Early empirical antibiotics and adverse clinical outcomes in infants born very preterm: A population-based cohort

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Objective The objective of this study was to evaluate the association between empirical antibiotic therapy in the first postnatal week in uninfected infants born very preterm and the risk of adverse outcomes until discharge.

Study design Population-based, nationwide registry study in Norway including all live-born infants with a gestational age <32 weeks surviving first postnatal week without sepsis, intestinal perforation, or necrotizing enterocolitis (NEC) between 2009 and 2018. Primary outcomes were severe NEC, death after the first postnatal week, and/or a composite outcome of severe morbidity (severe NEC, severe bronchopulmonary dysplasia [BPD], severe retinopathy of prematurity, late-onset sepsis, or cystic periventricular leukomalacia). The association between empirical antibiotics and adverse outcomes was assessed using multivariable logistic regression models, adjusting for known confounders.

Results Of 5296 live-born infants born very preterm, 4932 (93%) were included. Antibiotics were started in first postnatal week in 3790 of 4932 (77%) infants and were associated with higher aOR of death (aOR 9.33; 95% CI: 1.10-79.5, P = .041), severe morbidity (aOR 1.88; 95% CI: 1.16-3.05, P = .01), and severe BPD (aOR 2.17; 95% CI: 1.18-3.98; P = .012), compared with those not exposed. Antibiotics ≥ 5 days were associated with higher odds of severe NEC (aOR 2.27; 95% CI: 1.02-5.06; P = .045). Each additional day of antibiotics was associated with 14% higher aOR of death or severe morbidity and severe BPD.

Conclusions Early and prolonged antibiotic exposure within the first postnatal week was associated with severe NEC, severe BPD, and death after the first postnatal week. *(J Pediatr 2022;■:1-8)*.

Antibiotics are the most commonly prescribed medication in the neonatal intensive care unit (NICU).[1,2] Over 75% of infants with very low birth weight (<1500 g) and over 90% of infants born extremely preterm (<28 weeks of gestation) receive empirical antibiotics within the first week after birth due to risk of early-onset sepsis (EOS).[2-5] Many infants receive prolonged courses of antibiotics,[4,6] despite the absence of positive blood cultures or clinical signs to support EOS.[2,7,8]

Prolonged antibiotic exposure in early life may have lasting effects on the intestinal microbiota.[9,10] Studies have reported associations between early and prolonged antibiotic exposure in infants born very preterm (<32 weeks of gestation) and adverse clinical outcomes, including increased risk of necrotizing enterocolitis (NEC) and death.[2,6,11-13] Recent studies have challenged these findings, reporting either no association between prolonged early antibiotics and risk of death or NEC[14] or even a protective effect against NEC when antibiotics are given in the first days after birth, compared with no antibiotics.[15,16]

Observational studies reporting associations between antibiotics and adverse outcomes are prone to different types of bias, including selection bias and confounding by indication.[17,18] An ongoing randomized clinical trial is investigating the effects of early antibiotics vs no antibiotics; however, results are not expected until the earliest in 2024.[19] High-quality, population-based studies are probably the best alternative to randomized clinical trials to elucidate on this complex

BPD	Bronchopulmonary dysplasia
BW	Birth weight
CRIB	Clinical risk index for babies
EOS	Early-onset sepsis
IVH	Intraventricular hemorrhage
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit

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All phases of this study were supported by Stavanger University Hospital, Norway, and research grants from the Western and Northern Norway Regional Health Trusts. The authors declare no conflicts of interest.

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https://doi.org/10.1016/j.jpeds.2022.09.029

topic. As controversy remains, we aimed to describe associations between empiric antibiotic exposure during the first postnatal week and adverse clinical outcomes in an unselected population of all infants born very preterm in Norway during 2009 to 2018.

Methods

This population-based study included all live-born infants with a gestational age <32 weeks, born in Norway from January 1, 2009, through December 31, 2018. Infants who developed culture-proven sepsis, intestinal perforation, NEC, or who died during the first postnatal week were excluded, in line with previous studies.[2,14,20-22]

All infants born very preterm in Norway are admitted to 1 of 21 NICUs across 4 health trust regions. All NICUs have donor milk available from breast milk banks for infants born very preterm. Very few infants receive formula prior to 33-34 weeks postmenstrual age. Probiotics were sporadically used for infants born extremely preterm in Norway between 2014 and 2017. There was no national guideline for empirical antibiotic therapy for EOS, but all units used ampicillin or penicillin combined with an aminoglycoside.

Data were obtained from the Norwegian Neonatal Network, a consistent and reliable[23] national population-based health registry where data on investigations, treatments, and diagnoses on all infants admitted to a NICU are registered daily by the attending physician.[23-25] We retrieved background data including birth region, year of birth, mode of delivery, birth weight (BW), BW *z* score,[26] gestational age, clinical risk index for babies (CRIB2),[27] Apgar score, plurality, sex, antenatal steroids, and clinical data including antibiotic use in calendar days, mechanical ventilation, growth velocity, common morbidities of prematurity, and mortality before discharge. The total number of live-born infants was obtained from the medical birth registry of Norway.[28] The regional ethical committee for medical and health research ethics approved this project (REK Helse Sør Øst 2012/944).

