Neonatal listeriosis during a countrywide epidemic in South Africa: A tertiary hospital’s experience

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Background. A countrywide epidemic of *Listeria monocytogenes* (LM) in South Africa began in the first quarter of 2017, rapidly becoming the world’s largest LM outbreak to date.

Methods. We describe the clinical course of neonates with culture-confirmed LM infection admitted to a tertiary neonatal unit at Tygerberg Hospital, Cape Town (1 January 2017 – 31 January 2018). Current epidemic LM cases were compared with a historical cohort of sporadic neonatal LM cases at our institution (2006 - 2016). The global literature on epidemic neonatal LM outbreaks (1 January 1978 - 31 December 2017) was reviewed.

Results. Twelve neonates (median gestational age 35 weeks, median birth weight 2 020 g) were treated for confirmed LM bacteraemia in 2017/18, presenting at a median age of 0.5 days. In 5 cases, neurolisterosis was suspected. Three neonates died (25.0%) v. 8/13 neonatal deaths (61.6%) in the sporadic listeriosis cohort (2006 - 2016) (p=0.075). The institution’s neonatal LM infection incidence increased significantly in 2017 from a historical rate of 0.17/1 000 live births to 1.4/1 000 (p<0.001). During the current LM epidemic, the crude neonatal fatality rate exceeded the average calculated global epidemic neonatal LM mortality (3/12 (25.0%) v. 50/290 (17.2%); p=0.448). Possible factors contributing to the high mortality rate in this epidemic LM neonatal cohort may include more virulent disease associated with sequence type 6 and the predominance of early-onset disease.

Conclusions. Epidemic neonatal listeriosis at Tygerberg Hospital was associated with a predominance of bacteraemic, early-onset disease. Listeriosis-associated mortality rates were higher than previously published, but lower than the rate in a historical institutional cohort.


*Listeria monocytogenes* (LM) is a food-borne pathogen that causes a range of clinical syndromes including self-limiting gastroenteritis, bacteraemia and central nervous system disease. In immunocompetent hosts, the disease profile is usually mild and self-limiting, whereas immunocompromised hosts (including pregnant women and newborns) suffer severe and invasive forms of listeriosis. Numerous case reports of sporadic and epidemic human LM infection have been published, mainly from high-income countries.[1-4] Of the seven known LM serotypes, four infect humans: historically, serotype 4b has been the most common serotype associated with LM outbreaks.[5,6]

In South Africa (SA), epidemic listeriosis was first reported from Johannesburg in 1977/78, with 14 individuals infected (9 neonates and 5 adults) and an overall mortality rate of 43%.7 In the following four decades, few sporadic LM cases and suspected clusters were reported.[8,9] Owing to the low background incidence of infection, invasive LM infection was not previously a notifiable disease in SA. In the first quarter of 2017, a countrywide increase in laboratory-confirmed LM infections was noted, prompting a large-scale public health investigation by the National Institute of Communicable Diseases (NICD) to determine the source(s) of infection, the LM sequence-type(s) involved and the profile of affected cases. As at 9 April 2018, 1 011 laboratory-confirmed cases of LM had been documented, with a mortality rate of 28% among cases with a known outcome (193/691). Most cases to date have been reported from Gauteng (59%), Western Cape (12%) and KwaZulu-Natal (7%) provinces. Of cases with documented age, 41% (418/1 011) were neonates aged ≤28 days, most of whom (96%) experienced disease onset in the first week of life.[10] On 4 March 2018, the NICD announced that the source of the outbreak had been identified as ready-to-eat processed meat products manufactured at the Enterprise Foods Polokwane production facility, and a countrywide recall of the implicated food products began. Although the LM incidence rate has declined dramatically, a further 43 outbreak-related cases have been confirmed since the recall owing to the long disease incubation period, a long refrigeration shelf-life of the contaminated products and the possibility of cross-contamination of other types of foods in the retail or home setting.[10]

Neonates with LM infection present with severe disease and experience high mortality rates.[11,12] Most cases of neonatal listeriosis present within 7 days of birth (early-onset disease), although cases can occur up to 90 days of life (so-called late-onset disease). Early-
onset infection tends to present with bacteraemia and higher case
fatality rates, whereas late-onset disease is more likely to cause
meningitis and central nervous system sequelae. In Cape Town’s
Metro East area, newborns with severe bacterial infection or other
conditions requiring tertiary-level care are referred to the Tygerberg
Hospital neonatal service. Of the 34 reported neonatal listeriosis
cases in the Western Cape to date, 12 (35%) were managed at
Tygerberg Hospital.

