Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Perinatal Antibiotic Prophylaxis Exposure and Neonatal Sepsis in Indonesia: A Prospective Cohort Study

Ariesti Karmila

a.karmila@unsri.ac.id

Sriwijaya University

Indrayady Brachia

Sriwijaya University

Afifa Ramadanti

Sriwijaya University

Yulia Iriani

Sriwijaya University

Abarham Martadiansyah

Sriwijaya University

Nuswil Bernolian

Sriwijaya University

Ahmad B. Alfarizi

Palembang BARI Hospital

Muhammad Prasetya Wibowo

Indonesia Navy

Joseph Gardiner

Michigan State University

Lixin Zhang

Michigan State University

Research Article

Keywords: neonatal sepsis, antibiotic prophylaxis, early-onset sepsis, late-onset sepsis, antimicrobial stewardship, Indonesia, prospective cohort, inverse probability weighting

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11419372/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Perinatal Antibiotic Prophylaxis Exposure and Neonatal Sepsis in Indonesia: A Prospective Cohort Study

Ariesti Karmila[1*], Indrayady Brachia[1], Afifa Ramadanti[1], Yulia Iriani[1], Abarham Martadiansyah[2], Nuswil Bernolian[2], Ahmad B. Alfarizi[3], Muhammad Prasetya Wibowo[4], Joseph Gardiner[5], Lixin Zhang[5]

1. Department of Pediatrics, Faculty of Medicine, University of Sriwijaya, Jl. Jend. Sudirman, KM 3.5, Palembang, 30126, Indonesia;
2. Department of Obstetrics and Gynecology, Faculty of Medicine, University of Sriwijaya, Jl. Jend. Sudirman, KM 3.5, Palembang, 30126, Indonesia;
3. Department of Child Health, Palembang BARI Hospital, Jl. Panca Usaha No.1, 5 Ulu, Palembang, 30254, Indonesia
4. Department of Naval Health, Indonesia Navy, Jl. Cilangkap Raya No.62 3, Cilangkap, Kec. Cipayung, East Jakarta, Jakarta 13870, Indonesia
5. Department of Epidemiology and Biostatistics, Michigan State University, 909 Fee Rd Room B601, East Lansing, MI, 48824, USA

*Corresponding author: Ariesti Karmila
Department of Pediatrics, Faculty of Medicine, University of Sriwijaya,
Jl. Jend. Sudirman, KM 3.5, Palembang, 30126, Indonesia
Email: a.karmila@unsri.ac.id

Abstract

Background

Perinatal antibiotic prophylaxis is widely used to prevent early neonatal infection, but extensive exposure may alter neonatal-sepsis epidemiology. We assessed the association between perinatal antibiotic-prophylaxis exposure and neonatal sepsis in two Indonesian referral hospitals.

Methods

We conducted a prospective cohort study of mother-newborn dyads enrolled at delivery and followed through 28 days of life. Maternal and neonatal prophylactic antibiotic exposure was ascertained from medical records. Early-onset sepsis (EOS) occurred within 72 hours and late-onset sepsis (LOS) thereafter. Because conventional inverse probability weighting showed poor

covariate overlap and extreme weights, propensity-score overlap weights estimated separately within each hospital were used to estimate adjusted risk differences in the overlap population.

Results

Among 904 analyzed dyads, 651 newborns (72.0%) were exposed to maternal and/or neonatal prophylactic antibiotics. Ninety-four neonates developed sepsis (46 EOS and 48 LOS); 25 cases were culture proven. In the primary overlap-weighted analysis, the estimated risks of overall sepsis were 3.4% without prophylaxis and 9.4% with any prophylaxis (adjusted risk difference [RD], 0.060; 95% confidence interval [CI], 0.012 to 0.109). The adjusted RD was 0.015 (95% CI, -0.022 to 0.052) for EOS and 0.045 (95% CI, 0.013 to 0.078) for LOS. In exploratory pairwise analyses, neonatal prophylaxis alone was associated with higher risks of overall sepsis (RD, 0.149; 95% CI, 0.044 to 0.255) and LOS (RD, 0.097; 95% CI, 0.023 to 0.171).

Conclusions

Among mother-newborn dyads with overlapping measured probabilities of receiving prophylaxis, perinatal antibiotic-prophylaxis exposure was associated with a higher risk of neonatal sepsis, particularly LOS. Limited positivity, confounding by indication, sparse events among unexposed neonates, and limited culture confirmation preclude causal interpretation and limit generalizability to the full cohort.

Keywords: neonatal sepsis; antibiotic prophylaxis; early-onset sepsis; late-onset sepsis; antimicrobial stewardship; Indonesia; prospective cohort; inverse probability weighting

BACKGROUND

Neonatal sepsis remains a major contributor to neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries (LMICs), where diagnostic capacity,

antimicrobial stewardship, and infection surveillance are often limited.[1,2] Early-onset sepsis (EOS), occurring within the first 72 hours of life, is commonly attributed to vertical transmission of maternal pathogens, whereas late-onset sepsis (LOS) is more frequently associated with postnatal exposures such as prolonged hospitalization, invasive procedures, and antimicrobial selective pressure.[3,4] Despite advances in perinatal care, the burden of neonatal sepsis in LMICs remains disproportionately high, with case fatality rates exceeding those reported in high-income countries.[5]

The widespread adoption of intrapartum and postnatal antibiotic prophylaxis has substantially increased neonatal exposure to antibiotics during the perinatal period. An estimated >40% of neonates are exposed to antibiotics administered to their mothers immediately before delivery, [6] a proportion that would likely be higher if direct neonatal prophylaxis were included. Concerns regarding antibiotic overuse during the perinatal period have therefore intensified, particularly in LMICs, where antibiotic utilization and inappropriate prescribing tend to be more frequent but remain poorly characterized.[7]

Although perinatal antibiotic prophylaxis may reduce short-term maternal and neonatal infectious complications, accumulating evidence suggests that widespread exposure is associated with an increased incidence of LOS, gram-negative sepsis, and antibiotic-resistant infections.[8–12] These observations indicate that the epidemiology of neonatal sepsis is evolving in parallel with expanding antibiotic prophylaxis practices. Consequently, a clearer understanding of neonatal sepsis patterns in the context of perinatal antibiotic exposure is needed, particularly in LMIC settings. This study assessed the association between perinatal antibiotic-prophylaxis exposure and neonatal sepsis incidence in an LMIC context.

METHODS

Study design, setting, and participants

This prospective cohort study was conducted at Mohammad Hoesin Hospital and Palembang BARI Hospital, two tertiary referral hospitals in Palembang, Indonesia, from September 2019 to March 2021. Consecutive mother-viable-newborn dyads admitted for delivery were eligible when a legal guardian consented and resided within the city. Dyads were excluded when the mother received antibiotics for a documented therapeutic indication during the delivery admission. Of 1,316 eligible dyads, 1,002 were enrolled; 98 did not complete follow-up, leaving 904 dyads with complete 28-day outcome follow-up for analysis.

Exposure ascertainment and follow-up

Recruitment occurred from before delivery until approximately two hours after birth. Maternal and neonatal prophylaxis indications, agents, doses, intervals, and durations were abstracted from medical records. Maternal clinical and demographic characteristics were recorded at enrolment. Prophylaxis was classified according to the documented intent at administration; cases with documented therapeutic intent were excluded. Maternal prophylaxis included procedural indications and locally defined risk-factor–based indications. Neonatal prophylaxis referred to antibiotics initiated after birth because of perinatal risk assessment rather than established infection. During the study period, neonatal prophylaxis consisted of standardized 3-day regimen of ampicillin plus gentamicin.

During hospitalization, newborns were assessed every six hours until discharge or a sepsis diagnosis. After discharge without sepsis, follow-up continued weekly until day 28, initially at a scheduled well-baby visit and subsequently by telephone. Caregivers were asked about general

condition, feeding, sleep, temperature instability, respiratory or gastrointestinal symptoms, lethargy or irritability, urine output, healthcare visits, and antibiotic use. Families could contact the study team between scheduled calls and were advised to return for clinical evaluation when concerning symptoms were reported.

Outcome definitions and microbiological procedures

Perinatal antibiotic prophylaxis was defined as systemic antibiotics administered to the mother during the intrapartum or immediate peripartum period and/or to the neonate shortly after birth, without a documented diagnosis of infection and in accordance with local protocols. Local maternal indications included cesarean delivery, antepartum hemorrhage due to placenta previa, prolonged rupture of membranes, intrapartum fever, and maternal leukocyte count >15,000/mm^3.[13] Local neonatal indications included rupture of membranes >12 hours, maternal intrapartum fever, maternal leukocyte count >15,000/mm^3, and foul-smelling amniotic fluid.[14] Some indications overlap with infection risk; this was considered a source of confounding by indication rather than evidence that prophylaxis caused sepsis.