Exposures

Early empirical antibiotics was defined as antibiotics given within the first postnatal week. In order to compare our results with other studies,[2,11,14,15,22] we explored different categories of early empirical antibiotics: any exposure to antibiotics in the first 3 or 7 days after birth and antibiotic duration in the first postnatal week subdivided into 3 categories; a short course (1-3 days) and 2 prolonged course categories (4-7 days and 5-7 days). We also examined the effect of each additional day of antibiotic exposure as a continuous measure.

Covariates and Confounders

Gestational age was based on prenatal ultrasound in week 17-19. BW < 10th percentile was classified as small for gestational age.[26] Unadjusted comparisons of antibiotic exposure groups will be biased due to confounding by indication. The following potential confounders were therefore registered in the study and controlled for in the analyses: gestational age (in days), sex, multiple births, mode of delivery, CRIB2, Apgar score at 5 minutes, intraventricular hemorrhage[29] (grade 3 or 4), receiving antenatal steroids or not, days of mechanical ventilation within the first postnatal week, BW *z* score, year of birth, and health trust region.

Outcomes and Definitions

Primary outcomes were severe NEC, death after the first postnatal week, or the composite outcome of severe morbidity including any of the following outcomes diagnosed after the first postnatal week and until discharge; severe NEC (defined as Bells stage ≥2b treated with laparotomy after the first postnatal week[30]), severe bronchopulmonary dysplasia (BPD, receiving any respiratory support at 36 weeks postmenstrual age), severe retinopathy of prematurity[31,32] (stages 3-5 and/or treated with laser or antivascular endothelial growth factor, in either eye), late-onset sepsis (LOS) or cystic periventricular leukomalacia (stage ≥2[33]). Secondary outcomes were the individual components of severe morbidity. Sepsis was defined as growth of a pathogen in a blood culture and antibiotic treatment for ≥5 days or death before 5 days during the episode. Sepsis was classified as EOS (≤72 hours)[34] or LOS (>72 hours).[35] Growth of coagulase-negative staphylococci in a single blood culture (obtained >72 hours) was classified as sepsis if the baby had clinical symptoms, received minimum 5 days antibiotic therapy, and had C-reactive protein > 10 mg/L.

Statistical Analyses

Descriptive results are expressed as counts and proportions for categorical variables and as means and SD for continuous variables. Group comparisons were performed with χ^2 and ANOVA/Student *t* tests, respectively. Annual proportions of antibiotic exposure and treatment duration were assessed and compared in regression models (logistic and linear), and are presented with 95% CIs allowing for clustering on siblings. Two-sided *P* values <.05 were considered significant.

Missing values (**Table I**; available at www.jpeds.com) were imputed using multiple imputation by chained equations using logistic regression or predictive mean matching with 5 nearest neighbors for categorical and continuous variables, respectively. All confounders were included in the imputation models, along with all individual outcomes, the exposures number of days of antibiotics within the first postnatal week and antibiotics given the first 3 days after birth (yes/no), and the variables CRIB2 and growth velocity.[36] The variables gestational age, BW *z* score, year of birth, Apgar score at 5 minutes, and days with antibiotics were all introduced into the imputation models as restricted cubic splines with 3 knots. Twenty imputed data sets were created. The main analyses were binary logistic regression with allowance for clustering on siblings. All potential confounders were included in the models. The effects of gestational age, BW *z* scores, and year of birth were modeled nonlinearly using restricted cubic splines with 3 knots. Results were averaged over imputation

samples by Rubins rule and are reported as aORs with 95% CIs. The set of confounders was highly predictive with an area under receiver operating curves above 0.87 for both the composite outcome of severe morbidity and mortality (**Table II**; available at www.jpeds.com).[37] Finally, we assessed the linearity of the effects of each day of antibiotic exposure on the outcomes in complete case logistic regression models, using restricted cubic splines with up to 5 knots. We used IBM SPSS Statistics (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0), and Stata (StataCorp. 2021. Stata Statistical Software: Release 17) for analyses.

Results

There were 601 668 live-born infants in Norway between 2009 and 2018. Of these, 5296 (0.88%) infants were born at <32 weeks; 3646 (69%) at 28-31 weeks and 1650 (31%) before 28 weeks. Within the first postnatal week, 239 of 5296 (4.5%) infants died and 87 of 5296 (1.6%) had culture-proven sepsis. **Figure 1** (available at www.jpeds.com) shows the 4932 infants who survived the first 7 days without sepsis, intestinal perforation or NEC and were included in the final analysis. There were marked differences in baseline characteristics between infants receiving 0, 1-3 days, 4-7 days, or 5-7 days of antibiotics in the first postnatal week (**Table III**). Infants receiving prolonged antibiotics were smaller, had lower Apgar, and higher CRIB2 scores.

