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Characteristics and Outcomes of Neonates With Blood Stream Infection Due to *Listeria monocytogenes*

Nandi Ntuli, FC Paed, Jeannette Wadula, FC Path,† Firdose Nakwa, MMed, FC Paed,* Reenu Thomas, MMed, FC Paed,* Alison Van Kwawegen, FC Paed,* Letlhogonolo Sepeng, MMed, FC Paed,* Karabo Seake, MMed, FC Paed,* Dikeledi Kgwadi, FC Paed,* Lino Sono, FC Paed,* Claude Ondongo-Ezhet, MMed, FC Paed,* and Sithembiso Velaphi, FC Paed, PhD**

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Background: Infection due to *Listeria monocytogenes* (LM) is rare in neonates; thus, its clinical presentation and outcomes are not commonly reported, especially in low- and middle-income countries. In 2017, South Africa had an outbreak due to LM.

Objective: To determine demographic characteristics, clinical and laboratory findings and outcomes of all neonates infected with LM during the outbreak period.

Methods: This is a retrospective analytic study. Clinical and laboratory records of neonates admitted at Chris Hani Baragwanath Academic Hospital from January 2017 to May 2018 with positive blood and cerebrospinal fluid culture with LM were reviewed for demographic characteristics, clinical presentation, ancillary laboratory test results and outcomes at hospital discharge.

Results: There were 42 neonates with positive cultures due to LM. Thirty-four (81%) were born preterm. Mode of delivery was vaginal in 78.6% and 31.0% were HIV exposed. All patients presented within the first 6 days of life as an early-onset disease. Common clinical presentation was respiratory depression (52.4%) and respiratory distress (38.1%) with 69% requiring invasive or noninvasive respiratory support. Common abnormal laboratory findings were high C-reactive protein (77.1%) followed by leukopenia (23.8%). Fourteen patients (40%) had features of meningitis based on blood and cerebrospinal fluid findings (4 culture proven). There were 11 deaths at hospital discharge, giving a mortality rate of 26.2%.

Conclusions: The majority of neonates infected with LM were born preterm, raising the possibility that LM itself may have been responsible for preterm labor. All presented in the first 6 days of life and most presented with respiratory distress or depression. A high proportion had meningitis, and there was a high-mortality overall.

Key Words: listeriosis, neonatal sepsis, outbreak

(*Pediatr Infect Dis J* 2021;40:917–921)

Listeriosis is a rare foodborne illness caused by *Listeria monocytogenes* (LM), a Gram-positive, nonspore forming, and facultative anaerobic bacteria, which grows between –0.4 and 45°C.[1,2] It is commonly due to 3 serotypes: 1a, 1b and 4b. Serotype 4b is responsible for almost all outbreaks of listeriosis.[3] The incubation period has not been well-established but is estimated to be 3 weeks.[4] LM infections have a predilection to affect immunocompromised patients, elderly people, pregnant women and neonates. In particular, pregnant women are 18–20 times more likely to be affected by this infection than the general population due to specific pregnancy-related suppressed cell-mediated immunity and placental tropism of LM.[5–7] Vertical transmission of the bacterium is the source of neonatal infection in most cases of LM. Neonatal cases of listeriosis are classified into early onset (0–6 days) and late onset (7–28 days) depending on the time of development of symptoms after birth. Two-thirds of infants born to mothers with listeriosis will develop the disease. The infants are often born preterm, and the mean postnatal age at onset of symptoms for early-onset disease is 1.5 days.[8,9] Clinical presentations of neonatal listeriosis include septicemia (81%–88%), respiratory distress or pneumonia (38%), meningitis (24%) and more rarely myocarditis and granulomatosis infantisepticum.[10–12] Neonatal disease and outcomes are often more severe in contrast to mild maternal disease. It has been reported that the annual incidence of listeriosis in the world is between 1 and 10 per million population.[13] In neonates, the incidence of listeriosis is reported to be approximately 8.6/100,000 live births and is associated with a high-mortality rate ranging from 20% to 60% despite adequate antimicrobial treatment.[14] The risk of death due to listeriosis in infants is inversely related to gestational age.[15]

Recently an outbreak of LM infection occurred countrywide in South Africa, with Gauteng being a leading province in the number of confirmed cases. This outbreak is believed to be the largest-ever outbreak of this bacterial disease in the world. During this outbreak, 39% of cases were neonates, with 96% presenting with early-onset disease.[16] The characteristics and outcome of neonates infected with LM from low- and middle-income countries are not well known. The aim of the study was to determine demographic characteristics, clinical and laboratory findings and mortality rates of neonates infected with LM admitted to a neonatal unit in a public tertiary hospital in Gauteng during the reported outbreak in South Africa.