Neonatal sepsis required at least one compatible clinical sign and at least two supportive laboratory abnormalities according to local guidance. EOS was defined as onset within 72 hours of birth and LOS as onset thereafter through day 28.[15] Sepsis was categorized as culture-proven when a pathogenic organism was isolated from blood and as clinical sepsis when clinical and laboratory criteria were met without culture confirmation. Because these criteria may overlap with prophylaxis indications, culture-proven and clinical sepsis were distinguished in interpretation.

For neonates diagnosed with sepsis, two blood-culture sets were obtained from separate venipuncture sites and processed using the BD BACTEC™ automated system. Isolates and

antimicrobial susceptibility were determined with the VITEK® 2 Compact system (bioMérieux, France) under Clinical and Laboratory Standards Institute guidance. Coagulase-negative staphylococci (CoNS) were interpreted cautiously because of possible contamination. Multidrug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial classes.[16]

Statistical analysis

Maternal and neonatal characteristics were summarized as frequencies and proportions and compared using chi-squared or Fisher's exact tests, as appropriate. Crude risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using separate modified Poisson regression models with a log link and robust sandwich standard errors. Adjusted RRs were estimated from a common parsimonious model that included study hospital, cesarean delivery, rupture of membranes for more than 18 hours, foul-smelling amniotic fluid, maternal leukocyte count >15,000/mm³, birth weight <2,500 g, and 5-minute Apgar score <7. Birth weight was selected instead of prematurity, and rupture of membranes for more than 18 hours instead of the shorter-duration and PROM/PPROM variables, to avoid including highly correlated measures. Antepartum hemorrhage and intrapartum temperature ≥38 °C were not included in adjusted models because outcome events were absent or extremely sparse. Medical support and oral intake were reported only in crude analyses because their timing could overlap with evolving sepsis. The adjusted analyses used 709 complete records, including 80 neonates with overall sepsis, 41 with EOS, and 39 with LOS. EOS and LOS were analyzed as separate binary outcomes in the full cohort.

The primary exposure contrast was any maternal and/or neonatal prophylaxis versus no prophylaxis. Because prophylaxis was assigned according to clinical indications, confounding by

indication was anticipated. Propensity scores were estimated using logistic regression separately within each hospital. The models included maternal age group, maternal and spouse education, household size, pregnancy weight-gain category, parity, number of vaginal examinations, cesarean delivery, birth attendant, rupture of membranes for more than 18 hours, antepartum hemorrhage, foul-smelling amniotic fluid, maternal leukocyte count >15,000/mm3, intrapartum temperature >=38 degrees C, gestational-age group, birth weight <2,500 g, and 5-minute Apgar score <7. Feeding and medical support were excluded because they could occur after exposure or reflect evolving illness. Out-of-range values were treated as missing, and missing covariate values were handled using missingness indicators in propensity-score estimation.

Diagnostic evaluation of conventional inverse probability of treatment weights for the average treatment effect (ATE) showed poor overlap, extreme weights, and inadequate covariate balance. The revised primary analysis therefore used overlap weights, with exposed participants weighted by one minus the propensity score and unexposed participants weighted by the propensity score. This approach estimates the average treatment effect in the overlap population (ATO), comprising participants whose measured characteristics were compatible with either exposure strategy.17,18 Covariate balance was assessed using absolute standardized mean differences (SMDs), with <0.10 considered acceptable; weight distributions and effective sample sizes (ESSs) were also examined. Weighted outcome risks and adjusted absolute RDs with robust 95% CIs were estimated using survey-weighted linear probability models.

Exploratory route-specific analyses separately compared maternal prophylaxis only, neonatal prophylaxis only, and combined maternal and neonatal prophylaxis with no prophylaxis, using a new within-hospital overlap-weight model for each pair. Because each comparison targets a different overlap population, route-specific estimates were not directly compared with one another. Sensitivity analyses included a pooled overlap-weight model with prespecified hospital interactions, the original ATE weights, and ATE weights truncated at the 1st and 99th percentiles. Analyses were performed in R version 4.5.0 using WeightIt version 2.0.0, cobalt version 5.0.0, and survey version 4.5.

Ethics

The study protocol was approved by the Michigan State University Biomedical and Health Institutional Review Board (MSU Study ID: STUDY00001738). Continuing review was approved on 7 February 2020 under submission CR00001049 and remained effective until 6 February 2021. The study was reviewed through the expedited non-committee review procedure under categories 3, 5, and 7. Written informed consent was obtained from all participating mothers or legal guardians in a language they understood before enrollment.

Permission to conduct the study at the participating hospitals was granted by the Education and Research Division of Dr. Mohammad Hoesin General Hospital, Palembang (approval No. LB.02.03/XVII.2.3/534/2019, dated 17 June 2019), and by the Director of Palembang BARI Regional General Hospital (approval No. 420/0222/RSUD/2019, dated 22 July 2019). All study procedures were conducted in accordance with applicable institutional and national ethical standards and regulations governing research involving human participants.

RESULTS

During the study period, 1,316 mother-newborn dyads were assessed as eligible. Among these dyads, 786 (59.7%) underwent cesarean delivery and 530 (40.3%) underwent vaginal delivery. A total of 1,002 dyads were enrolled, of whom 904 completed the 28-day follow-up and were included in the final analysis. The remaining 98 dyads were excluded because follow-up was incomplete. Among the 904 analyzed neonates, 94 (10.4%) developed neonatal sepsis and 810 (89.6%) did not.

Maternal, obstetric, delivery, and neonatal characteristics according to neonatal-sepsis status are presented in Table 1. In crude analyses, pregnancy weight gain below the recommended level,

fewer than four antenatal visits, rupture of membranes for more than 12 or 18 hours, foul-smelling amniotic fluid, and maternal leukocyte count >15,000/mm³ were associated with neonatal sepsis. In the adjusted model, foul-smelling amniotic fluid remained associated with a higher risk of sepsis (aRR, 1.60; 95% CI, 1.06-2.40). The adjusted estimates for rupture of membranes for more than 18 hours (aRR, 1.54; 95% CI, 0.90–2.61) and maternal leukocyte count >15,000/mm³ (aRR, 1.16; 95% CI, 0.78–1.72) were imprecise and included the null.

Neonatal characteristics showed strong crude associations with sepsis (Table 1, Panel B). Preterm birth, low birth weight, low Apgar scores, medical support, and feeding other than breast milk were more frequent among neonates who developed sepsis. After adjustment, low birth weight (aRR, 4.80; 95% CI, 3.19-7.23) and a 5-minute Apgar score <7 (aRR, 3.25; 95% CI, 2.10-5.02) remained associated with a higher risk of neonatal sepsis. Medical support and oral intake had large crude associations but were not included in the adjusted model because they could reflect care provided after illness had begun.

Among the 94 neonates with sepsis, 46 (48.9%) had EOS and 48 (51.1%) had LOS. For EOS, low birth weight (aRR, 4.75; 95% CI, 2.63-8.58) and a 5-minute Apgar score <7 (aRR, 3.86; 95% CI, 2.01-7.40) remained associated with higher risk after adjustment. The adjusted estimates for rupture of membranes >18 hours (aRR, 1.80; 95% CI, 0.89-3.64) and foul-smelling amniotic fluid (aRR, 1.64; 95% CI, 0.92-2.93) included the null.

For LOS, cesarean delivery (aRR, 2.35; 95% CI, 1.15-4.79), low birth weight (aRR, 4.84; 95% CI, 2.52-9.31), and a 5-minute Apgar score <7 (aRR, 2.74; 95% CI, 1.25-6.04) remained associated with higher risk after adjustment. Maternal leukocyte count >15,000/mm^3 had an aRR of 1.85 (95% CI, 0.97–3.54). Medical support and restricted oral intake were strongly associated with EOS

and LOS in crude analyses, but their temporal relationship to sepsis onset prevents interpretation as antecedent risk factors (Table 2).