Most infants (3715 of 4932; 75%) started antibiotics within the first 3 days after birth (**Table IV**). During the study period there was a marked reduction in the proportion exposed to antibiotics during the first postnatal week declining from 82% (95% CI 78%-85%) in 2009 to 66% (95% CI 61%-71%) in 2018, $P < .001$ (**Figure 2**, A). There was also a reduction in the proportion of infants exposed to prolonged antibiotics (≥5 days) in the absence of sepsis, from 55% (95% CI 51%-60%) in 2009 to 24% (95% CI 20%-28%) in 2018, $P < .001$ (**Figure 2**, B). Among those receiving antibiotics, the duration of antibiotics decreased by approximately 1.5 days during the study period, $P < .001$ (**Figure 2**, C and D).

At least 1 severe morbidity was present in 1051 (21%) infants and 187 (3.8%) died >7 days after birth (**Table V**; available at www.jpeds.com). The infants born extremely preterm accounted for 60% (624 of 1051) of infants with severe morbidity and 84% (153 of 187) of all deaths. Severe NEC occurred in 1.4 % (71 of 4932) of all infants born very preterm and 4.3% (60 of 1403) of all infants born extremely preterm. Among infants with severe NEC, 22

Table III. Baseline characteristics of all very preterm (n = 4932) and extremely preterm infants (n = 1403) and early antibiotics

Antibiotic exposure, N (%)	No	1-3 d	4-7 d	≥5 d	P*	P†	P‡
• All <32 wk	n = 1142 (23.1%)	n = 1016 (20.6%)	n = 2774 (56.2%)	n = 2149 (43.5%)			
• Below 28 wk	n = 17 (1.2%)	n = 131 (9.3%)	n = 1255 (89.5%)	n = 1112 (79.2%)			
Antenatal steroids, N (%)							
• All < 32 wk	921 (81)	839 (83)	2371 (85)	1842 (86)	.01	.012	.007
• Below 28 wk	17 (100)	120 (92)	1127 (90)	992 (89)	.37	.65	.070
BW, mean (SD), g							
• All < 32 wk	1481 (297)	1379 (353)	1082 (383)	1027 (369)	<.001	<.001	<.001
• Below 28 wk	953 (3019	886 (238)	808 (201)	802 (197)	<.001	<.001	<.001
Gestational age, mean (SD), w							
• All < 32 wk	30.1 (1)	29.1 (1)	28.0 (2)	27.1 (2)	<.001	<.001	<.001
• Below 28 wk	26.5 (1)	26.5 (1)	26 (1)	25.1 (1)	<.001	<.001	<.001
Cesarean delivery, N (%)							
• All < 32 wk	629 (55)	450 (44)	1446 (52)	1156 (54)	<.001	<.001	.001
• Below 28 wk	10 (59)	50 (38)	583 (46)	531 (48)	.11	.07	.005
Multiple birth, N (%)							
• All < 32 wk	404 (35)	350 (34)	731 (26)	543 (25)	<.001	<.001	<.001
• Below 28 wk	3 (18)	36 (27)	308 (25)	278 (25)	.6	.46	.70
Small for gestational age, N (%)							
• All < 32 wk	343 (30)	200 (20)	771 (28)	627 (29)	<.001	<.001	<.001
• Below 28 wk	3 (18)	23 (18)	281 (22)	251 (23)	.41	.20	.23
Sex, male, N (%)							
• All < 32 wk	595 (52)	547 (54)	1546 (56)	1204 (56)	.1	.3	.061
• Below 28 wk	10 (59)	62 (47)	670 (53)	591 (53)	.37	.19	.74
Apgar score <7 at 5 min, N (%)							
• All < 32 wk	98 (9)	148 (15)	827 (30)	697 (32)	<.001	<.001	<.001
• Below 28 wk	4 (24)	36 (27)	495 (39)	445 (40)	.013	.007	.004
CRIB2 score, mean (SD)							
• All < 32 wk	4 (2)	5 (3)	8 (4)	9 (4)	.001	<.001	<.001
• Below 28 wk	11 (3)	11 (3)	12 (3)	12 (3)	0.16	<.001	<.001

Data are presented as No. (%) unless otherwise indicated.
*Comparison of 3 groups no antibiotics vs 1-3 days and 4-7 days using χ^2 test or ANOVA.
†Comparison of 2 groups 1-3 days vs 4-7 days using χ^2 test or Student *t* test.
‡Comparison of 2 groups 0-4 days of antibiotics vs ≥5 days using χ^2 test or Student *t* test.