PATIENTS AND STUDY METHODS

Study Design and Setting

This is a retrospective analytic study. It was conducted in the neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH), a public tertiary hospital situated in Soweto, Johannesburg, South Africa. The neonatal unit has a total of 185 beds, and it offers all levels of neonatal care. It caters for neonates requiring admission from approximately 20,000 and 8000 births conducted annually at the hospital (inborn) and local clinics, respectively, and for those requiring critical care from 3000 births from local district hospitals. After delivery, neonates born to mothers with obstetric risk factors (eg, preterm births, prolonged rupture of membranes, and presence of signs suggestive of chorioamnionitis), or neonates

Accepted for publication April 18, 2021
From the *School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; and †Department of Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand and National Health Laboratory Services, *Johannesburg, South Africa*.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Nandi Ntuli, FC Paed, Division of Neonatology, Department of Paediatrics, Metabolic Unit, Chris Hani Baragwanath Academic Hospital, P. O. Bertsham, Johannesburg 2013, South Africa. E-mail: Nandi.Ntuli@wits.ac.za.
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ISSN: 0891-3668/21/4010-0917
DOI: 10.1097/INF.0000000000003213

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with clinical signs suggestive of sepsis, have blood taken for full blood count with white cell differential count and blood culture. All neonates with suspected infections are started on parenteral antibiotics, ampicillin and gentamicin, soon after blood specimens have been taken for culture. In addition to the full blood count and blood cultures, blood for C-reactive protein (CRP) is taken 24–48 hours after birth. Cerebrospinal fluid is only taken if a neonate has neurologic signs in the absence of asphyxia or neurologic signs with high CRP or positive blood culture due to an organism considered to be a pathogen.

Study Population and Data Collection

All neonates admitted in the neonatal unit at CHBAH, with a positive blood and blood and cerebrospinal fluid (CSF) culture due to LM from January 1, 2017, to May 31, 2018, were included in the study. Data on maternal and infant demographic characteristics, clinical presentation, diagnosis and outcome at hospital discharge were retrieved from patients' medical records. Laboratory data on their hematologic parameters, C-reactive protein, cerebrospinal fluid, and on blood and CSF cultures were retrieved from National Health Laboratory Services' (NHLS) central data warehouse.

Definitions

Respiratory depression was defined as failure to initiate and maintain spontaneous breathing at birth requiring positive pressure ventilation and subsequent admission to the neonatal unit for observation. Respiratory distress was defined as tachypnea (respiratory rate >60 breaths per minute and chest retractions requiring supplemental oxygen). Neonatal leukocytosis was defined as a white cell count (WCC) $>30 \times 10^9$/L, leukopenia as a WCC $<5 \times 10^9$/L, thrombocytopenia as a platelet count $<100 \times 10^9$/L. C-reactive protein (CRP) levels of ≥10 mg/L were considered to be elevated. Cerebrospinal fluid with positive culture or pleocytosis (CSF WCC >20 cells/mm^3) or CSF protein >150 mg/dL was considered as meningitis.

Data Analysis

Data were entered into a Microsoft Excel spreadsheet, and statistical analysis was performed using Statistica. Descriptive summary of categorical variables is presented as frequencies and percentages, and that of continuous variables as means with standard deviation or medians with interquartile ranges depending on whether the data were normally distribution or not. Comparison was made between HIV-exposed and -unexposed neonates and between survivors and nonsurvivors. Comparison of categorical variables was performed using Fisher's exact test. Quantitative data were compared using either Student *t* test or Mann-Whitney *U* test. Differences with *P* values <0.05 were considered to be statistically significant for all analyses.

Ethical Approvals

Permission to access the microbiologic database and results of ancillary laboratory tests for sepsis was received from NHLS. Permission to conduct the study was attained from hospital management. Ethics approval was received from the University of the Witwatersrand, Human Resource Ethics Committee.