Objectives
In this report, we describe the clinical course and outcomes of the
12 neonates with epidemic listeriosis treated at Tygerberg Hospital,
comparing them with a historical institutional cohort of sporadic
neonatal LM cases and international publications reporting epidemic
neonatal LM.

Methods
Study setting
Tygerberg Hospital in Cape Town, SA, is a tertiary academic medical
complex with 1 384 beds, including 300 neonatal and paediatric beds.
The neonatal unit (124 beds) incorporates six clinical areas: an 8-bed
combined medical/surgical neonatal intensive care unit (NICU), a
4-bed neonatal high-care unit, 2 acute neonatal wards, 1 low-care
neonatal ward and 1 kangaroo mother care ward. There are ~8 000
births and ~2 000 neonatal ward admissions to Tygerberg Hospital
annually, including both inborn babies and ill neonates (<10 days of age)
transferred in from peripheral hospitals. The antenatal HIV
prevalence rate is ~17%, and the low birth weight rate (<2 500 g) was
37% in 2017.

Investigation for suspected neonatal sepsis
Well preterm (<37 completed weeks) and term neonates with
maternal indications for sepsis work-up (e.g. chorioamnionitis,
spontaneous preterm labour) and ill neonates with any clinical,
radiological and/or laboratory features suggesting infection
underwent at least one blood culture with/without accompanying
cerebrospinal fluid (CSF) specimens at the discretion of attending
clinicians. Symptoms and signs that triggered investigation for sepsis
included lethargy, apnoea, need for increased respiratory support,
poor feeding, temperature instability, abdominal distension and a
raised white cell count or C-reactive protein (CRP) level, among
others. The unit’s empirical antibiotic therapy regimen for early-onset
neonatal sepsis is ampicillin plus gentamicin, and for early-onset
meningitis cefotaxime plus ampicillin.

Blood culture sampling and laboratory analysis
Blood cultures and/or CSF samples were collected using an aseptic
technique and submitted to the National Health Laboratory Service
(NHLS) microbiology laboratory at Tygerberg Hospital. Blood
cultures were incubated at 37°C using the BacT/Alert 3D Microbial
Identification System (bioMérieux, France). On flagging positive,
an aliquot of the blood culture broth was used to perform a Gram
stain. In all cases (including the 12 neonatal LM cases reported
here, where small Gram-positive bacilli were observed on the Gram
stain) the microbiology laboratory promptly phoned out results to
the clinicians. An aliquot of the broth was plated onto blood agar
plates and incubated in a CO₂ incubator at 35°C overnight, and
a bile aesculin agar was inoculated. Colonies that appeared beta-
haemolytic on blood agar and hydrolysed aesculin were further
identified using a catalase test and the Vitek 2 automated system
(bioMérieux). Discrepancies in identification were resolved using the
BD BBL Crystal Gram positive identification kit (BD, USA) or Vitek
MS (bioMérieux). Penicillin Etests (bioMérieux) were performed to
determine the minimum inhibitory concentrations (MICs) for the
isolates. For CSF samples, a cell count, protein and glucose estimation
were performed, followed by performance of a Gram stain and
inoculation of blood and cooked blood agar plates with overnight
incubation in a CO₂ incubator at 35°C. A similar process to that
described above for blood cultures was followed for identification of
LM on CSF, resolution of discrepant results and sensitivity testing.
Blood and CSF isolates confirmed as LM were submitted to the
national reference laboratory at the NICD for sequence typing from
mid-August 2017 onwards.

Neonatal sepsis and LM outbreak surveillance
and management
The Unit for Infection Prevention and Control conducted routine
surveillance for bloodstream infections (including early-onset
neonatal sepsis and LM bacteremia) on the Tygerberg Hospital
neonatal platform in 2017/18. After declaration of the LM outbreak
by the National Department of Health, mandatory reporting of
LM infections to the provincial communicable disease control was
introduced. For each case, additional demographic and outcome
data, a case investigation form (including a history of the mother’s
food intake during pregnancy) and a clinical specimen for sequence
typing was submitted to the NICD. The infection prevention nurse
practitioner at our institution co-ordinated reporting of all LM cases
and communication with hospital staff regarding affected patients.
In view of several published cases of nosocomial transmission
of LM infection to neonates, an alert to attending clinicians
was distributed in January 2018 recommending use of contact
precautions for LM-infected patients.