Table IV. Distribution of mortality and morbidities among very preterm infants (n = 4932) and early empirical antibiotic exposure

Outcomes	Antibiotic (AB) exposure in first wk of life					
	No AB first 72 h n = 1217	No AB first wk of life n = 1142	Start AB first 72 h n = 3715	1-3 d AB duration n = 1016	4-7 d AB duration n = 2774	≥5 d AB duration n = 2149
Severe NEC*, N (%)	1 (0.1)	1 (0.1)	70 (2)	6 (0.6)	64 (2)	62 (3)
Death after first postnatal wk, N (%)	2 (0.2)	1 (0.1)	185 (5)	18 (2)	173 (6)	156 (7)
Severe morbidity† or death after first postnatal wk, N (%)	59 (5)	47 (4)	992 (27)	120 (12)	884 (32)	786 (37)
Severe morbidity† at discharge, N (%)	59 (5)	47 (4)	897 (24)	112 (11)	797 (29)	706 (33)
LOS after first postnatal wk,‡ N (%)	32 (3)	30 (3)	443 (12)	51 (5)	394 (14)	345 (16)
Severe BPD§ (36 wk), N (%)	37 (3)	32 (3)	649 (17)	75 (7)	579 (21)	513 (24)
Severe ROP¶ (treated), N (%)	11 (1)	10 (1)	207 (6)	16 (2)	192 (7)	178 (8)
Cystic periventricular leukomalacia, N (%)	16 (1)	11 (1)	123 (3)	26 (3)	102 (4)	86 (4)

ROP, retinopathy of prematurity.
Data are presented as No. (%).
Surgery for NEC was performed at median (IQR) 17 (11, 32) days of age.
*Severe NEC: necrotizing enterocolitis, defined as Bells stage 2 or 3 and diagnosed after the first postnatal week requiring severe intervention/review.
†Severe morbidity is any severe BPD, cystic PVL, severe NEC after the first postnatal week or severe ROP in either eye during the hospital stay, or death after the first postnatal week.
‡LOS: late-onset sepsis, culture-proven after the first postnatal week.
§Severe BPD: Severe bronchopulmonary dysplasia, defined as receiving any respiratory support (not solely oxygen) at 36 wk postmenstrual age.
¶ROP: severe retinopathy of prematurity, defined as stage 3-5 and/or any treated ROP (laser or antivascular endothelial growth factor therapy) at any stage in either eye.

(31%) died after the first postnatal week. Severe BPD occurred in 14% (686 of 4932) of all infants born very preterm and in 33% (457 of 1403) of all infants born extremely preterm. LOS was diagnosed in 10% (475 of 4932) of all infants born very preterm and 25% (352 of 1403) of all infants born extremely preterm. The first LOS episode was diagnosed at median 16 (10, 28) days of postnatal age.

After adjusting for CRIB2 and relevant confounders, infants exposed to any antibiotics within the first postnatal week had after the first postnatal week increased adjusted odds of death (aOR 9.33, 95% CI 1.10-79.5; $P = .041$), severe morbidity or death (aOR 2.07, 95% CI 1.30-3.30; $P = .002$), severe morbidity at discharge (aOR 1.88, 95% CI 1.16-3.05, $P = .01$), and severe BPD (aOR 2.17, 95% CI 1.18-3.98; $P = .012$), compared with infants not exposed to antibiotics in the first postnatal week. Similar or even stronger associations between antibiotic exposures and morbidities and mortality were found if only adjusted for CRIB2 (**Table VI**; available at www.jpeds.com) or if we analyzed infants exposed to antibiotics only within the first 3 postnatal days compared with no antibiotics (**Table VII**; available at www.jpeds.com).

Infants exposed to prolonged antibiotic courses ≥ 5 days had more than a double increase in adjusted odds of severe NEC compared with those exposed to antibiotics for 0-4 days. Compared with infants not exposed to antibiotics, those exposed to 1-3 days or 4-7 days of antibiotics during the first postnatal week had higher adjusted odds of death and/or severe morbidity (**Table VIII**). Overall, each additional day of empirical antibiotics was associated with 14% higher aOR for death and/or severe morbidity ($P = .001$) (**Table VIII**). Finally, prolonged courses of antibiotics (≥4 days) during the first week were associated with an increase in aOR of severe BPD compared with no antibiotics, and each additional day of empirical antibiotics increased the odds of severe BPD by 14% ($P = .005$). The increasing aORs for each day of antibiotics for both severe morbidity with or without death and severe BPD were tested for nonlinearity, and all P values were >0.35 (**Figure 3**; available at www.jpeds.com). Prolonged courses (4-7 days) of antibiotics were not associated with significantly increased odds of severe NEC, death or severe morbidity, and severe BPD, compared with a short course (1-3 days, **Table VIII**). For the other individual components (LOS, cystic periventricular leukomalacia, and retinopathy of prematurity) of the composite outcome of severe morbidity there were no significant differences in aORs in relation to antibiotic exposure. We performed supplemental analyses of the outcomes presented in **Tables VII** and **VIII** but without severe intraventricular hemorrhage as a confounder. These analyses showed very little change in the aORs and no differences in the statistical significance of the findings.