RESULTS

There were 42 neonates who had positive blood and CSF cultures with LM from January 1, 2017, to May 31, 2018, and of which 33 (78.6%) were inborn. There were 28,335 live birth at CHBAH during the same period giving an incidence of culture-proven sepsis due to LM at 1.16/1000 live births, almost a 23-fold increase from incidence of 0.05/1000 live births in 2016. There was a gradual increase in the number of patients with positive cultures for LM from 1 case per month in February 2017 to 6 cases per month in July and November 2017. This was followed by a gradual decrease to 1 case per month in April, with no case of positive culture reported in May 2018 (Fig. 1). Majority (95%) of neonates came from Soweto (83%) and surrounding areas (12%). The remainder (5%) came from outside Johannesburg but within Gauteng Province.

Eighty-eight percent were born to mothers who were of ages 20–35 years, 70.3% to mothers who were multiparous, and 31% were born to HIV-positive mothers (Table 1). Majority (78.6%) were born via normal vaginal delivery. All of the cases presented as early-onset disease, with 97.6% within the first 3 days and the remainder of the cases within 6 days of life, which indicates that the infection was acquired in-utero from the mother. The average gestational age and birth weights were 32 ± 4 weeks and 1855 ± 668 g, respectively, with 81% being born preterm. Seventy-one percent were male.

The most common clinical presentations at birth were respiratory depression (n = 26; 61.9%) and respiratory distress (n = 16; 38.1%) (Table 2). Cases with respiratory depression accounted for 11.7% of all neonates who had respiratory depression over the study period. All neonates required some form of respiratory support, such as nasal cannula oxygen in 31%, noninvasive ventilation (nasal continuous positive airway pressure) in 35.7% and invasive mechanical ventilation in 33.3%. One neonate (2.4%) presented with erythematous maculopapular rash, which was considered granulomatosis infantiseptica, and this neonate subsequently died from severe asphyxia and septic shock. Abnormal laboratory findings observed were leukopenia in 23.8%, thrombocytopenia in 7.1% and leukocytosis in 4.8% (Table 3). Among those with blood taken for CRP (n = 35), 34 (97.1%) had high CRP (CRP ≥10 mg/L) with 27 (77.1%) having a CRP >40 mg/L. Of the 35 patients who had a lumbar puncture done, 6/35 (17.1%) had high CSF cell count (cell count >20 cells/mm^3), 20/31 (64.5%) had high protein (protein >150 g/L) and 4/35 (11.4%) had LM isolated in CSF. Overall, 40% of patients had meningitis defined as culture-positive CSF for LM or a high CSF white cell or protein count.

There were no differences in demographic characteristics, clinical presentation, need for mechanical ventilation, laboratory findings and mortality between HIV-exposed and -unexposed neonates (Table 4). The all-cause mortality rate was 26%. The commonest cause of death seen in this study was severe asphyxia. In comparing survivors and nonsurvivors, there were no statistically significant differences in neonatal and maternal characteristics, clinical presentation and laboratory findings except for total WCC, in which more nonsurvivors than survivors had leukopenia (45.5% vs. 16.1%; *P* = 0.044) (Table 5).

DISCUSSION

Before 2017, LM was isolated in 2–3 cases per year at our hospital. With the recent outbreak of LM infection reported countrywide in South Africa,[17] the hospital noted an increase in the number of neonates with positive culture due to LM, ranging from 1 to 7 cases per month. In this study, we sought to describe the characteristics of neonates with listeriosis during the LM outbreak. The main findings in this study are that majority of neonates with LM infection are born preterm, present as an early-onset infection with respiratory depression or distress, have a high CRP and a high all-cause mortality rate of 26%.