Of the 46 EOS cases, 11 (23.9%) were culture proven, with coagulase-negative staphylococci (CoNS) accounting for 6 of the 11 isolates. Of the 48 LOS cases, 14 (29.2%) were culture proven; Klebsiella pneumoniae (6/14) and CoNS (5/14) were the most frequently isolated pathogens. Overall, 13 isolates were gram-positive and 12 were gram-negative. Gram-negative bacteria accounted for a larger proportion of LOS than EOS isolates (8/14 [57.1%] vs 4/11 [36.4%]). Eighteen of the 25 isolates (72.0%) were multidrug resistant (Table 3). Because CoNS may represent blood-culture contamination, the culture findings should be interpreted cautiously. Detailed organism-specific antimicrobial susceptibility results are provided in Additional file..

Table 3. Pathogens isolated from neonates with culture-proven sepsis

Isolated pathogen	EOS (n=11), n (MDR)	LOS (n=14), n (MDR)	Total (n=25), n (MDR)
Gram-negative bacteria	**4 (4)**	**8 (5)**	**12 (9)**
Acinetobacter baumannii	1 (1)	1 (1)	2 (2)
Enterobacter spp.	1 (1)	1 (1)	2 (2)
Klebsiella pneumoniae	2 (2)	6 (3)	8 (5)
Gram-positive bacteria	**7 (5)**	**6 (4)**	**13 (9)**
Coagulase-negative staphylococci	6 (4)	5 (3)	11 (7)
Staphylococcus aureus	1 (1)	1 (1)	2 (2)
Total	**11 (9)**	**14 (9)**	**25 (18)**

EOS, early-onset sepsis; LOS, late-onset sepsis; MDR, multidrug resistant. Values in parentheses indicate the number of MDR isolates.

Among the 904 analyzed dyads, 519 mothers (57.4%) received maternal antibiotic prophylaxis and 394 neonates (43.6%) received neonatal antibiotic prophylaxis. Overall, 651 neonates (72.0%) were exposed through at least one route. Of the total cohort, 257 (28.4%) were exposed to maternal

prophylaxis only, 132 (14.6%) to neonatal prophylaxis only, and 262 (29.0%) to both maternal and neonatal prophylaxis. The remaining 253 neonates (28.0%) were unexposed. Participant characteristics according to prophylaxis exposure are presented in Table 4.

The exposed and unexposed groups differed across several measured maternal, obstetric, and neonatal characteristics, including maternal and spouse education, household income, antenatal-visit frequency, birth attendant, mode of delivery, PROM/PPROM, prolonged rupture of membranes, foul-smelling amniotic fluid, maternal leukocyte count, birth weight, and Apgar scores (Table 4). These substantial baseline differences support the presence of confounding by indication and motivated the propensity-score weighted analysis.

Table 4. Characteristics of participants according to perinatal antibiotic-prophylaxis exposure

Panel A. Sociodemographic and maternal characteristics

Characteristic	Exposed (n=651), n (%)	Unexposed (n=253), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Maternal age			0.39		
<20 years	26 (4.0)	12 (4.7)		0.79 (0.39–1.61)	—
20–35 years	497 (76.3)	182 (71.9)		Reference	—
>35 years	128 (19.7)	59 (23.3)		0.79 (0.56–1.13)	—
Maternal education			<0.0001		
Less than high school	286 (43.9)	53 (21.0)		3.95 (2.40–6.50)	2.35 (1.16–4.75)
High school graduate	309 (47.5)	159 (62.9)		1.42 (0.91–2.22)	1.24 (0.69–2.23)
College or higher	56 (8.6)	41 (16.2)		Reference	Reference
Spouse's education			<0.0001		
Less than high school	253 (38.9)	48 (19.0)		3.95 (2.41–6.48)	1.74 (0.87–3.47)
High school graduate	338 (51.9)	160 (63.2)		1.58 (1.03–2.44)	1.38 (0.78–2.42)
College or higher	60 (9.2)	45 (17.8)		Reference	Reference
Persons per household			0.73		
<5	440 (67.6)	168 (66.4)		Reference	—
≥5	211 (32.4)	85 (33.6)		0.95 (0.70–1.29)	—
Household income			0.002		
Above poverty level	504 (77.4)	170 (67.2)		Reference	Reference
Below poverty level	147 (22.6)	83 (32.8)		0.60 (0.43–0.82)	0.69 (0.46–1.03)
Maternal smoking	0 (0)	0 (0)	—	—	—
Diabetes/gestational diabetes	4 (0.6)	0 (0)	0.58	3.53 (0.13–93.05)	—
Pre-pregnancy BMI			0.01		

Characteristic	Exposed (n=651), n (%)	Unexposed (n=253), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Underweight	87 (13.4)	26 (10.3)		1.54 (0.96–2.47)	1.19 (0.79–1.73)
Normal weight	389 (60.0)	179 (71.0)		Reference	Reference
Overweight or obese	172 (26.5)	47 (18.7)		1.68 (1.17–2.43)	1.50 (0.97–2.32)
Missing	3	1			
Pregnancy weight gain			0.02		
Below recommendation	380 (58.6)	123 (48.8)		1.61 (1.20–3.76)	1.17 (0.79–1.73)
Within recommendation	161 (24.8)	84 (33.3)		Reference	Reference
Above recommendation	107 (16.5)	45 (17.9)		1.24 (0.80–1.92)	0.89 (0.53–1.48)
Missing	3	1			
At least one antenatal visit	581 (89.3)	225 (88.9)	0.89	1.03 (0.65–1.64)	—
≥4 antenatal visits	316 (48.5)	146 (57.7)	0.01	0.69 (0.52–0.93)	0.87 (0.62–1.22)
Birth attendant			<0.0001		
Midwife	172 (26.4)	42 (16.6)		0.59 (0.38–0.92)	0.47 (0.23–0.75)
Resident	373 (57.3)	54 (21.3)		0.10 (0.07–0.14)	0.12 (0.08–0.18)
Obstetrician/gynecologist	106 (16.3)	157 (62.1)		Reference	Reference

250 **Panel B. Obstetric and neonatal characteristics**

Characteristic	Exposed (n=651), n (%)	Unexposed (n=253), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Obstetric Charateristics					
Parity			0.10		
<5	636 (97.7)	253 (100)		Reference	Reference
≥5	15 (2.3)	0 (0)		12.37 (0.67–228.13)	4.75 (0.22–104.59)
≥4 vaginal examinations	142 (21.8)	64 (25.3)	0.26	0.82 (0.29–1.16)	—
Mode of delivery			<0.0001		
Vaginal delivery	217 (33.3)	132 (52.2)		Reference	Reference
Cesarean delivery	434 (66.7)	121 (47.8)		2.18 (1.62–2.93)	2.92 (1.95–4.38)
Pregnancy type			0.02		
Singleton	609 (93.5)	250 (98.8)		Reference	Reference
Twin	28 (4.3)	3 (1.2)		3.74 (1.13–12.41)	2.71 (0.63–11.75)
Missing	14 (2.2)	0			
PROM/PPROM	199 (30.6)	9 (3.6)	<0.0001	11.93 (6.01–23.68)	12.29 (5.41–27.91)
Rupture of membranes >12 hours	99 (15.2)	2 (0.8)	<0.0001	22.50 (5.51–91.95)	—
Antepartum hemorrhage	7 (1.1)	0 (0)	0.20	5.90 (0.28–126.10)	3.58 (0.12–104.57)
Foul-smelling amniotic fluid	102 (15.7)	5 (2.0)	<0.0001	9.21 (3.70–22.89)	4.69 (1.82–12.05)
Maternal leukocyte count >15,000/mm³	141 (25.1)[a]	24 (16.3)[b]	0.03	1.72 (1.07–2.77)	1.16 (0.69–1.96)

