CSF = cerebrospinal fluid.)

(*n*=12; 18.5%), *E. coli* (*n*=7; 10.8%), *E. faecalis* (*n*=7; 10.8%) and *S. viridans* (*n*=7; 10.8%) were the commonest organisms cultured. Probable contaminants were identified in 380 cases investigated for sepsis, including 274 from blood and 106 from CSF (Table 3).

Of the 53 *S. viridans* isolates, antimicrobial sensitivities were reported in 3 cases (5.7%) only; these isolates were sensitive to penicillin. All the *S. agalactiae* and 23 of 25 (92.0%) of *S. aureus* isolates were sensitive to penicillin and cloxacillin/flucloxacillin, respectively. Two *S. aureus* isolates (8.0%) were methicillin resistant. Antimicrobial sensitivities were reported in 18 (90.0%) of 20 *E. coli* isolates: all isolates were sensitive to cefotaxime and ceftriaxone and resistant to ampicillin. Regarding *E. faecium*, antimicrobial sensitivities were reported in 11 (64.7%) of 17 isolates: 2 were sensitive to ampicillin and all were sensitive to vancomycin. Antimicrobial sensitivities were reported in 12 (80.0%) of 15 *E. faecalis* isolates: all were sensitive to ampicillin. Regarding multidrug-resistant pathogens, all *A. baumannii* isolates (*n*=3) were sensitive to ceftazidime; 2 were also sensitive to piperacillin-tazobactam, while meropenem resistance was reported in 1 isolate. All 7 *K. pneumoniae* isolates were resistant to ampicillin; a further 2 were also resistant to cefotaxime and ceftriaxone but sensitive to carbapenems.

HIV exposure was documented in 1 605 (87.9%) of 1 826 neonates: 11 (0.6%) were HIV-infected, 372 (20.4%) were HEU, and 1 222 (66.9%) were HIV unexposed (HU). Among 149 neonates with culture-confirmed sepsis and known HIV status, 52 (34.9%) and 97 (65.1%) were HEU and HU, respectively; HEU neonates were admitted at an older age (median 12 v. 10 days; *p*=0.007) (Table 4).

For all 1 826 admitted neonates, the overall case fatality rate (CFR) was 2.7% (*n*=50). The CFR for neonates with culture-confirmed sepsis and culture-negative sepsis was 10.8% and 2.6%, respectively (Table 1). HEU compared with HU neonates had higher death rates (25.0% v. 4.1%; *p*=0.001) (Table 4). Neonates with culture-confirmed sepsis had a 10 times (95% confidence interval 3.7 - 26.9) higher odds of death compared with culture-negative sepsis cases. Nineteen pathogens were isolated from 18 neonates with culture-confirmed sepsis who died during hospitalisation. The commonest pathogens in these neonates were *S. agalactiae* (*n*=8; 42.1%), *E. coli* (*n*=3; 15.7% and *S. pneumoniae* (*n*=2; 10.5%).

Discussion

Our study shows that physician-diagnosed sepsis (either culture confirmed or culture negative) accounted for just over half (56.1%) of neonates admitted from home to the general paediatric wards at CHBAH. Neonates with culture-confirmed sepsis had a significantly longer duration of hospitalisation and higher mortality rates.

The commonest pathogenic isolates were *S. viridans*, *S. agalactiae* and *S. aureus*. Polymicrobial infection was documented in ~10% of culture-confirmed neonatal sepsis cases. Pathogens that typically cause nosocomial infection were relatively uncommon causes of culture-confirmed neonatal sepsis during the study period, and there was one neonate with a carbapenem-resistant isolate. Nonetheless, their emergence as pathogens causing neonatal sepsis is concerning and warrants ongoing surveillance. Our results are mainly consistent with the data obtained from a recent meta-analysis describing the

Table 3. Contaminant isolates recovered from neonates admitted from home to Chris Hani Baragwanath Academic Hospital

	Blood, *n* isolates	CSF, *n* isolates	Total, *n* isolates
Bacillus species	15	12	27
Brevundimonas vesicularis	1	0	1
Coagulase-negative staphylococcus	229	91	320
Corynebacterium species	14	0	14
Micrococcus species	13	0	13
Ochrobactrum anthropi	1	1	2
Pseudomonas luteola	1	0	1
P. stutzeri	0	1	1
Streptococcal species	0	1	1
Total	274	106	380

CSF = cerebrospinal fluid.