Cell-mediated immunity is a major defense mechanism against LM and therefore those with T-cell dysfunction, for example, due to HIV infection, are considered to be at particularly high-risk of disease.[15] With South Africa having a higher prevalence of

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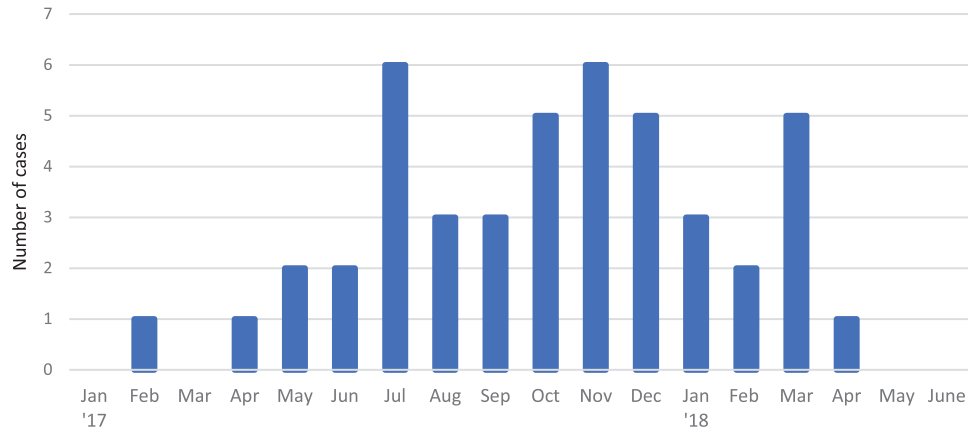


FIGURE 1. Monthly number of neonates with culture-positive infection due to *Listeria monocytogenes*. full color online

HIV infection in pregnant mothers, 1 expected that more neonates with LM would be born to HIV-positive mothers. This however was not the case as 31% of neonates were born to HIV-positive mothers, which is similar to the HIV prevalence rate of 30% in pregnant women in Gauteng.[18] This is most likely due to an increase in the number of HIV-positive pregnant women who are on antiretroviral therapy, thus decreasing the severity of immunosuppression, leading to a decrease in the incidence of AIDS as a predisposing factor for listeriosis.

It has also been reported that pregnancy-associated listeriosis commonly affects healthy women without predisposing conditions.[10,19] The risk of infection in pregnancy also varies depending on ethnicity, food consumption habits and socioeconomic status. This cohort of patients came from a poor socioeconomic background, with the most predominant age group being women of childbearing age, with 88% at 20–35 years of age. The food that was found to be the source of the outbreak was processed cold meat, which is commonly used as part of regular diet in Soweto and surrounding areas.[17]

The majority (81%) of neonates with infection were born preterm, supporting the concept that LM infection predisposes to preterm labor. This correlates with other studies that showed that preterm labor was common among pregnant women infected with LM.[10,20–23] All of the neonates presented as early-onset disease suggesting that the infection was acquired intrapartum as ascending

TABLE 1. Maternal and Infant Characteristics of Neonates With Positive Culture Due to *Listeria monocytogenes*

Characteristics	Number (%)
Maternal characteristics	
Maternal age (yrs)	
<20	2 (4.8)
20–35	37 (88.1)
>35	3 (7.1)
Primigravida	11 (29.7)
Antenatal care	33 (97.1)
Human immunodeficiency virus positive	13 (31.0)
Place of birth	
Inborn	33 (78.6)
Referrals	7 (16.7)
Home	2 (4.7)
Vaginal delivery	33 (78.6)
Infant characteristics	
Birth weight (g)	
Average	1855 ± 668*
<1000	3 (7.1)
1000–499	14 (33.3)
1500–2499	18 (42.9)
≥2500	7 (16.7)
Gestational age (wks)	
Average	32 ± 4*
<34	22 (52.4)
34–36	12 (28.6)
≥37	8 (19.0)
Male sex	30 (71.4)

*Mean ± standard deviation.

TABLE 2. Clinical Presentation, Diagnosis and Management of Neonates With Positive Culture Due to *Listeria monocytogenes*

Variables	Number (%)
Clinical presentation	
Respiratory depression	26 (61.9)
Respiratory distress	16 (38.1)
Clinical diagnosis	
Respiratory distress syndrome	12 (28.6)
Congenital pneumonia	14 (33.3)
Meconium aspiration syndrome	3 (7.1)
Neonatal encephalopathy	13 (31.0)
Respiratory support required	
Nasal cannula oxygen	13 (31.0)
Nasal continuous positive airway pressure	15 (35.7)
Conventional mechanical ventilation	14 (33.3)

TABLE 3. Laboratory Findings in Neonates With Positive Culture Because of *Listeria monocytogenes*