Characteristic	Exposed (n=651), n (%)	Unexposed (n=253), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Intrapartum temperature ≥38°C	7 (1.1)	0 (0)	0.20	5.90 (0.28–126.10)	3.45 (0.09–136.80)
Neonatal Characteristics					
Sex			0.70		
Male	331 (50.8)	125 (49.4)		Reference	—
Female	320 (49.2)	128 (50.6)		0.94 (0.71–1.26)	—
Gestational age			0.08		
<32 weeks	31 (4.8)	4 (1.6)		3.15 (3.15–9.03)‡	0.53 (0.13–2.24)
32–36 weeks	140 (21.5)	54 (21.3)		1.05 (0.74–1.50)	0.88 (0.48–1.61)
≥37 weeks	480 (73.7)	195 (77.1)		Reference	Reference
Prematurity (<37 weeks)	171 (26.3)	58 (22.9)	0.31	1.20 (0.85–1.69)	—
Birth weight			0.01		
<1,000 g	5 (0.8)	0 (0)		4.73 (0.20–113.33)	2.03 (0.04–100.26)
1,000–1,499 g	26 (4.0)	2 (0.8)		4.55 (1.20–17.21)	2.40 (0.32–17.79)
1,500–2,499 g	142 (21.8)	46 (18.2)		1.32 (0.91–1.91)	0.84 (0.45–1.60)
≥2,500 g	478 (73.4)	205 (81.0)		Reference	Reference
Low birth weight (<2,500 g)	173 (26.6)	48 (19.0)	0.02	1.54 (1.07–2.20)	—
Apgar score at 1 minute			<0.001		
<7	109 (16.7)	17 (6.7)		2.73 (1.61–4.63)	2.96 (1.21–7.25)
≥7	542 (83.3)	236 (93.3)		Reference	Reference
Apgar score at 5 minutes			0.002		
<7	56 (8.6)	7 (2.8)		3.12 (1.43–6.82)	0.42 (0.14–1.27)
≥7	595 (91.4)	246 (97.2)		Reference	Reference

Data are presented as n (%) unless otherwise indicated. RR, relative risk; CI, confidence interval; BMI, body mass index; PROM, premature rupture of membranes; PPROM, preterm premature rupture of membranes. Reference denotes the reference category. Percentages for BMI and pregnancy weight gain were calculated using the available observations. [a]Eighty-nine exposed participants and [b]106 unexposed participants had missing maternal leukocyte-count data.

The documented indications for maternal and neonatal antibiotic prophylaxis are presented in Table 5. Multiple indications could be recorded for each participant. No documented indication was identified for 54 of 519 mothers (10.4%) and 173 of 394 neonates (43.9%) who received antibiotic prophylaxis.

Table 5. Documented indications for maternal and neonatal antibiotic prophylaxis

Prophylaxis recipient and documented indication	n (%)
Maternal prophylaxis (n=519)	
Cesarean delivery	358 (69.0)
PROM/PPROM	199 (38.3)
Intrapartum temperature ≥38°C	6 (1.2)
Maternal leukocyte count >15,000/mm³	109 (21.0)
Antepartum hemorrhage	6 (1.2)
No documented indication	54 (10.4)
Neonatal prophylaxis (n=394)	
Foul-smelling amniotic fluid	98 (24.9)
Rupture of membranes >12 hours	90 (22.8)
Maternal intrapartum temperature ≥38°C	6 (1.5)
Maternal leukocyte count >15,000/mm³	130 (33.0)
No documented indication	173 (43.9)

Data are presented as n (%). PROM, premature rupture of membranes; PPROM, preterm premature rupture of membranes. Participants could have more than one documented indication; therefore, percentages within each prophylaxis group do not sum to 100%.

Neonatal sepsis occurred in 90 of 651 exposed neonates (13.8%) and 4 of 253 unexposed neonates (1.6%; P<0.001). Sepsis occurred in 4 of 257 neonates exposed to maternal prophylaxis only (1.6%), 39 of 132 exposed to neonatal prophylaxis only (29.5%), and 47 of 262 exposed through both routes (17.9%). EOS occurred in 43 exposed neonates (6.6%) and 3 unexposed neonates (1.2%), whereas LOS occurred in 47 exposed neonates (7.2%) and 1 unexposed neonate (0.4%). These unadjusted comparisons do not account for the substantial baseline differences between exposure groups.

Table 6. Overlap-weighted associations between antibiotic-prophylaxis exposure and neonatal sepsis

Outcome and exposure comparison	Weighted risk, reference (%)	Weighted risk, exposed (%)	Adjusted RD (95% CI)	P value
Overall neonatal sepsis				
Any prophylaxis vs no prophylaxis	3.4	9.4	0.060 (0.012 to 0.109)	0.015
Maternal prophylaxis only vs no prophylaxis	2.3	1.4	-0.010 (-0.038 to 0.019)	0.503
Neonatal prophylaxis only vs no prophylaxis	5.5	20.4	0.149 (0.044 to 0.255)	0.006
Combined maternal and neonatal prophylaxis vs no prophylaxis	7.5	11.8	0.043 (-0.061 to 0.148)	0.417

Outcome and exposure comparison	Weighted risk, reference (%)	Weighted risk, exposed (%)	Adjusted RD (95% CI)	P value
Early-onset sepsis				
Any prophylaxis vs no prophylaxis	2.5	4.0	0.015 (-0.022 to 0.052)	0.432
Maternal prophylaxis only vs no prophylaxis	2.0	0.6	-0.014 (-0.040 to 0.011)	0.272
Neonatal prophylaxis only vs no prophylaxis	4.1	9.3	0.052 (-0.028 to 0.132)	0.204
Combined maternal and neonatal prophylaxis vs no prophylaxis	6.3	5.4	-0.010 (-0.092 to 0.073)	0.818
Late-onset sepsis				
Any prophylaxis vs no prophylaxis	0.8	5.4	0.045 (0.013 to 0.078)	0.006
Maternal prophylaxis only vs no prophylaxis	0.3	0.8	0.005 (-0.007 to 0.017)	0.439
Neonatal prophylaxis only vs no prophylaxis	1.4	11.2	0.097 (0.023 to 0.171)	0.010
Combined maternal and neonatal prophylaxis vs no prophylaxis	1.2	6.5	0.053 (-0.014 to 0.120)	0.121

Values are weighted outcome risks and adjusted absolute risk differences (RDs) estimated using within-hospital propensity-score overlap weights. The comparison of any prophylaxis with no prophylaxis was the primary analysis. Route-specific estimates were obtained from separate exploratory pairwise overlap-weight models; each has a different overlap population and reference risk and should not be directly compared across routes. CI, confidence interval; EOS, early-onset sepsis; LOS, late-onset sepsis. Positive RDs indicate higher weighted risk in the exposed group.

The original ATE-weighted model did not achieve adequate balance: 26 covariate indicators had an absolute SMD >=0.10, the maximum absolute SMD was 1.19, the maximum weight was 90.9, and the ESS among unexposed neonates was 9.2. Truncation at the 1st and 99th percentiles left 16 covariate indicators imbalanced (maximum absolute SMD, 0.38). In contrast, the primary within-hospital overlap-weight model balanced all included covariate indicators (maximum absolute SMD <0.001); the ESS was 181.4 among unexposed and 199.4 among exposed neonates, and the maximum weight was 1.00. Nevertheless, 45 of 904 participants (5.0%) had estimated propensity scores within 0.000001 of 0 or 1, confirming limited positivity and restricting inference to the overlap population. Detailed propensity-score diagnostics, covariate-balance results, weight distributions, and sensitivity analyses are provided in Additional file.

In the primary overlap-weighted analysis, the estimated risk of overall neonatal sepsis was 3.4% without prophylaxis and 9.4% with any prophylaxis (adjusted RD, 0.060; 95% CI, 0.012 to 0.109; P=0.015). The corresponding estimates were 2.5% and 4.0% for EOS (RD, 0.015; 95% CI, -0.022 to 0.052; P=0.432) and 0.8% and 5.4% for LOS (RD, 0.045; 95% CI, 0.013 to 0.078; P=0.006). In the exploratory pairwise analyses, neonatal prophylaxis alone was associated with a higher weighted risk of overall sepsis (RD, 0.149; 95% CI, 0.044 to 0.255; P=0.006) and LOS (RD, 0.097; 95% CI, 0.023 to 0.171; P=0.010). Maternal prophylaxis alone and combined maternal and neonatal prophylaxis were not associated with statistically significant risk differences for overall sepsis, EOS, or LOS (Table 6).

DISCUSSION

This prospective cohort study documented a high burden of neonatal sepsis and perinatal antibiotic exposure in two Indonesian referral hospitals. Neonatal sepsis occurred in 10.4% of the cohort, while 57.4% of mothers and 43.6% of neonates received antibiotic prophylaxis; 72.0% of neonates were exposed through at least one route. Although comparisons with other settings should account for differences in referral patterns, patient severity, prophylaxis protocols, and exposure definitions, the observed exposure was high.[17–20] The proportion of prophylaxis without a documented indication, particularly among neonates, identifies an important opportunity to strengthen documentation and antimicrobial stewardship.