Literature search terms
We searched PubMed, African Journals Online and Google
Scholar using the terms ‘neonate’, ‘pregnancy’, ‘listeria’, ‘listeriosis’,
‘neurolisteriosis’ and ‘outbreaks’ for articles published from 1 January
1978 to 31 January 2017. We excluded publications that described
sporadic neonatal LM infections only and epidemics with fewer than
five neonatal cases reported. Each publication or outbreak database
record was reviewed to extract the following information (when
available): year/s reported, country, number of neonates infected,
mortality rate and predominant serotype/s or sequence type identified.

Study design
Neonatal bloodstream infection episodes occurring between 1 Janu-
ary 2017 and 31 January 2018 were prospectively identified and
recorded during routine surveillance activities. This dataset was
searched to identify neonatal LM infections and cross-checked
against neonatal admission records and the NHLS laboratory list
of LM isolates on blood and CSF cultures. For calculation of LM
infection incidence rates (historical and current), we divided the
number of neonatal LM infections managed at the Tygerberg
neonatal unit per year by the number of live births at the hospital in
the same year. Additional demographic data on disease presentation,
clinical course and therapy were obtained by neonatal folder review.
Clinical data on the historical cohort of sporadic neonatal LM cases
were obtained from a recently completed study in our department.

Data handling, statistical analysis and ethical approval
For comparison of patient demographics and outcomes between the
historical cohort and the current epidemic LM cases, we used Student’s
on the neonatal wards, infection was confirmed in 13 infants treated between 2006 and 2016, sporadic LM infections at Tygerberg Hospital are confirmed neonatal listeriosis cases were identified, although there is currently no standardised protocol for investigation for LM infection in such cases at our institution.

Case series of neonatal LM during the 2017 nationwide epidemic

Twelve mothers from geographically diverse areas in the Cape Metro gave birth to 13 newborns (1 set of twins) (Table 1). LM bacteremia was confirmed by culture in 12/13 infants, although all received therapy for listeriosis. The mothers’ median age was 31 years (interquartile range (IQR) 29 - 35). Caesarean sections were performed in 5/12 cases (41.7%). Eight of 12 mothers (66.7%) delivered at Tygerberg Hospital. Only 2/12 mothers (16.7%) were HIV-positive (with viral loads of 1 345 copies/mL and lower than detectable levels, respectively). Among the 9/12 mothers (75.0%) who went into spontaneous preterm labour, receipt of intrapartum antibiotics was documented in 6/9 (66.7%) and unknown in the remaining 3. One mother was diagnosed with chorioamnionitis, 2 mothers had urinary tract infections and 1 mother had reported diarrhoea and decreased fetal movements 1 day prior to delivery. Histology reports available on 2 placentas showed macroscopic calcifications. No cases of fetal loss or stillbirth following maternal listeriosis were identified, although there is currently no

t-tests and Fisher’s exact tests or χ² tests for analysis of continuous and categorical variables, respectively. A p-value of <0.05 was considered statistically significant. Stata statistical software version 13.1 (StataCorp, USA) was used. Ethical approval and waiver of individual informed consent were obtained from the Human Health Research Ethics Committee of Stellenbosch University (ref. no. S13/09/171).

Results

Epidemiology of neonatal LM infections at Tygerberg Hospital

Between 2006 and 2016, sporadic LM infections at Tygerberg Hospital were considered statistically significant. Stata software version 13.1 (StataCorp, USA) was used. Ethical approval and waiver of individual informed consent were obtained from the Human Health Research Ethics Committee of Stellenbosch University (ref. no. S13/09/171).

Case series of neonatal LM during the 2017 nationwide epidemic

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standardised protocol for investigation for LM infection in such cases at our institution. None of the mothers whose infants had culture-confirmed LM infection had growth of LM from clinical specimens.