Discussion

In this 10-year population-based nationwide study, we examined associations between early empirical antibiotics and severe morbidity/death in infants born very preterm who survived for 7 days after birth free of NEC, intestinal perforation, and sepsis. In these infants, exposure to empirical antibiotics within the first 3 or 7 days after birth, independent of duration, was associated with increased odds of severe morbidity or death and severe BPD after adjusting for established indicators of illness severity and potential confounders.[38,39] Antibiotics administered ≥5 days were associated with a more than 2-fold increased adjusted odds

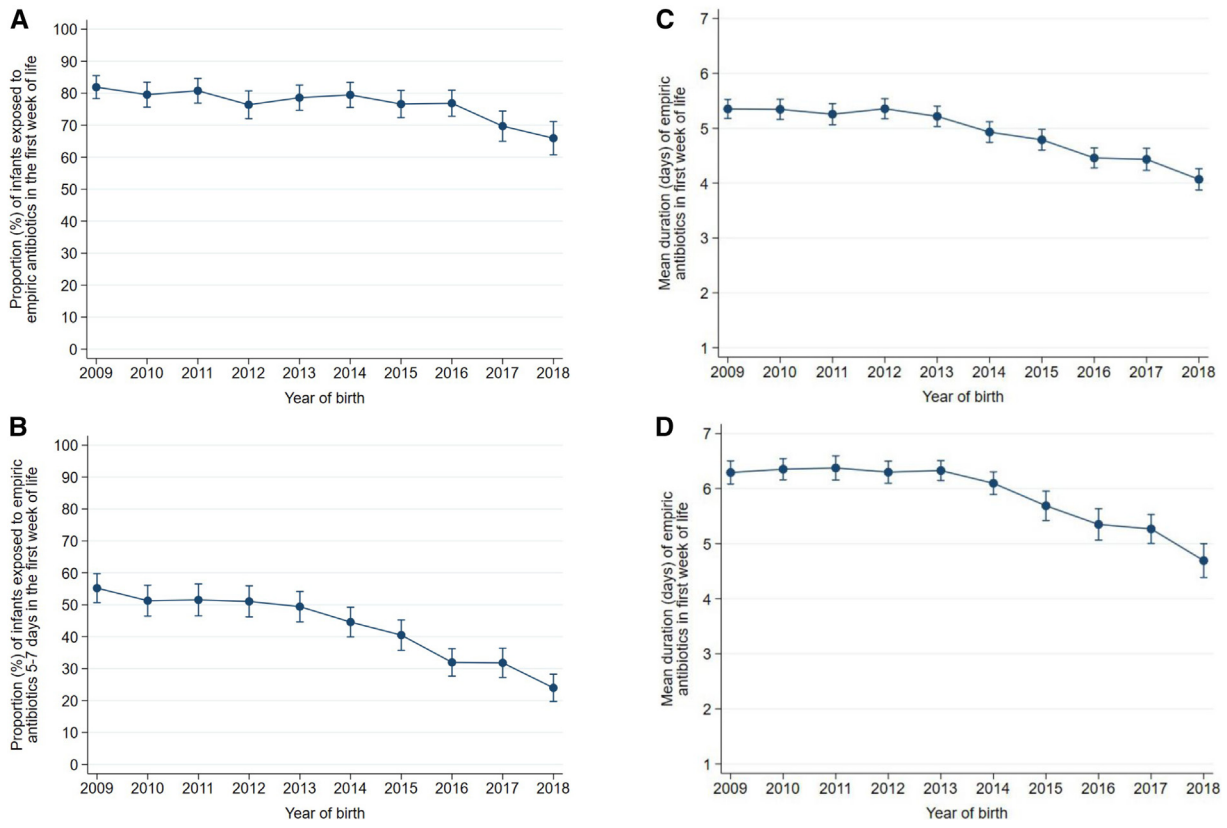

Figure 2. Empirical antibiotics; the first postnatal week in infants born very preterm, Norway 2009-2018. Error bars: 95% CI. **A**: Proportion (%) exposed to antibiotics overall (n = 4932). **B**: Proportion (%) exposed to antibiotics ≥5 days (n = 4932). **C**: Mean duration (days) of antibiotics, among all infants treated (n = 3790). **D**: Mean duration (days) of antibiotics, among treated infants <28 weeks (n = 1386).

of severe NEC and with increased odds of severe BPD. During the 10-year study period, there was an overall decrease in exposure and duration of empirical antibiotics.

Infants exposed to any antibiotics during first postnatal week had an approximately 9-fold increased aOR of death compared with no exposure, verified using multiple statistical models. However, we appreciate wide CIs for all analyses indicating uncertainty with effect estimates and a risk of residual confounding when evaluating mortality in observational trials.[37] Moreover, 41 of 187 infants born very preterm who died after the first postnatal week had severe intraventricular hemorrhage, and some deaths were due to withdrawal of care. Still, our results suggest that empirical antibiotics within the first postnatal week may be associated with increased risk of death in noninfected infants, as observed by others.[13,21] Any antibiotic exposure was also associated with increased odds of severe morbidity, mainly due to increased odds of severe BPD and NEC. We found a linear dose-effect with increasing days of exposure associated with increasingly adjusted odds of severe morbidities.