Laboratory Findings	Number (%)
WCC	
Leukopenia (WCC $<5 \times 10^9$/L)	10 (23.8)
Normal (WCC ≥5-30 $\times 10^9$/L)	30 (71.4)
Leukocytosis (WCC $>30 \times 10^9$/L)	2 (4.8)
Thrombocytopenia (platelet $<100 \times 10^9$/L)	3 (7.1)
C-reactive protein (n = 35)	
<10 mg/L	1 (2.9)
≥10–40 mg/L	7[20]
>40 mg/L	27 (77.1)
Cerebrospinal fluid	
Total WCC >20 cells/mm^3 (n = 35)	6 (17.1)
Protein >1.5 g/L (n = 31)	20 (64.5)

WCC indicates white cell count.

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TABLE 4. Comparing Characteristics, Presentation and Outcomes of Neonates Infected With *Listeria monocytogenes* According to the Human Immunodeficiency Virus Exposure

Characteristics	HIV Negative, N = 29	HIV Positive, N = 13	*P*
Vaginal delivery	21 (72.4)	12 (92.3)	0.146
Birth weight, in g			0.616
<1500	11 (37.9)	6 (46.2)	
≥1500	18 (62.1)	7 (53.8)	
Gestational age, in wks			0.899
<34	15 (51.7)	7 (53.8)	
≥34	14 (48.3)	6 (46.2)	
Male sex	21 (72.4)	9 (69.2)	0.833
Clinical presentation			0.513
Respiratory depression	17 (58.6)	9 (69.2)	
Respiratory distress	12 (41.4)	4 (30.8)	
Respiratory support			0.481
Not ventilated	8 (27.6)	5 (38.5)	
Ventilated	21 (72.4)	8 (61.5)	
White cell count			0.598
Normal (5–25 × 109/L)	20 (69.0)	10 (76.9)	
Abnormal (<5 or >25 × 109/L)	9 (31.0)	3 (23.1)	
C-reactive protein, in mg/L (n = 35)			0.674
≤40	5 (20.8)	3 (27.3)	
>40	19 (79.2)	8 (72.7)	
Died	6 (20.7)	5 (38.5)	0.226

infection or in-utero via transplacental spread from the mother. Early onset disease is associated with maternal sepsis and chorioamnionitis and may also result in abortions and stillbirths.[24] Most patients presented within the first day of life, with the onset of symptoms occurring within minutes to hours from delivery.

All of the patients in this cohort required respiratory support in the first few hours postnatally in the form of invasive mechanical ventilation, noninvasive respiratory support (NCPAP) or nasal cannula oxygen. This is because the commonest clinical presentation was involvement of the respiratory system with respiratory depression or distress requiring respiratory support in the form of positive pressure ventilation in 61.9% of patients at the time of delivery. In the study by McLauchlin et al,[10] involvement of the respiratory tract in the neonate together with prematurity, maternal fever and isolation of LM from maternal sites was a common feature of the early onset disease.

Granulomatosis infantiseptica are pathognomonic pustular skin lesions that are characteristic of severe neonatal infection.[12,25,26] This characteristic rash is associated with a mortality rate of more than 80% and distinguishes listeriosis from other bacterial infections, thus it may facilitate early diagnosis. These maculopapular or papulovesicular skin lesions are usually seen on the trunk or extremities. Skin lesions were observed in only 1 neonate (2.4%) in this cohort, who subsequently demised shortly after admission from severe asphyxia and septic shock.

Elevated CRP was a striking feature of the laboratory results in this neonatal cohort with 34/35 (97%) with CRP >10 mg/dL and 27/35 (77%) with CRP >40 mg/dL. This is similar to findings from

TABLE 5. Comparison of Maternal and Infant Characteristics, and Laboratory Findings Between Survivors and Nonsurvivors