Neonates

The median gestational age for the 12 newborns with culture-confirmed listeriosis (Table 1) was 35 weeks (IQR 33 - 38) and the median birth weight was 2 020 g (IQR 1 635 - 2 810) (Table 2). A 13th baby (twin of a baby with culture-confirmed LM) had respiratory distress at birth and an elevated CRP level (61 mg/dL) and was fully treated for LM infection, although blood and CSF cultures were negative.

Of the 12 babies with culture-confirmed LM, 9 (75.0%) were premature and of low birth weight (<2 500 g). All newborns had respiratory distress at birth and an elevated CRP level (61 mg/dL) and was fully treated for LM infection, although blood and CSF cultures were negative.

Of the 12 babies with culture-confirmed LM, 9 (75.0%) were premature and of low birth weight (<2 500 g). All newborns had growth of LM from blood cultures within the first 5 days of life, with 6 positive cultures (50.0%) on the first day of life. Lumbar punctures were performed in all but
## Table 1. Clinical characteristics and outcome of hospitalised newborns with confirmed *Listeria monocytogenes* infection (N=12)

<table>
<thead>
<tr>
<th>Maternal history</th>
<th>Neonatal demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of delivery</strong></td>
<td><strong>Peripartum illnesses/events</strong></td>
</tr>
<tr>
<td>NVD</td>
<td>Gestational diabetes mellitus</td>
</tr>
<tr>
<td>NVD</td>
<td>Spontaneous preterm labour</td>
</tr>
<tr>
<td>CS</td>
<td>Spontaneous preterm labour</td>
</tr>
<tr>
<td>CS</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>CS</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>NVD</td>
<td>None</td>
</tr>
<tr>
<td>NVD</td>
<td>Spontaneous preterm labour</td>
</tr>
<tr>
<td>NVD</td>
<td>Chorioamnionitis</td>
</tr>
</tbody>
</table>

Continued...
<table>
<thead>
<tr>
<th>Maternal history</th>
<th>Neonatal demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of delivery</td>
<td>Gestational age (wk)</td>
</tr>
<tr>
<td>CS</td>
<td>35</td>
</tr>
<tr>
<td>CS</td>
<td>38</td>
</tr>
<tr>
<td>NVD</td>
<td>32</td>
</tr>
<tr>
<td>NVD</td>
<td>31</td>
</tr>
</tbody>
</table>

CXR = chest radiograph; CSF = cerebrospinal fluid; NVD = normal vertex delivery; CS = caesarean section; ART = antiretroviral therapy; F = female; M = male; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome; TTN = transient tachypnoea of the newborn; nCPAP = nasal continuous positive airways pressure; NPO = nasal prong oxygen; HFOV = high-frequency oscillatory ventilation; IPPV = intermittent positive-pressure ventilation; LP = lumbar puncture; LM = L. monocytogenes; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia.
IN PRACTICE

Table 2. Comparison of historical v. epidemic neonatal *Listeria* cohorts

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>9 (36.0)</td>
<td>4 (30.8)</td>
<td>5 (41.6)</td>
<td>0.039</td>
</tr>
<tr>
<td>Neurological</td>
<td>2 (8.0)</td>
<td>0</td>
<td>2 (16.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>2 (8.0)</td>
<td>0</td>
<td>2 (16.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Combined</td>
<td>12 (48.0)</td>
<td>9 (69.2)</td>
<td>3 (25.0)</td>
<td>0.073</td>
</tr>
<tr>
<td>Highest level of neonatal care required, n (%)</td>
<td>19 (76.0)</td>
<td>12 (92.3)</td>
<td>7 (58.3)</td>
<td>0.088</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>6 (24.0)</td>
<td>1 (7.7)</td>
<td>5 (41.7)</td>
<td>0.387</td>
</tr>
<tr>
<td>High-care unit</td>
<td>2 (8.0)</td>
<td>0</td>
<td>2 (16.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>nCPAP</td>
<td>5 (20.0)</td>
<td>1 (7.7)</td>
<td>4 (33.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>IPPV</td>
<td>9 (36.0)</td>
<td>7 (53.8)</td>
<td>2 (16.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>HFOV</td>
<td>9 (36.0)</td>
<td>5 (38.5)</td>
<td>4 (33.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Inotropic support required, n (%)</td>
<td>13 (52.0)</td>
<td>10 (76.9)</td>
<td>3 (25.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Normal</td>
<td>3 (12.0)</td>
<td>0</td>
<td>3 (25.0)</td>
<td>0.387</td>
</tr>
<tr>
<td>IVH and/or PVL</td>
<td>4 (16.0)</td>
<td>2 (15.4)</td>
<td>2 (16.7)</td>
<td>0.387</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>4 (16.0)</td>
<td>3 (23.1)</td>
<td>1 (8.3)</td>
<td>0.387</td>
</tr>
<tr>
<td>No neuroimaging done</td>
<td>14 (56.0)</td>
<td>8 (61.5)</td>
<td>6 (50.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Outcome death, n (%)</td>
<td>11 (44.0)</td>
<td>8 (61.5)</td>
<td>3 (25.0)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Length of stay in tertiary neonatal care.*