NEC definitions vary in the literature.[40] Our "severe NEC" definition is in line with the one used by the UK neonatal network.[30] We excluded NEC-cases in the first postnatal week for 3 reasons. First, if there is a causality between antibiotic exposure and adverse outcomes related to gut microbiome disruption, we aimed to assess all outcomes after and not during exposure. Second, "preterm NEC" more commonly occurs after first postnatal week.[41] Third, spontaneous intestinal perforation may be misclassified as NEC but usually occurs earlier, thus by excluding the early "NEC-cases," we pragmatically reduce misclassifications.[41-43] Using a strict NEC definition is important to identify infants that may benefit most from interventions or prophylactic strategies.[30]

We found neither a protective nor a harmful effect of shorter antibiotic exposure initiated within the first days after birth in relation to severe NEC. Our data contradicts a suggested protective effect of early antibiotics against NEC, proposed in recent studies applying wider NEC definitions, including studies with a majority of medical NEC cases.[13,15,16,44] In 2009, Cotten et al[2] reported an association between prolonged empirical antibiotics and NEC. This association was subsequently reported by many others.[13,20,45,46] However, a later study from the US Neonatal Research Network revealed no association between prolonged antibiotics and NEC/death.[14] In contrast, a Canadian study showed that prolonged early antibiotic exposure in infants with very low birth weights was associated with increased odds of the

Table VIII. aOR for mortality and morbidities among very preterm infants (n = 4932) and early empirical antibiotic exposure

	aOR for adverse outcomes in re lation to antibiotic (AB) exposure					
	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)
Outcomes	Any AB vs no AB first 7 d†	1–3 d vs no AB†	4–7 d vs no AB†	4–7 d vs 1–3 d AB‡	≥ 5 d vs 0-4 d AB§	Each additional day of AB
Severe NEC¶	2.25 (0.28-18.4)	2.02 (0.22-18.3)	2.37 (0.28-19.8)	1.17 (0.46-2.98)	**2.27 (1.02-5.06)**	1.18 (0.97-1.43)
Death after the first postnatal wk	**9.33 (1.10-79.5)**	**10.2 (1.14-91)**	**8.9 (1.03-77)**	0.87 (0.43-1.79)	1.27 (0.70-2.31)	1.16 (0.99-1.35)
Severe morbidity** or death after the first postnatal wk	**2.07 (1.30-3.30)**	**1.87 (1.11-3.13)**	**2.22 (1.35-3.64)**	1.19 (0.81-1.74)	**1.59 (1.15-2.20)**	**1.14 (1.05-1.22)**
Severe morbidity at discharge**,††	**1.88 (1.16-3.05)**	1.69 (0.99-2.88)	**2.03 (1.22-3.38)**	1.20 (0.80-1.80)	**1.58 (1.12-2.21)**	**1.12 (1.04-1.21)**
LOS after the first postnatal wk‡‡	0.92 (0.56-1.50)	0.84 (0.48-1.46)	0.97 (0.58-1.62)	1.16 (0.77-1.74)	1.21 (0.88-1.68)	1.01 (0.93-1.09)
Severe BPD (36 wk)§§	**2.17 (1.18-3.98)**	1.89 (0.97-3.71)	**2.36 (1.25-4.47)**	1.25 (0.77-2.03)	**1.61 (1.08-2.39)**	**1.14 (1.04-1.25)**
Severe ROP (treated)¶¶	0.68 (0.23-2.03)	0.46 (0.12-1.71)	0.81 (0.26-2.51)	1.76 (0.70-4.44)	1.55 (0.81-2.96)	1.07 (0.92-1.25)
cPVL, N (%)	1.35 (0.57-3.16)	1.68 (0.67-4.20)	1.10 (0.45-2.72)	0.66 (0.34-1.28)	0.83 (0.46-1.48)	0.96 (0.84-1.10)

AB, antibiotics; *cPVL*, cystic periventricular leukomalacia.
P values <.05 are indicated in bold.
*Adjusted for gestational age (nonlinear), sex, multiple births, mode of delivery, antibiotics (AB); CRIB2, Apgar score at 5 min, antenatal steroids, days of mechanical ventilation within the first postnatal week, birth weight Z score (nonlinear), intraventricular hemorrhage grade 3-4, year of birth (nonlinear) and birth region.
†Reference is 0 days.
‡Reference is 1-3 days.
§Reference is 0-4 days.
¶Severe NEC; necrotizing enterocolitis, defined as Bells stage 2 or 3 and diagnosed after the first postnatal week requiring severe intervention/review. Surgery for NEC was performed at median 17 (11, 32) days of age.
**Severe morbidity; any severe BPD, cPVL, severe NEC after the first postnatal week or severe ROP in either eye during the hospital stay.
††Deaths (n = 187) excluded from the analysis.
‡‡LOS; late-onset sepsis, culture-proven.
§§Severe BPD; severe bronchopulmonary dysplasia, defined as receiving any respiratory support (not solely oxygen) at 36 weeks postmenstrual age.
¶¶ROP; severe retinopathy of prematurity, defined as stage 3-5 and/or any treated ROP in either eye.