After restricting inference to neonates with overlapping measured probabilities of receiving either exposure strategy, any perinatal prophylaxis was associated with higher weighted risks of overall sepsis and LOS, whereas the EOS estimate was small and imprecise. In exploratory pairwise analyses, neonatal prophylaxis alone was associated with higher weighted risks of overall

sepsis and LOS; maternal prophylaxis alone and combined prophylaxis were not associated with statistically significant risk differences. These route-specific estimates arise from different overlap populations and should not be interpreted as a direct comparison or ranking of prophylaxis routes. Previous studies have described changes in neonatal-sepsis pathogens and antimicrobial resistance after widespread perinatal prophylaxis, including increases in gram-negative, Escherichia coli, or antimicrobial-resistant infections in some settings.[10–12,21–23] However, the present findings do not establish that prophylaxis caused sepsis. Clinical indications, neonatal vulnerability, and care intensity remain plausible sources of residual confounding despite excellent balance in the measured covariates.[24,25]

Only 25 of the 94 sepsis cases were culture proven, and 18 of the 25 isolates were multidrug resistant. Gram-negative organisms accounted for a larger proportion of LOS than EOS isolates, with Klebsiella pneumoniae being the most frequent LOS pathogen. These findings may inform empirical treatment and stewardship policies, but the small number of isolates precluded reliable pathogen-specific or resistance-specific analyses. The high proportion of culture-negative cases may reflect prior antibiotic exposure, limited blood-culture sensitivity, low blood-sample volume, timing of specimen collection, or misclassification under the clinical-sepsis definition.20,27,28 In addition, CoNS accounted for more than half of the culture-proven EOS isolates and may have represented contamination in some cases.[18,26,27]

The risk-factor analysis identified low birth weight and a 5-minute Apgar score <7 as independent markers of overall sepsis, EOS, and LOS. Foul-smelling amniotic fluid was associated with overall sepsis, while cesarean delivery was associated with LOS. These estimates describe associations and should not be interpreted as causal effects. The models were limited by sparse

subtype events and complete-case analysis, and the large crude associations for medical support and oral intake may reflect care delivered in response to early illness.

A potential biological explanation for an association between early antibiotic exposure and later infection is disruption of neonatal microbial colonization and immune development.[28–30] However, microbiome composition was not measured, and this mechanism remains speculative. Alternative explanations include unmeasured differences in illness severity, invasive care, feeding, clinical surveillance, duration of hospitalization, and infection-prevention practices. Medical support and feeding status may also have reflected evolving illness rather than factors preceding sepsis and were therefore not included in the propensity-score models.

The strengths of this study include its prospective design, enrollment of 904 mother-newborn dyads, 28-day follow-up, inclusion of two referral hospitals, and detailed maternal and neonatal exposure data. The revised overlap-weight analysis directly addressed the severe instability and imbalance observed with conventional ATE weighting and achieved excellent balance in the measured covariates. Several limitations remain. First, overlap weighting changes the target population: the estimates apply to dyads whose measured characteristics were compatible with either exposure strategy and should not be generalized to all eligible dyads. The finding that 5.0% of propensity scores were extremely close to 0 or 1, together with markedly different prescribing patterns between hospitals, confirms limited positivity. Second, prophylaxis was not randomized, so unmeasured confounding by indication remains possible despite measured covariate balance. Third, only four unexposed neonates developed sepsis, including one LOS case, and the route-specific comparisons were sparse; estimates are consequently uncertain and each pairwise analysis pertains to a different overlap population. Fourth, clinical-sepsis criteria overlapped with some prophylaxis indications, creating potential circularity and outcome misclassification. Fifth, most

cases were not culture confirmed, and possible CoNS contamination limited microbiological certainty. Sixth, 98 enrolled dyads did not complete follow-up, introducing possible attrition bias. Seventh, the adjusted risk-factor models were complete-case analyses limited to 709 neonates because maternal leukocyte counts were missing for 195 participants; residual confounding and imprecision remain possible. Finally, maternal agent- and duration-specific analyses were limited by incomplete regimen documentation. Neonatal prophylaxis, however, consisted of a fixed 3-day ampicillin-gentamicin regimen; therefore, comparison according to neonatal antibiotic agent or duration were not applicable. Invalid source values prevented inclusion of the 1-minute Apgar score in the propensity models.

Conclusions

In this prospective cohort from two Indonesian referral hospitals, perinatal antibiotic-prophylaxis exposure was associated with higher risks of overall neonatal sepsis and LOS among dyads in the measured overlap population, while no clear association was observed for EOS. The route-specific findings were exploratory and do not support direct comparisons between prophylaxis strategies. Limited positivity, confounding by indication, sparse unexposed events, limited culture confirmation, and possible outcome misclassification preclude causal interpretation. The findings support improved prophylaxis documentation, stronger antimicrobial stewardship, standardized sepsis assessment, and prospective studies with prespecified exposure protocols and detailed microbiological data.

Ethics approval and consent to participate

The study protocol was approved by the Michigan State University Biomedical and Health Institutional Review Board (Study ID: STUDY00001738). Continuing ethical approval was

granted under reference number CR00001049 on 7 February 2020 and remained valid through 6 February 2021. Permission to conduct the study was also obtained from Dr. Mohammad Hoesin General Hospital (No. LB.02.03/XVII.2.3/534/2019; 17 June 2019) and Palembang BARI Hospital (No. 420/0222/RSUD/2019; 22 July 2019). Written informed consent was obtained from the mother or legal guardian of each participating newborn before enrollment. All procedures were performed in accordance with the applicable institutional ethical requirements.

Consent for publication

Not applicable; the manuscript does not report identifiable individual participant information.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was partially supported by the Michigan State University Asian Studies Center through the Koo Endowment. The funder had no role in the study design; data collection, management, analysis, or interpretation; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Authors' contributions

AK conceived the study, developed the study methodology, coordinated the investigation and data collection, interpreted the findings, and drafted the original manuscript. IB, AR, and YI contributed

to participant recruitment, clinical data collection, follow-up, and data curation. AM and NB contributed to the obstetric components of the study, including maternal assessment, participant recruitment, and interpretation of maternal and perinatal findings. ABA coordinated study implementation and data collection at Palembang BARI Hospital and contributed to the interpretation of the neonatal findings. MPW conducted additional data analyses, contributed to the interpretation of the findings, participated in manuscript drafting and critical revision, and assisted in preparing and finalizing the manuscript for submission. JG contributed to the statistical methodology, formal analysis, and interpretation of the results. LZ contributed to study conceptualization and methodology, supervised the study, and critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the mothers, neonates, and families who participated in this study. The authors also acknowledge the clinical, laboratory, and research staff of Dr. Mohammad Hoesin General Hospital and Palembang BARI Regional General Hospital for their assistance with participant recruitment, follow-up, clinical assessment, specimen processing, and data collection.

References

1. Sankar MJ. Neonatal sepsis in South Asia: huge burden and spiralling antimicrobial resistance. BMJ. 2019;1. doi:10.1136/bmj.k5314

2. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Bulletin of the World Health Organization Neonatal cause - of - death estimates for the early and late neonatal periods for 194 countries : 2000 – 2013. 2015;(April 2014):1–13.

3. World Health Organizaiton. Pocket Book of Hospital care for children. WHO. 2013. 1–399 p. doi:10.1111/j.1553-2712.1996.tb03308.x PubMed PMID: 8749973.

4. Schrag SJ, Zywicki SS, Farley MM, Reingold A, Harrison LH, Lefkowitz LB, et al. Group B Streptococcal Disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med. 2000;342(1):15–20.

5. Le Doare K, O'Driscoll M, Turner K, Seedat F, Russell NJ, Seale AC, et al. Intrapartum Antibiotic Chemoprophylaxis Policies for the Prevention of Group B Streptococcal Disease Worldwide: Systematic Review. Clin Infect Dis. 2017;65(Suppl 2):S143–51. doi:10.1093/cid/cix654 PubMed PMID: 29117324.

6. Ledger WJ, Blaser MJ. Are we using too many antibiotics during pregnancy? BJOG Int J Obstet Gynaecol. 2013;120(12):1450–2. doi:10.1111/1471-0528.12371 PubMed PMID: 24118809.

7. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463–70. doi:10.1073/pnas.1717295115 PubMed PMID: 29581252.

8. Seedat F, Stinton C, Patterson J, Geppert J, Tan B, Robinson ER, et al. Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: A systematic review. BMC Pregnancy Childbirth. 2017;17(1):1–14. doi:10.1186/s12884-017-1432-3 PubMed PMID: 28747160.