the 3 newborns who died (2 were too unstable and 1 had severe thrombocytopenia). Neurolistiosis was clinically suspected in 5/12 newborns (41.7%); however, only a single CSF sample cultured LM.

Half of the cohort required invasive ventilatory support and 3 needed inotropic support. Ten babies had a chest radiograph taken on admission: 7/10 had changes in keeping with pneumonia, 2/10 had features of transient tachypnoea of the newborn, and 1/10 was of poor quality (unable to interpret). Fifty percent (6/12) of the babies had cranial ultrasound scans. Half of these babies (3/6) had scans that were normal for their gestational age. Three babies had abnormalities detected. One had resolving grade 1 intraventricular haemorrhage (IVH), and another grade 1 IVH with grade 2 - 3 periventricular leukomalacia (PVL). The third baby had two scans, the initial one showing fibrin strands in the lateral ventricles (day 6) and a subsequent one demonstrating ventriculomegaly in keeping with hydrocephalus, as well as grade 2 PVL (day 15).

All 12 babies underwent laboratory investigations for sepsis on hospital admission, with the following results: median CRP 70 mg/dL (IQR 14 - 298), median white cell count 10 × 10^9/L (IQR 8 - 15) and median platelet count 169 × 10^10/L (IQR 124 - 241). All 12 newborns were commenced empirically on intravenous ampicillin and gentamicin on hospital admission; those who survived completed a total of 21 days on ampicillin, with an initial 7 days of gentamicin. In 10/12 cultures where MIC determination was performed, the MIC to penicillin was <0.5 μg/mL, i.e. susceptible. Only 2 of the 12 neonatal cases’ specimens were processed at the NICD for sequence typing; both belonged to sequence type 6 (ST-6), which has been identified in >90% of the SA LM epidemic isolates.

**Comparison with the historical cohort**

From 2006 to 2016, 13 sporadic cases of listeriosis were managed on the Tygerberg Hospital neonatal wards v. 12 epidemic neonatal *Listeria* cases in 2017/18. There was only a single statistically significant difference between the cohorts (Table 2): the epidemic cohort had a higher incidence of neurolistiosis and mixed respiratory/neurological presentations. The sporadic cases experienced a higher case fatality rate (62% v. 25%; p=0.075), had a higher proportion of neonates admitted to the NICU (92% v. 58%; p=0.073) and included more infants who required ventilation (92% v. 50%; p=0.088), although these differences did not achieve statistical significance.

In the historical cohort, 9/13 infants (69.2%) received appropriate empirical cover for LM infection with ampicillin (v. 12/12 (100%) of the epidemic cohort). When analysing the combined historical and epidemic cohort (N=25), factors associated with neonatal LM-associated mortality on univariate analysis were being part of the historical cohort, need for NICU admission, need for inotropic support, and respiratory support required.
support, and high-frequency oscillatory ventilation. In a multivariate regression analysis, the requirement for inotropic support was the only significant factor predicting mortality (Table 3).

**Publications reporting neonatal listeriosis (1978 - 2017)**

We identified 15 publications that met our search criteria (Table 4). A single report from Africa was identified (in a large teaching hospital in SA).[19] Most LM outbreaks described occurred in the 1980s, with only two outbreaks involving neonates described since 1990.[28,29] The largest outbreak affected 142 individuals,[20] although most reports described small-scale epidemics and one described both epidemic and sporadic LM cases affecting neonates.[19] Four publications reported neonatal cases only; in the articles describing mixed populations, neonates generally made up at least one-third of the cases. Overall mortality in neonatal listeriosis was high (mean 17%, range 0 - 44%). Of publications that reported the LM outbreak serotype involved, 1a/b and 4b were most prevalent.