Table 4. Clinical characteristics and outcomes in HEU and HU neonates with culture-confirmed sepsis

	HEU (*N*=52)	HU (*N*=97)	*p*-value*
Male gender, *n* (%)	38 (73.1)	54 (55.7)	0.037
Age (days), median (IQR)	12 (9 -22)	10 (5 -16)	0.007
Length of stay (days), median (IQR)	8 (4 - 16)	7 (4 - 12)	0.785
Weight (g), median (IQR)	*n*=48	*n*=90	0.245
	2 900 (2 300 - 3 500)	3 000 (2 800 - 3 500)	
Length (cm), median (IQR)	*n*=39	*n*=66	0.458
	50 (47 - 52)	50 (48 - 53)	
Final outcome, *n* (%)			0.001
Discharged home	36 (69.2)	88 (90.7)	
Transfer to other hospital	3 (5.8)	4 (4.1)	
Refused treatment	0	1 (1.0)	
Death	13 (25.0)	4 (4.1)	

HEU = HIV exposed but uninfected; HU = HIV unexposed; IQR = interquartile range.
*Medians were compared using the Mann-Whitney *U*-test and categorical variables were compared using the χ^2 test or Fisher's exact test.

aetiological burden of neonatal infections in sub-Saharan Africa.[1] In our setting, the pathogen responsible for most deaths in neonates with sepsis was *S. agalactiae*,[14] and this finding affirms the importance of much-needed group B streptococcus (GBS) vaccination trials in our region. In contrast, in South Asia, most neonatal infections are caused by Gram-negative pathogens, while a minority of infections are caused by GBS,[15,16] highlighting the need to conduct regular aetiological surveys to determine the cause of neonatal sepsis in different geographical regions.

Antimicrobial sensitivities were reported independently by the microbiologists at the NHLS. Common Gram-positive organisms (such as *S. agalactiae* and *S. aureus*) were sensitive to first-line antibiotics. All *E. coli* and *K. pneumoniae* isolates were resistant to ampicillin, but most (92%) were sensitive to third-generation cephalosporins; sensitivities to aminoglycosides were not reported by the laboratory. In future, routine antimicrobial sensitivities to aminoglycosides should be reported at our institution if ampicillin and gentamicin/amikacin are to be used as first-line antimicrobials for physician-diagnosed neonatal sepsis.

Our study highlights an association between culture-confirmed neonatal sepsis and HIV exposure, and shows a significantly increased mortality risk in neonates with culture-confirmed sepsis who are HEU; this finding suggests that HIV exposure is an important risk factor for increased neonatal mortality in our setting. GBS was the commonest pathogen isolated (38.5%) from HEU neonates with culture-confirmed sepsis who died during hospitalisation, and this is in keeping with the increased risk of GBS disease described in HEU neonates.[17]

Study limitations

This study has several limitations. In neonates who are admitted from home, most cases of physician-diagnosed sepsis were culture negative. This category probably consists of a heterogeneous group of neonates, including some with true sepsis who remained undetected because of sterile or contaminant blood and/or CSF cultures. Contaminant isolates were recovered from the majority of blood and CSF specimens, and continued efforts are required to minimise this problem. The role of *S. viridans* as an established neonatal pathogen is not universally accepted, even at our institution, and antimicrobial sensitivities were not reported by the microbiologists in the vast majority of cases. If *S. viridans* is disregarded as an established pathogen, then other Gram-negative pathogens such as *E. coli*, *E. faecium* and *E. faecalis* would be the commonest pathogens after *S. agalactiae* and *S. aureus*. In this study, we had *a priori* considered *S. viridans* as a possible neonatal pathogen, based on the recommendations advised by *Remington and Klein*[10] and Simonsen *et al.*;[11] however, we acknowledge that other authorities consider *S. viridans* to be a contaminant.[13] Another study limitation is that we have not considered the role of viral infections, such as those caused by herpex simplex virus, enteroviruses and parechoviruses, which can cause a sepsis-like syndrome.[11] The retrospective study design based on information obtained from discharge summaries may contain classification biases. The study has missing data, especially with regard to anthropometric data and the final HIV status of the neonates, and it is likely that the discharge summaries did not include information about failed attempts to obtain CSF samples from neonates. We did not collect information on drug sensitivities for the microbial agents causing sepsis. To mitigate against some of these limitations, we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for reporting retrospective studies,[18] and independently verified all culture results and the final neonatal HIV status on our institution's laboratory database.

Conclusions

Our study shows that physician-diagnosed sepsis represents a huge disease burden in neonates hospitalised from home. The study provides important and updated aetiological data regarding the causes of neonatal sepsis in Soweto, SA.