composite outcome mortality or any severe morbidity (severe neurologic injury, retinopathy of prematurity, NEC, BPD, or hospital-acquired infection).[11] We also found that antibiotic courses ≥5 days in uninfected infants born very preterm was strongly associated with increased odds of severe NEC. Our data support a policy of restrictive use of empirical antibiotics in the first postnatal week, limiting antibiotic exposure to 48-72 hours if sterile blood cultures and withholding antibiotics in low-risk infants.[11,47,48]

We found a more than 2-fold increase in adjusted odds of severe BPD in infants exposed to antibiotics during the first postnatal week and a dose-effect with increasing days of exposure. In our model, we adjusted for days on mechanical ventilation in the first postnatal week as an important measure of early respiratory disease severity.[22] Other studies have also explored the association between early antibiotics and BPD.[11,21,22,45,46] One study found no association between early antibiotics and BPD, after adjusting for early respiratory support.[22] In contrast, 3 other large North American studies reported associations between antibiotic duration and increased risk of and/or severity of BPD.[11,21,45] Finally, among low-risk infants born extremely preterm in a French population-based study, early antibiotics usage was associated with a 2.3 aOR of moderate-severe BPD.[46] There is a paucity of biological data explaining the mechanism between antibiotic exposure and BPD, but respiratory tract dysbiosis has been linked to onset, progression, and severity of BPD.[49-52] It has also been speculated that gut dysbiosis may trigger systemic inflammation, influencing BPD development.[53,54] Finally, we cannot exclude residual confounding, for example, that an early noninfectious inflammatory response may have led to more antibiotic therapy in the first postnatal week and also a higher risk of later BPD.

The proportion of infants exposed to prolonged empirical antibiotics (≥5 days) in our study was high. This may have increased the statistical power to find differences and thereby show that prolonged antibiotics were associated with adverse outcomes, in line with studies in similar populations.[11,16,21] We were encouraged by observing a large reduction in antibiotic use among infants born very preterm in Norway from 2009 to 2018 and believe this is the result of increasing national focus on antibiotic overuse over the last decade. Similar trends were also reported in a US cohort of infants with very low birth weights.[14] There are ongoing quality improvement projects in Norway aiming at reducing antibiotic use in infants.[55,56] These and other antibiotic stewardship programs have shown it feasible and safe to reduce unnecessary antibiotics in infants born at term[24,55,56] and preterm.[57]

The population-based design is a major strength and avoids selection bias. Daily prospective recording in the registry ensures almost complete data sets. It is impossible to adjust and control for all potential confounders,[39] but we adjusted for established predictors for mortality and morbidity. Definitions and categorical groupings were chosen to align with other relevant studies,[2,6,11,14,15,21,22,58] but we acknowledge that 2 of these studies[2,14] included smaller infants than our cohort. The main limitation is the observational study design with potential for confounding by indication; the sickest babies receive more antibiotics. We carefully adjusted for a set of confounders showing high predictive values for morbidity and mortality and thereby reducing

risk of confounding.[37] However, there was also a correlation between our set of confounders and antibiotic exposure, but to a lower degree for antibiotic duration in days, therefore reducing the likelihood of confounding by indication for these analyses. We also acknowledge that, in line with similar observational studies,[11,14] we did not adjust *P* values for multiple outcome measures. We were unable to report data on chorioamnionitis or intrapartum antibiotics. In Norway, all infants born very preterm receive human milk in the first several weeks after birth. Our findings may not be generalizable to settings with different nutritional practices. We included a 10-year cohort with almost 5000 infants, but larger studies with inclusion of more infants born extremely preterm may be needed to identify robust estimates on possible harmful effects of different durations of antibiotics on low-incidence outcomes like NEC.

In this population-based study, any early empiric antibiotic exposure was associated with increased adjusted odds of severe morbidity, severe BPD, and death in infants born very preterm. The adjusted odds of severe NEC increased after more than 4 days of antibiotic exposure during the first postnatal week. A significant reduction in early antibiotic use was observed during the study period. Our study underscores the need for continuous efforts to reduce unnecessary antibiotics. ■

We thank professor Knut Øymar at Stavanger University Hospital for statistical advice and for reviewing the manuscript and we thank participating hospitals contributing with data to the Norwegian Neonatal Network and thus making this study possible.

Submitted for publication Apr 7, 2022; last revision received Sep 15, 2022; accepted Sep 22, 2022.

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Data Statement

Data sharing statement available at www.jpeds.com.