**Table 3. Factors associated with mortality from neonatal listeriosis (combined historical and epidemic cohorts, N=25)***

<table>
<thead>
<tr>
<th>Factor</th>
<th>Survived (N=14)</th>
<th>Died (N=11)</th>
<th>Univariate analysis, p-value</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk), median (IQR)</td>
<td>34 (32 - 37)</td>
<td>35 (31 - 36)</td>
<td>0.847</td>
<td>-</td>
</tr>
<tr>
<td>Birth weight in (kg), median (IQR)</td>
<td>1.8 (1.2 - 2.6)</td>
<td>2.3 (1.8 - 2.5)</td>
<td>0.311</td>
<td>-</td>
</tr>
<tr>
<td>Age at presentation (d), median (IQR)</td>
<td>0.5 (0 - 2)</td>
<td>2.0 (0 - 3)</td>
<td>0.180</td>
<td>-</td>
</tr>
<tr>
<td>Cohort group (historical), n (%)</td>
<td>5 (35.7)</td>
<td>8 (72.7)</td>
<td>0.075</td>
<td>1.1 (0.9 - 13.9)</td>
</tr>
<tr>
<td>SGA, n (%)</td>
<td>4 (28.6)</td>
<td>2 (18.2)</td>
<td>0.452</td>
<td>-</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>9 (64.3)</td>
<td>8 (72.7)</td>
<td>0.496</td>
<td>-</td>
</tr>
<tr>
<td>Place of birth (Tygerberg Hospital), n (%)</td>
<td>6 (42.9)</td>
<td>8 (72.7)</td>
<td>0.138</td>
<td>-</td>
</tr>
<tr>
<td>Ampicillin included in empirical antibiotic therapy regimen, n (%)</td>
<td>13 (92.9)</td>
<td>9 (81.8)</td>
<td>0.564</td>
<td>-</td>
</tr>
<tr>
<td>HIV exposure status (HIV-exposed), n (%)</td>
<td>4 (28.6)</td>
<td>2 (18.2)</td>
<td>0.452</td>
<td>-</td>
</tr>
<tr>
<td>Highest level of care (NICU), n (%)</td>
<td>8 (57.1)</td>
<td>11 (100)</td>
<td>0.017</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory support (oscillation), n (%)</td>
<td>2 (14.3)</td>
<td>7 (63.6)</td>
<td>0.016</td>
<td>-</td>
</tr>
<tr>
<td>Inotropic support (required), n (%)</td>
<td>3 (21.4)</td>
<td>10 (90.9)</td>
<td>0.001</td>
<td>34.9 (2.3 - 532.1)</td>
</tr>
</tbody>
</table>

SGA = small for gestational age; IQR = interquartile range; NICU = neonatal intensive care unit.