9. Tejada BM. Antibiotic use and misuse during pregnancy and delivery: Benefits and risks. Int J Environ Res Public Health. 2014;11(8):7993–8009. doi:10.3390/ijerph110807993

10. Levine EM, Ghai V, Barton JJ, Strom CM. Intrapartum antibiotic prophylaxis increases the incidence of gram-negative neonatal sepsis. Infect Dis Obstet Gynecol. 1999;7(4):210–3. doi:10.1155/S106474499900037X PubMed PMID: 10449272.

11. Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A, et al. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics. 2002 Oct 1;110(4):690–5. doi:10.1542/PEDS.110.4.690 PubMed PMID: 12359781.

12. Lin CY, Hsu CH, Huang FY, Chang JH, Hung HY, Kao HA, et al. The changing face of early-onset neonatal sepsis after the implementation of a maternal group b streptococcus screening and intrapartum prophylaxis policy - A study in one medical center. Pediatr Neonatol. 2011;52(2):78–84. doi:10.1016/j.pedneo.2011.02.001 PubMed PMID: 21524627.

13. Departemen Kebidanan & Penyakit Kandungan. Panduan Pelayanan Klinis Kebidanan dan Penyakit Kandungan. Palembang: RSUP dr. Mohammad Hoesin Palembang; 2012.

14. Departemen/SMF Keshatan Anak. Panduan Praktik Klinik (PPK). Palembang; 2014.

15. American Academy of Pediatrics. Committee on Infectious Diseases, Kimberlin DW, Brady MT, Jackson MA, Long SS. Red book : 2015 report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2015. 1151 p.

16. Clinical and Laboratory Standards Institute. Autoverification of Medical Laboratory Results for Specific Disciplines. 1st, editor. Wayne, PA: Clinical and Laboratory Standards Institute; 2019.

17. Pirracchio R, Carone M, Rigon MR, Caruana E, Mebazaa A, Chevret S. Propensity score estimators for the average treatment effect and the average treatment effect on the treated may yield very different estimates. Stat Methods Med Res. 2016 Oct 1;25(5):1938–54. doi:10.1177/0962280213507034

18. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol. 2019;188(1):250-257. doi:10.1093/aje/kwy201.

19. Sharma M, Sanneving L, Mahadik K, Santacatterina M, Dhaneria S, Stålsby Lundborg C. Antibiotic prescribing in women during and after delivery in a non-teaching, tertiary care hospital in Ujjain, India: a prospective cross-sectional study. J Pharm Policy Pract. 2013;6:9. doi:10.1186/2052-3211-6-9 PubMed PMID: 25848538; PubMed Central PMCID: PMC4366931.

20. Persaud RR, Azad MB, Chari RS, Sears MR, Becker AB, Kozyrskyj AL. Perinatal antibiotic exposure of neonates in Canada and associated risk factors: a population-based study. J Matern Fetal Neonatal Med. 2015 Jul 3;28(10):1190–5. doi:10.3109/14767058.2014.947578 PubMed PMID: 25053193.

21. Stokholm J, Schjørring S, Pedersen L, Bischoff AL, Følsgaard N, Carson CG, et al. Prevalence and Predictors of Antibiotic Administration during Pregnancy and Birth. PLOS ONE. 2013 Dec 10;8(12):e82932. doi:10.1371/journal.pone.0082932

22. Mensah KB, Opoku-Agyeman K, Ansah C. Antibiotic use during pregnancy: a retrospective study of prescription patterns and birth outcomes at an antenatal clinic in rural Ghana. J Pharm Policy Pract. 2017 Aug 9;10:24. doi:10.1186/s40545-017-0111-0 PubMed PMID: 28808578; PubMed Central PMCID: PMC5551012.

23. Shim GH, Kim SD, Kim HS, Kim ES, Lee HJ, Lee JA, et al. Trends in Epidemiology of Neonatal Sepsis in a Tertiary Center in Korea: A 26-Year Longitudinal Analysis, 1980-2005. J Korean Med Sci. 2011 Feb;26(2):284–9. doi:10.3346/jkms.2011.26.2.284 PubMed PMID: 21286023; PubMed Central PMCID: PMC3031016.

24. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in Pathogens Causing Early-Onset Sepsis in Very-Low-Birth-Weight Infants. N Engl J Med. 2002 Jul 25;347(4):240–7. doi:10.1056/NEJMoa012657

25. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-Five Years of Neonatal Sepsis at Yale: 1928–2003. Pediatrics. 2005 Sep 1;116(3):595–602. doi:10.1542/peds.2005-0552

26. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivar Behav Res. 2011 May;46(3):399–424. doi:10.1080/00273171.2011.568786 PubMed PMID: 21818162; PubMed Central PMCID: PMC3144483.

27. Hasibuan B. Comparison of microbial pattern in early and late onset neonatal sepsis in referral center Haji Adam Malik hospital Medan Indonesia. IOP Conf Ser Earth Environ Sci. 2018 Mar 23;125:012053. doi:10.1088/1755-1315/125/1/012053

28. Karmila A, Barchia I, Ramandati A, Zhang L. Clinical and bacteriological profile of culture-negative and culture-proven neonatal sepsis in Palembang, Indonesia. J Infect Dev Ctries. 2022 Dec 31;16(12):1887–96. doi:10.3855/jidc.14638 PubMed PMID: 36753657.

29. Keeney K, Yurist-Doutsch S, Arrieta MC, Finlay B. Effects of Antibiotics on Human Microbiota and Subsequent Disease. Annu Rev Microbiol. 2014 Sep 8;68:217–35. doi:10.1146/annurev-micro-091313-103456

30. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006 Aug;118(2):511–21. doi:10.1542/peds.2005-2824 PubMed PMID: 16882802.

31. Deshmukh HS, Liu Y, Menkiti OR, Mei J, Dai N, O'Leary CE, et al. The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice. Nat Med. 2014 May;20(5):524–30. doi:10.1038/nm.3542 PubMed PMID: 24747744; PubMed Central PMCID: PMC4016187.

Table 1. Association of maternal, obstetric, delivery, and neonatal characteristics with neonatal sepsis

Panel A. Maternal, obstetric, and delivery characteristics

Characteristic	Sepsis (n=94), n (%)	No sepsis (n=810), n (%)	Total (n=904), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Maternal age				0.263		
<20 years	6 (6.4)	32 (4.0)	38 (4.2)		1.65 (0.76–3.56)	—
20–35 years	65 (69.1)	614 (75.8)	679 (75.1)		Reference	—
>35 years	23 (24.5)	164 (20.2)	187 (20.7)		1.28 (0.82–2.01)	—
Maternal education				0.062		
Less than high school	42 (44.7)	297 (36.7)	339 (37.5)		3.00 (1.10–8.17)	—
High school graduate	48 (51.1)	420 (51.9)	468 (51.8)		2.49 (0.92–6.74)	—
College or higher	4 (4.3)	93 (11.5)	97 (10.7)		Reference	—
Spouse's education				0.554		
Less than high school	36 (38.3)	265 (32.7)	301 (33.3)		1.26 (0.65–2.44)	—
High school graduate	48 (51.1)	450 (55.6)	498 (55.1)		1.01 (0.53–1.93)	—
College or higher	10 (10.6)	95 (11.7)	105 (11.6)		Reference	—
Persons per household				0.380		
<5	67 (71.3)	541 (66.8)	608 (67.3)		Reference	—
≥5	27 (28.7)	269 (33.2)	296 (32.7)		0.83 (0.54–1.27)	—
Household income				0.108		
Above poverty level	77 (81.9)	597 (74.3)	674 (75.1)		Reference	—
Below poverty level	17 (18.1)	206 (25.7)	223 (24.9)		0.67 (0.40–1.10)	—
Missing	0	7	7			
Maternal smoking	0 (0)	0 (0)	0 (0)	1.000	NE	—
Diabetes/gestational diabetes	0 (0)	4 (0.5)	4 (0.4)	1.000	NE	—
Pre-pregnancy BMI				0.584		
Underweight	14 (15.1)	97 (12.0)	111 (12.4)		1.31 (0.76–2.27)	—
Normal weight	56 (60.2)	525 (65.2)	581 (64.7)		Reference	—
Overweight or obese	23 (24.7)	183 (22.7)	206 (22.9)		1.16 (0.73–1.83)	—
Missing	1	5	6			