	Survivors, N = 31, n (%)	Nonsurvivors, N = 11, n (%)	*P*
Maternal and infant characteristics			
Vaginal delivery	23 (74.2)	10 (90.9)	0.423
Birth weight, in g			0.399
<1500	12 (38,6)	5 (45.4)	
≥1500	19 (61.4)	6 (44.5)	
Gestational age, in wks			0.271
<37	25 (80.6)	9 (81.7)	
≥37	6 (19.4)	2 (18.2)	
Male, sex	22 (71.0)	8 (72.7)	0.943
Clinical presentation			0.324
Respiratory depression	18 (58.1)	8 (72.7)	
Respiratory distress	13 (41.9)	3 (27.3)	
Diagnosis on admission			0.637
Respiratory distress syndrome	8 (25.8)	4 (36.4)	
Congenital pneumonia	13 (41.9)	1 (9.1)	
Meconium aspiration syndrome	2 (6.5)	1 (9.1)	
Neonatal encephalopathy	8 (25.8)	5 (45.4)	
Respiratory support			0.126
Nasal prong oxygen	10 (32.3)	3 (27.3)	
Nasal continuous airway pressure	14 (45.2)	1 (9.1)	
Conventional mechanical ventilation	7 (22.6)	7 (63.6)	
Laboratory findings			
WCC			0.044
Leukopenia (WCC < 5 × 10^9/L)	5 (16.1)	5 (45.5)	
Normal (WCC 5–30 × 10^9/L)	24 (77.4)	6 (54.5)	
Leukocytosis (WCC >30 × 10^9/L)	2 (6.5)	0 (0)	
Thrombocytopenia platelet count (<100 × 10^9/L)	2 (6.5)	1 (9.1)	0.798
C-reactive peptide, in mg/L			0.569
<10	1 (3.4)	0 (0)	
≥10–40	5 (17.2	2 (33.3)	
>40	23 (79.3)	4 (66.7)	
Cerebrospinal fluid cell count >20 cells/mm^3	6 (20.7)	0 (0)	0.241
Cerebrospinal fluid protein >1.5 g/L	14 (56)	6 (100)	0.104

WCC indicates white cell count.

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a hospital-based study from Taiwan by Tai et al,[27] where 92% of their patients had an elevated CRP (>10 mg/L). Most of their neonates (77%) had leukocytosis or leukopenia and 77% had thrombocytopenia. Leukocytosis was also a predominant feature in a case report from Taiwan by Shih-Yu Chen et al.[28] This infection appears to trigger a strong inflammatory response. This is most likely the reason why many patients were born preterm, as the in-utero infection could have triggered an inflammatory response in the mother, which led to preterm dilatation of the cervix.

Neonatal meningitis is a typical feature of "late-onset" neonatal listeriosis. All patients in this study had early-onset disease. Of those who had a lumbar puncture, 40% had meningitis, defined as culture-positive CSF for LM or a high CSF white cell or protein count. Only 11% had culture-positive LM meningitis. This is most likely an underestimate as not all patients with possible infection had LP done. Previous articles on analysis of CSF in patients with listeriosis indicated that the CSF may show a negative Gram stain, with an increase in WCC and protein.[24] This high number of neonates who had meningitis might be associated with abnormal neurodevelopmental outcome, therefore highlighting the need for long-term follow up of these neonates.

Mortality rate in this study was 26%, similar to that observed in another tertiary hospital in South Africa during the similar outbreak.[9] Listeriosis is known to have an average case-fatality rate of 20%–30% despite adequate antimicrobial treatment. The frequency of abortion and stillbirth increases the overall mortality rate to >50%,[24] although this was not looked at in this study. The risk of death due to listeriosis in an infant is inversely related to gestational age.[15,24] This was also shown in the MONALISA study, where the risk of fetal death due to listeriosis was minimal when the infection occurred after 29 weeks gestation.[23]

The strength of this study was the use of laboratory-confirmed cases of LM. One of the limitations is the retrospective nature of the study, which relies on the audit of data from existing records. Some of the records were not complete, and some information was missing, which might have weakened the validity of the findings, but we think the extent of this was low as the variable with highest missing data was CRP at 17%. The incidence of stillbirths due to Listeria infection was not investigated. This study was hospital based; therefore, infants with mild or asymptomatic infection who did not require admission or died in the community might have been missed, and thus, these findings are not generalizable to the whole population.

In conclusion, early recognition and treatment of neonatal listeriosis is critical due to the high-mortality rate associated with the disease. Neonatal listeriosis in this cohort was associated with prematurity and early onset disease with respiratory embarrassment requiring respiratory support in all infected patients.

ACKNOWLEDGMENTS

We thank National Health Laboratory Services of South Africa for giving us access to laboratory results from their Corporate Data Warehouse.

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