**Table 4. Published epidemic listeriosis events affecting neonates (1978 - 2017)**

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Country</th>
<th>Epidemic ± sporadic cases</th>
<th>Year/s reported</th>
<th>Cases, N</th>
<th>Liveborn neonates, n (%)</th>
<th>Neonatal mortality rate*, n (%)</th>
<th>Predominant serotype/s*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs et al.,[19] 1978</td>
<td>SA</td>
<td>Epidemic</td>
<td>1977 - 1978</td>
<td>14</td>
<td>9 (64.3)</td>
<td>4/9 (44.4)</td>
<td>4b</td>
</tr>
<tr>
<td>Filice et al.,[20] 1983</td>
<td>USA</td>
<td>Epidemic</td>
<td>1975</td>
<td>7</td>
<td>7 (100.0)</td>
<td>0</td>
<td>4b</td>
</tr>
<tr>
<td>Schlech et al.,[21] 1983</td>
<td>Canada</td>
<td>Epidemic</td>
<td>1981</td>
<td>41</td>
<td>25 (61.0)</td>
<td>7/25 (28.0)</td>
<td>4b</td>
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<td>Lennon et al.,[22] 1984</td>
<td>New Zealand</td>
<td>Epidemic</td>
<td>1980</td>
<td>22</td>
<td>14 (63.6)</td>
<td>1/14 (7.1)</td>
<td>1b</td>
</tr>
<tr>
<td>Malinverni et al.,[23] 1985</td>
<td>Switzerland</td>
<td>Epidemic</td>
<td>1983 - 1984</td>
<td>25</td>
<td>11 (44.0)</td>
<td>NR</td>
<td>4b</td>
</tr>
<tr>
<td>Tulzer et al.,[24] 1987</td>
<td>Austria</td>
<td>Epidemic</td>
<td>1986</td>
<td>20</td>
<td>20 (100.0)</td>
<td>5/20 (25.0)</td>
<td>1/2a</td>
</tr>
<tr>
<td>Teberg et al.,[25] 1987</td>
<td>USA</td>
<td>Epidemic</td>
<td>1986</td>
<td>23</td>
<td>23 (100.0)</td>
<td>5/23 (21.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Linnan et al.,[26] 1988</td>
<td>USA</td>
<td>Epidemic</td>
<td>1985</td>
<td>142</td>
<td>93 (65.5)</td>
<td>10/93 (10.8)</td>
<td>4b</td>
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<tr>
<td>Mascola et al.,[27] 1989</td>
<td>USA</td>
<td>Epidemic</td>
<td>1985 - 1986</td>
<td>94</td>
<td>37 (39.4)</td>
<td>6/37 (16.2)</td>
<td>4b and 1a/b</td>
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<tr>
<td>Bucher et al.,[28] 1989</td>
<td>Switzerland</td>
<td>Epidemic</td>
<td>1983 - 1987</td>
<td>35</td>
<td>35 (100.0)</td>
<td>5 (14.3)</td>
<td>NR</td>
</tr>
<tr>
<td>Allerberger et al.,[29] 1989</td>
<td>Austria</td>
<td>Epidemic</td>
<td>1986</td>
<td>28</td>
<td>24 (85.7)</td>
<td>5/24 (20.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Frederiksen and Samuelsson,[31] 1992</td>
<td>Denmark</td>
<td>Epidemic + sporadic</td>
<td>1981 - 1988</td>
<td>30</td>
<td>16 (53.3)</td>
<td>2/16 (12.5)</td>
<td>4 and 1</td>
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<tr>
<td>Pérez-Trallero et al.,[33] 2014</td>
<td>Spain</td>
<td>Epidemic</td>
<td>2013 - 2014</td>
<td>27</td>
<td>5 (18.5)</td>
<td>0</td>
<td>1a/b and 4b</td>
</tr>
</tbody>
</table>

SA = South Africa; NR = not reported.

*Total epidemic listeriosis mortality rate = 50/290 (17.2%).

**Discussion**

We present the only case series of epidemic neonatal listeriosis reported from Africa, and compare this cohort with historical sporadic neonatal LM cases at our institution and the international literature. The only other African case series of epidemic listeriosis (adults and neonates) reporting clinical data was also published from SA, nearly four decades ago, and involved 9 neonates.[19] The cases reported here represent one-third of the neonatal cases identified in our province (Western Cape).[10]

The mean pre-epidemic, or historical, incidence of sporadic neonatal listeriosis at our institution (2006 - 2016) was 0.17 cases per 1 000 live births (annual range 0 - 0.5), substantially exceeding...
rates reported from the UK, The Netherlands and the USA (0.05, 0.01 and 0.09 per 1000 live births, respectively). Both the historical and epidemic listeriosis rates at our institution may be an underestimation, as these data reflect laboratory-confirmed cases only; some neonates may not have had lumbar punctures performed owing to clinical instability, others may have had antibiotics prior to blood/CSF culturing, and some may have died before the diagnosis was made.

A possible explanation for the apparently high historical rate of sporadic neonatal LM infection at Tygerberg Hospital is the use of the live births at this tertiary referral neonatal centre as the denominator, as opposed to the total population of the hospital's catchment area. An alternative hypothesis is that the high rate of 'sporadic' neonatal LM may include unrecognised prior outbreaks, as LM infections were not notifiable in SA before 2017. Other possible factors that may contribute to the comparatively high LM incidence in SA could include a more vulnerable population of pregnant women owing to high antenatal HIV prevalence and a higher prevalence of LM-contaminated food and water sources than in high-income countries. Although HIV infection is not traditionally cited as a

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**Practice Points**

- **Contact precautions:** Henceforth all neonates who test positive for *Listeria* must be placed on contact precautions until effective antibiotic treatment has been completed.