Declaration. The research for this study was done in partial fulfilment of the requirements for NSM's MMed (Paediatrics) degree at the University of the Witwatersrand.

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Author contributions. NSM, ZD and SGL conceptualised and designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. FS, AI and SAM were involved in data collection. SV and SAM contributed to the conception and design of the study. FS, AI, SAM and SV critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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1. Okomo U, Akpalu ENK, le Doare K, et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: A systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. Lancet Infect Dis 2019;19(11):1219-1234. https:doi.org/10.1016/S1473-3099(19)30414-1
2. Molyneux EM, Dube Q, Banda FM, et al. The treatment of possible severe infection in infants: An open randomised safety trial of parenteral benzylpenicillin and gentamicin versus ceftriaxone in infants <60 days of age in Malawi. Pediatr Infect Dis J 2017;36(12):e328-e333. https://doi.org/10.1097/INF.0000000000001576
3. Velaphi SC, Westercamp M, Moleleki M, et al. Surveillance for incidence and etiology of early-onset neonatal sepsis in Soweto, South Africa. PloS ONE 2019;14(4):e0214077. https://doi.org/10.1371/journal.pone.0214077
4. Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: A cohort study. Lancet Glob Health 2016;4(10):e752-e760. https://doi.org/10.1016/S2214-109X(16)30148-6
5. Madhi SA, Pathirana J, Baillie V, et al. Unraveling specific causes of neonatal mortality using minimally invasive tissue sampling: An observational study. Clin Infect Dis 2019;69(Suppl_4):S351-S360. https://doi.org/10.1093/cid/ciz574
6. Singh S, Solomon F, Madhi SA, Dangor Z, Lala SG. An evaluation of the quality of discharge summaries from the general paediatric wards at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa. S Afr Med J 2018;108(11):953-956. https://doi.org/10.7196/SAMJ.2018.v108i11.12966
7. Buchmann EJ, Mnyani CN, Frank KA, Chersich MF, McIntyre JA. Declining maternal mortality in the face of persistently high HIV prevalence in a middle-income country. Br J Obstet Gynaecol 2015;122(2):220-227. https://doi.org/10.1111/1471-0528.13064
8. Barron P, Pillay Y, Doherty T, et al. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ 2013;91(1):70-74. https://doi.org/10.2471/BLT.12.106807
9. Seale AC, Blencowe H, Manu AA, et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: A systematic review and meta-analysis. Lancet Infect Dis 2014;14(8):731-741. https://doi.org/10.1016/S1473-3099(14)70804-7
10. Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Wilson C, Nizet V, Maldonado Y, Remington J, Klein J, eds. Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant. 8th ed. Philadelphia, Pa.: Elsevier, 2016:217-227.
11. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev 2014;27(1):21-47. https://doi.org/10.1128/CMR.00031-13
12. Bizzarro MJ, Shabanova V, Baltimore RS, et al. Neonatal sepsis 2004 - 2013: The rise and fall of coagulase-negative staphylococci. J Pediatr 2015;166(5):1193-1199. https://doi.org/10.1016/j.jpeds.2015.02.009
13. Dargère S, Cormier H, Verdon R. Contaminants in blood cultures: Importance, implications, interpretation and prevention. Clin Microbiol Infect 2018;24(9):964-969. https://doi.org/10.1016/j.cmi.2018.03.030
14. Dangor Z, Lala SG, Cutland CL, et al. Burden of invasive group B streptococcus disease and early neurological sequelae in South African infants. PloS ONE 2015;10(4):e0123014. https://doi.org/10.1371/journal.pone.0123014
15. Saha SK, Schrag SJ, El Arifeen S, et al. Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): An observational cohort study. Lancet 2018;392(10142):145-159. https://doi.org/10.1016/S0140-6736(18)31127-9
16. Chaurasia S, Sivanandan S, Agarwal R, Ellis S, Sharland M, Sankar MJ. Neonatal sepsis in South Asia: Huge burden and spiralling antimicrobial resistance. BMJ 2019;364:k5314. https://doi.org/10.1136/bmj.k5314
17. Cools P, van de Wijgert J, Jespers V, et al. Role of HIV exposure and infection in relation to neonatal GBS disease and rectovaginal GBS carriage: A systematic review and meta-analysis. Sci Rep 2017;7(1):13820. https://doi.org/10.1038/s41598-017-13218-1
18. Fitchett EJA, Seale AC, Vergnano S, et al. Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): An extension of the STROBE statement for neonatal infection research. Lancet Infect Dis 2016;16(10):e202-e213. https://doi.org/10.1016/S1473-3099(16)30082-2

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