Characteristic	Sepsis (n=94), n (%)	No sepsis (n=810), n (%)	Total (n=904), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Pregnancy weight gain				0.015		
Below recommendation	65 (69.9)	438 (54.3)	503 (55.9)		1.98 (1.17–3.35)	—
Within recommendation	16 (17.2)	229 (28.4)	245 (27.2)		Reference	—
Above recommendation	12 (12.9)	140 (17.3)	152 (16.9)		1.21 (0.59–2.49)	—
Missing	1	3	4			
At least one antenatal visit	85 (90.4)	721 (89.0)	806 (89.2)	0.677	1.15 (0.60–2.21)	—
≥4 antenatal visits	37 (39.4)	425 (52.5)	462 (51.1)	0.016	0.62 (0.42–0.92)	—
Parity				1.000		
<5	93 (98.9)	796 (98.3)	889 (98.3)		Reference	—
≥5	1 (1.1)	14 (1.7)	15 (1.7)		0.64 (0.10–4.27)	—
≥4 vaginal examinations	16 (17.0)	190 (23.5)	206 (22.8)	0.159	0.70 (0.42–1.16)	—
Mode of delivery				0.608		
Vaginal delivery	34 (36.2)	315 (38.9)	349 (38.6)		Reference	Reference
Cesarean delivery	60 (63.8)	495 (61.1)	555 (61.4)		1.11 (0.74–1.65)	1.18 (0.80–1.73)
Birth attendant				0.003		
Midwife	27 (28.7)	187 (23.1)	214 (23.7)		1.00 (0.65–1.54)	—
Resident	13 (13.8)	250 (30.9)	263 (29.1)		0.39 (0.22–0.70)	—
Obstetrician/gynecologist	54 (57.4)	373 (46.0)	427 (47.2)		Reference	—
Pregnancy type				0.361		
Singleton	89 (94.7)	784 (96.8)	873 (96.6)		Reference	—
Twin	5 (5.3)	26 (3.2)	31 (3.4)		1.58 (0.69–3.62)	—
PROM/PPROM	29 (30.9)	179 (22.1)	208 (23.0)	0.056	1.49 (0.99–2.25)	—
Rupture of membranes >12 hours	17 (18.1)	84 (10.4)	101 (11.2)	0.025	1.76 (1.08–2.84)	—
Rupture of membranes >18 hours	12 (12.8)	34 (4.2)	46 (5.1)	0.002	2.73 (1.61–4.63)	1.54 (0.90–2.61)
Antepartum hemorrhage	1 (1.1)	6 (0.7)	7 (0.8)	0.538	1.38 (0.22–8.54)	—
Foul-smelling amniotic fluid	24 (25.5)	83 (10.2)	107 (11.8)	<0.001	2.55 (1.68–3.88)	1.60 (1.06–2.40)
Maternal leukocyte count >15,000/mm³	30 (37.5)	135 (21.5)	165 (23.3)	0.001	1.98 (1.30–3.00)	1.16 (0.78–1.72)
Missing	14	181	195			
Intrapartum temperature ≥38 °C	0 (0)	6 (0.7)	6 (0.7)	1.000	NE	—

527

Panel B. Neonatal characteristics

Characteristic	Sepsis (n=94), n (%)	No sepsis (n=810), n (%)	Total (n=904), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Sex				0.098		
Male	55 (58.5)	401 (49.5)	456 (50.4)		Reference	—
Female	39 (41.5)	409 (50.5)	448 (49.6)		0.72 (0.49–1.06)	—
Gestational age				<0.001		
<32 weeks	8 (8.5)	27 (3.3)	35 (3.9)		3.59 (1.83–7.04)	—
32–36 weeks	43 (45.7)	151 (18.6)	194 (21.5)		3.48 (2.35–5.15)	—
≥37 weeks	43 (45.7)	632 (78.0)	675 (74.7)		Reference	—
Prematurity (<37 weeks)	51 (54.3)	178 (22.0)	229 (25.3)	<0.001	3.50 (2.40–5.10)	—
Birth weight				<0.001		
<1,000 g	2 (2.1)	3 (0.4)	5 (0.6)		7.59 (2.48–23.25)	—
1,000–1,499 g	12 (12.8)	16 (2.0)	28 (3.1)		8.13 (4.77–13.85)	—
1,500–2,499 g	44 (46.8)	144 (17.8)	188 (20.8)		4.44 (2.95–6.69)	—
≥2,500 g	36 (38.3)	647 (79.9)	683 (75.6)		Reference	—
Low birth weight (<2,500 g)	58 (61.7)	163 (20.1)	221 (24.4)	<0.001	4.98 (3.38–7.33)	4.80 (3.19–7.23)
Early initiation of breastfeeding	8 (8.5)	250 (30.9)	258 (28.5)	<0.001	0.23 (0.11–0.47)	—
Apgar score at 1 minute				<0.001		
<7	38 (49.4)	88 (11.3)	126 (14.7)		5.65 (3.77–8.47)	—
≥7	39 (50.6)	692 (88.7)	731 (85.3)		Reference	—
Missing	17	30	47			
Apgar score at 5 minutes				<0.001		
<7	24 (25.5)	39 (4.8)	63 (7.0)		4.58 (3.11–6.74)	3.25 (2.10–5.02)
≥7	70 (74.5)	771 (95.2)	841 (93.0)		Reference	Reference
Medical support				<0.001		
None	31 (33.0)	708 (87.4)	739 (81.7)		Reference	—
Non-invasive support	59 (62.8)	96 (11.9)	155 (17.1)		9.07 (6.09–13.52)	—
Invasive support	4 (4.3)	6 (0.7)	10 (1.1)		9.54 (4.14–21.95)	—
Oral intake during the first days of life for >24 hours				<0.001		

Characteristic	Sepsis (n=94), n (%)	No sepsis (n=810), n (%)	Total (n=904), n (%)	P value	Crude RR (95% CI)	Adjusted RR (95% CI)
Breast milk	27 (28.7)	619 (76.4)	646 (71.5)		Reference	—
Breast milk and infant formula	15 (16.0)	151 (18.6)	166 (18.4)		2.16 (1.18–3.97)	—
Infant formula	6 (6.4)	8 (1.0)	14 (1.5)		10.25 (5.05–20.83)	—
Nothing orally	46 (48.9)	32 (4.0)	78 (8.6)		14.11 (9.34–21.33)	—

Data are presented as n (%) unless otherwise indicated. RR, risk ratio; aRR, adjusted risk ratio; CI, confidence interval; BMI, body mass index; PROM, premature rupture of membranes; PPROM, preterm premature rupture of membranes; NE, not estimable. Crude and adjusted RRs were estimated using modified Poisson regression with robust standard errors. The adjusted model included study hospital, cesarean delivery, rupture of membranes >18 hours, foul-smelling amniotic fluid, maternal leukocyte count >15,000/mm³, birth weight <2,500 g, and 5-minute Apgar score <7. Adjusted estimates are shown only for variables included in this model. The adjusted analysis included 709 complete records. For binary characteristics shown as a single row, absence of the characteristic was the reference category. Percentages were calculated from available observations. Missing values were recorded for household income (n=7), BMI (n=6), pregnancy weight gain (n=4), maternal leukocyte count (n=195), and 1-minute Apgar score (n=47). One implausible birth-weight entry of 35,000 g was corrected to 3,500 g.

Table 2. Associations of maternal, obstetric, delivery, and neonatal characteristics with early- and late-onset neonatal sepsis