- **Respiratory resuscitation equipment** (laryngoscope handles, laryngoscope blades, introducers) must be cleaned meticulously between patients. Here are the steps for cleaning:
  - Wash thoroughly with soap and water. Clean grooves and connection points with a brush.
  - Rinse and dry.
  - Wipe over with 70% alcohol.

  Ideally the equipment must be sent to the CSSD for autoclaving.

- **Hand hygiene:** Contaminated hands always play an important role in the transfer of infection. Make therefore sure that you clean your hands between babies 100% of the time.

- **Neonatal face masks (except the silicone ones) and their tubing** are single-use items and must NOT be sent to the CSSD for reprocessing.

Please report all suspected listeriosis cases (expecting mothers, neonates) to the UIPC.

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Fig. 3. Infection prevention clinical alert to obstetric and paediatric staff. (CSSD = Central Sterilisation Supply Department; UIPC = Unit for Infection Prevention and Control.)
risk factor for listeriosis, it emerged as an important risk factor during the SA epidemic. However, in our epidemic cohort, only a single confirmed antenal LM infection and two HIV-positive mothers of LM neonatal cases were identified.

Historically and during the current outbreak, LM bacteraemia events constitute a small percentage of the overall burden of bloodstream infections among hospitalised neonates at our institution. Even in the outbreak year (2017), the vast majority of neonatal bloodstream infections were hospital acquired, with LM cases peaking in quarter 3 at 15% of all bacteraemia events. However, LM neonatal infections at our institution were associated with high mortality (sporadic 62% and outbreak 25%), substantially exceeding the published crude fatality rate for neonatal nosocomial bloodstream infections at Tygerberg Hospital of 16%. Although LM is well documented as a nosocomial pathogen in neonates, we did not identify any nosocomial LM infections during 2017. Given the concerns regarding the potential for nosocomial LM transmission and the increasing incidence of neonatal infections in our unit, an infection control alert was issued to the hospital's obstetric and neonatal staff (Fig. 3).

Few major differences were observed between the historical and epidemic cohorts. In the epidemic cohort there was a larger proportion of babies with mixed respiratory and neuroinvasive presentations, although only one baby cultured LM on CSF and just 3 of 6 cranial ultrasound scans performed had abnormal cranial ultrasound findings. However, 2 babies died before cranial ultrasound could be performed, and in the third baby who died, the scan was performed on day 4 of life, which may have been too early to detect all abnormalities. Although not reaching statistical significance owing to the small sample size, mortality was much lower in the epidemic cohort (25% vs. 62%), with a lower proportion of neonates requiring NICU admission, mechanical ventilation and inotropic support. In a multivariate analysis to identify factors associated with mortality from neonatal listeriosis (combined cohorts), the only factor that reached significance, with an odds ratio (OR) of 35, was inotropic support. However, this probably reflects the group of babies with refractory shock who had the most severe disease manifestations. In a recently published review of >800 cases of LM infection in neonates refractory shock who had the most severe disease manifestations. In a recently published review of >800 cases of LM infection in neonates,

Conclusions

EPIDEMIC NEONATAL LISTERIOSIS AT TYGERBERG HOSPITAL WAS ASSOCIATED WITH A PREDOMINANCE OF BACTERAMIC DISEASE AND SEVERE RESPIRATORY COMPLICATIONS. LISTERIOSIS-ASSOCIATED MORTALITY RATES WERE HIGHER THAN PREVIOUSLY PUBLISHED, BUT LOWER THAN THE RATE IN A HISTORICAL INSTITUTIONAL COHORT. ALTHOUGH WE DID NOT IDENTIFY ANY CASES, THE DOCUMENTED RISK OF NOSOCOMIAL LM TRANSMISSION WARRANTS APPLICATION OF TRANSMISSION-BASED PRECAUTIONS FOR LM CASES DURING OUTBREAKS.

Acknowledgements. The authors thank the NHLS, the NICD and the patients and staff of Tygerberg Hospital.

Author contributions. All authors contributed to the study design and data collection. AB, AD and LGL completed the data analysis. AD produced the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version.

Funding. National Research Foundation rated researcher incentive fund.

Conflicts of interest. None.

References