Panel A. Maternal, obstetric, and delivery characteristics

Characteristic	EOS (n=46), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	LOS (n=48), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Maternal age						
<20 years	3 (6.5)	1.68 (0.54–5.22)	—	3 (6.2)	1.62 (0.52–5.06)	—
20–35 years	32 (69.6)	Reference	—	33 (68.8)	Reference	—
>35 years	11 (23.9)	1.25 (0.64–2.43)	—	12 (25.0)	1.32 (0.70–2.51)	—
Maternal education						
Less than high school	20 (43.5)	1.91 (0.58–6.29)	—	22 (45.8)	6.29 (0.86–46.11)	—
High school graduate	23 (50.0)	1.59 (0.49–5.19)	—	25 (52.1)	5.18 (0.71–37.79)	—
College or higher	3 (6.5)	Reference	—	1 (2.1)	Reference	—
Spouse's education						
Less than high school	17 (37.0)	0.74 (0.33–1.67)	—	19 (39.6)	3.31 (0.79–13.99)	—
High school graduate	21 (45.7)	0.55 (0.25–1.22)	—	27 (56.2)	2.85 (0.69–11.79)	—
College or higher	8 (17.4)	Reference	—	2 (4.2)	Reference	—
Persons per household						
<5	31 (67.4)	Reference	—	36 (75.0)	Reference	—
≥5	15 (32.6)	0.99 (0.55–1.81)	—	12 (25.0)	0.68 (0.36–1.30)	—
Household income						
Above poverty level	37 (80.4)	Reference	—	40 (83.3)	Reference	—
Below poverty level	9 (19.6)	0.74 (0.36–1.50)	—	8 (16.7)	0.60 (0.29–1.27)	—
Missing	0			0		
Maternal smoking	0 (0)	NE	—	0 (0)	NE	—
Diabetes/gestational diabetes	0 (0)	NE	—	0 (0)	NE	—
Pre-pregnancy BMI						
Underweight	7 (15.2)	1.31 (0.59–2.92)	—	7 (14.9)	1.31 (0.59–2.92)	—
Normal weight	28 (60.9)	Reference	—	28 (59.6)	Reference	—
Overweight or obese	11 (23.9)	1.11 (0.56–2.19)	—	12 (25.5)	1.21 (0.63–2.33)	—
Missing	0			1		
Pregnancy weight gain						
Below recommendation	33 (71.7)	2.30 (1.03–5.12)	—	32 (68.1)	1.73 (0.84–3.57)	—
Within recommendation	7 (15.2)	Reference	—	9 (19.1)	Reference	—
Above recommendation	6 (13.0)	1.38 (0.47–4.03)	—	6 (12.8)	1.07 (0.39–2.96)	—
Missing	0			1		
At least one antenatal visit	42 (91.3)	1.28 (0.47–3.48)	—	43 (89.6)	1.05 (0.42–2.58)	—
≥4 antenatal visits	18 (39.1)	0.62 (0.35–1.10)	—	19 (39.6)	0.63 (0.36–1.10)	—

Characteristic	EOS (n=46), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	LOS (n=48), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Parity						
<5	45 (97.8)	Reference	—	48 (100.0)	Reference	—
≥5	1 (2.2)	1.32 (0.19–8.94)	—	0 (0)	NE	—
≥4 vaginal examinations	12 (26.1)	1.20 (0.63–2.27)	—	4 (8.3)	0.31 (0.11–0.85)	—
Mode of delivery						
Vaginal delivery	24 (52.2)	Reference	Reference	10 (20.8)	Reference	Reference
Cesarean delivery	22 (47.8)	0.58 (0.33–1.01)	0.67 (0.38–1.19)	38 (79.2)	2.39 (1.21–4.73)	2.35 (1.15–4.79)
Birth attendant						
Midwife	18 (39.1)	1.50 (0.83–2.70)	—	9 (18.8)	0.60 (0.29–1.24)	—
Resident	4 (8.7)	0.27 (0.09–0.77)	—	9 (18.8)	0.49 (0.23–1.01)	—
Obstetrician/gynecologist	24 (52.2)	Reference	—	30 (62.5)	Reference	—
Pregnancy type						
Singleton	42 (91.3)	Reference	—	47 (97.9)	Reference	—
Twin	4 (8.7)	2.68 (1.03–7.01)	—	1 (2.1)	0.60 (0.09–4.20)	—
PROM/PPROM	14 (30.4)	1.46 (0.80–2.69)	—	15 (31.2)	1.52 (0.84–2.74)	—
Rupture of membranes >12 hours	9 (19.6)	1.93 (0.96–3.89)	—	8 (16.7)	1.59 (0.77–3.30)	—
Rupture of membranes >18 hours	7 (15.2)	3.35 (1.58–7.07)	1.80 (0.89–3.64)	5 (10.4)	2.17 (0.90–5.21)	1.33 (0.51–3.50)
Antepartum hemorrhage	0 (0)	NE	—	1 (2.1)	2.73 (0.43–17.10)	—
Foul-smelling amniotic fluid	14 (30.4)	3.26 (1.80–5.91)	1.64 (0.92–2.93)	10 (20.8)	1.96 (1.01–3.82)	1.51 (0.76–3.01)
Maternal leukocyte count >15,000/mm³	12 (29.3)	1.36 (0.71–2.61)	0.70 (0.39–1.27)	18 (46.2)	2.83 (1.54–5.18)	1.85 (0.97–3.54)
Missing	5			9		
Intrapartum temperature ≥38 °C	0 (0)	NE	—	0 (0)	NE	—

Panel B. Neonatal characteristics

Characteristic	EOS (n=46), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	LOS (n=48), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Sex						
Male	25 (54.3)	Reference	—	30 (62.5)	Reference	—
Female	21 (45.7)	0.86 (0.49–1.50)	—	18 (37.5)	0.61 (0.35–1.08)	—
Gestational age						
<32 weeks	3 (6.5)	2.14 (0.68–6.72)	—	5 (10.4)	6.03 (2.34–15.51)	—
32–36 weeks	16 (34.8)	2.06 (1.13–3.75)	—	27 (56.2)	5.87 (3.23–10.67)	—
≥37 weeks	27 (58.7)	Reference	—	16 (33.3)	Reference	—
Prematurity (<37 weeks)	19 (41.3)	2.07 (1.18–3.66)	—	32 (66.7)	5.90 (3.30–10.54)	—

Characteristic	EOS (n=46), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	LOS (n=48), n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Birth weight						
<1,000 g	1 (2.2)	6.83 (1.12–41.55)	—	1 (2.1)	8.54 (1.39–52.63)	—
1,000–1,499 g	2 (4.3)	2.44 (0.60–9.93)	—	10 (20.8)	15.25 (7.62–30.51)	—
1,500–2,499 g	23 (50.0)	4.18 (2.35–7.44)	—	21 (43.8)	4.77 (2.54–8.95)	—
≥2,500 g	20 (43.5)	Reference	—	16 (33.3)	Reference	—
Low birth weight (<2,500 g)	26 (56.5)	4.02 (2.29–7.05)	4.75 (2.63–8.58)	32 (66.7)	6.18 (3.46–11.05)	4.84 (2.52–9.31)
Early initiation of breastfeeding	4 (8.7)	0.24 (0.09–0.66)	—	4 (8.3)	0.23 (0.08–0.63)	—
Apgar score at 1 minute						
<7	16 (42.1)	4.22 (2.28–7.81)	—	22 (56.4)	7.51 (4.10–13.74)	—
≥7	22 (57.9)	Reference	—	17 (43.6)	Reference	—
Missing	8			9		
Apgar score at 5 minutes						
<7	12 (26.1)	4.71 (2.57–8.64)	3.86 (2.01–7.40)	12 (25.0)	4.45 (2.44–8.12)	2.74 (1.25–6.04)
≥7	34 (73.9)	Reference	Reference	36 (75.0)	Reference	Reference
Medical support						
None	17 (37.0)	Reference	—	14 (29.2)	Reference	—
Non-invasive support	27 (58.7)	7.57 (4.23–13.55)	—	32 (66.7)	10.90 (5.96–19.93)	—
Invasive support	2 (4.3)	8.69 (2.31–32.73)	—	2 (4.2)	10.56 (2.75–40.47)	—
Oral intake during the first days of life for >24 hours						
Breast milk	11 (23.9)	Reference	—	16 (33.3)	Reference	—
Breast milk and infant formula	9 (19.6)	3.18 (1.34–7.56)	—	6 (12.5)	1.46 (0.58–3.67)	—
Infant formula	3 (6.5)	12.58 (3.94–40.21)	—	3 (6.2)	8.65 (2.84–26.35)	—
Nothing orally	23 (50.0)	17.32 (8.78–34.15)	—	23 (47.9)	11.91 (6.58–21.55)	—

Data are presented as n (%) among EOS or LOS cases unless otherwise indicated. EOS, early-onset sepsis; LOS, late-onset sepsis; RR, risk ratio; aRR, adjusted risk ratio; CI, confidence interval; BMI, body mass index; PROM, premature rupture of membranes; PPROM, preterm premature rupture of membranes; NE, not estimable. Crude and adjusted RRs were estimated for each subtype as a binary outcome in the full cohort using modified Poisson regression with robust standard errors. The adjusted model included study hospital, cesarean delivery, rupture of membranes >18 hours, foul-smelling amniotic fluid, maternal leukocyte count >15,000/mm³, birth weight <2,500 g, and 5-minute Apgar score <7. Adjusted estimates are shown only for variables included in this model. The adjusted analyses included 709 complete records, including 41 EOS and 39 LOS events. For binary characteristics shown as a single row, absence of the characteristic was the reference category. Maternal leukocyte-count data were missing for five EOS and nine LOS cases; 1-minute Apgar scores were invalid or missing for eight EOS and nine LOS cases.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2.xlsx
- Additionalfile1.docx