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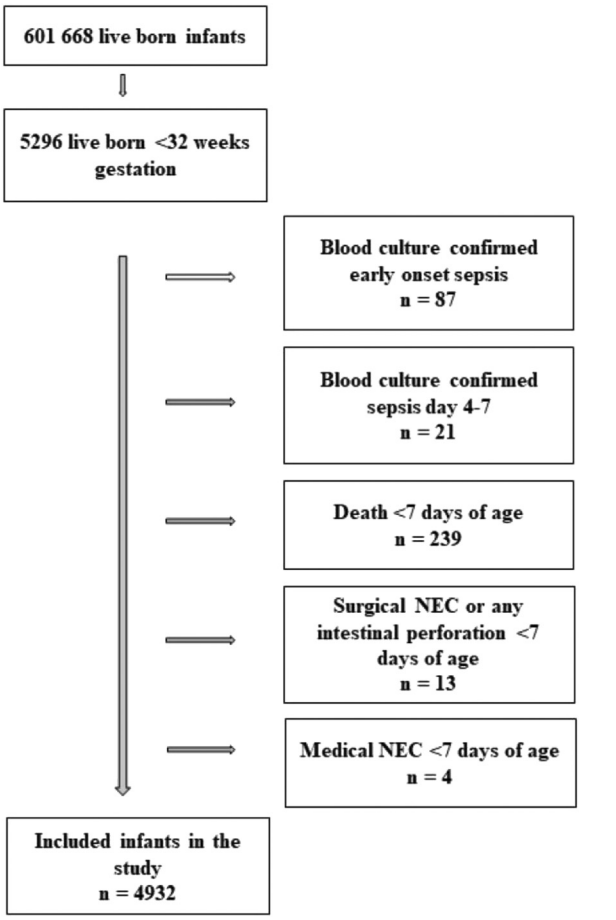

Figure 1. Infants born very preterm in Norway during 2009-2018 and study inclusion.

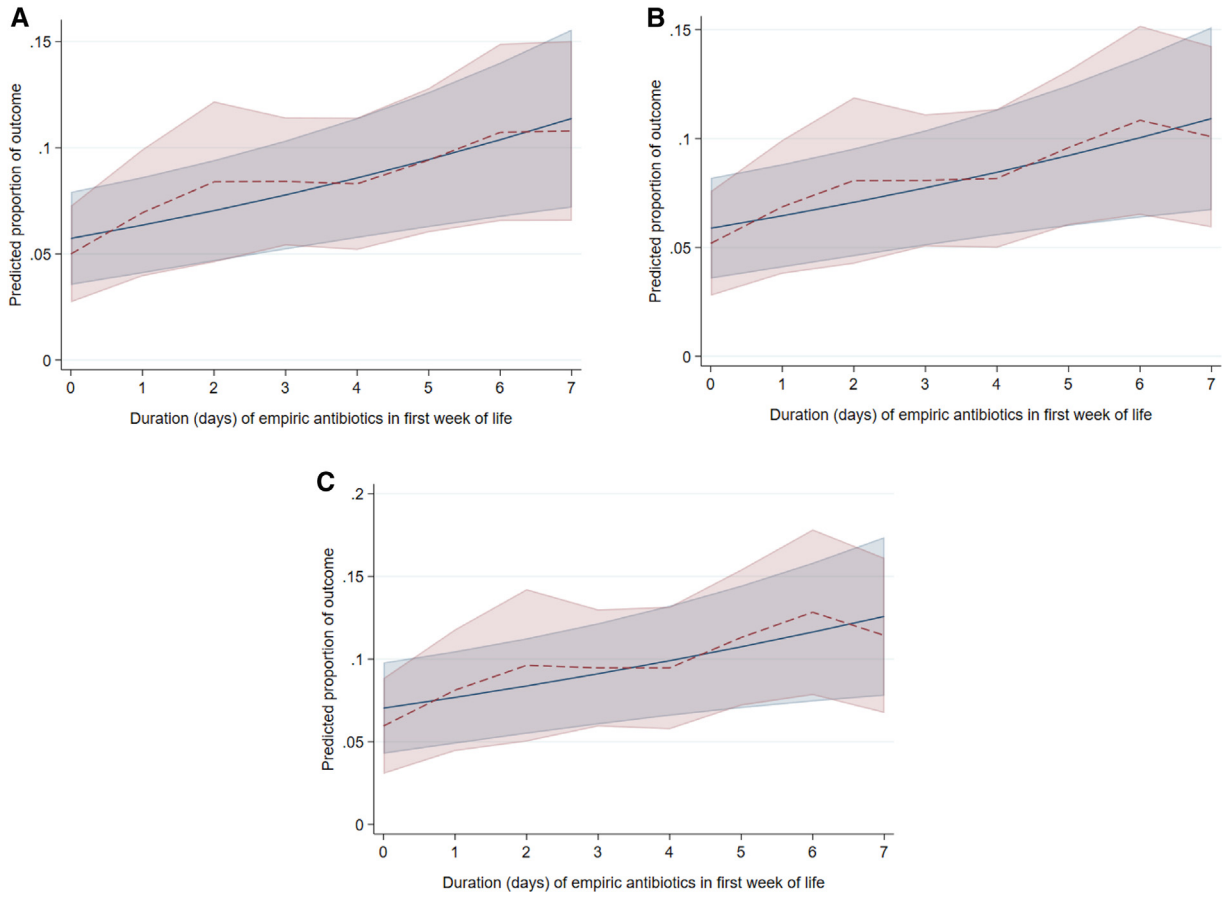

Figure 3. Assessment of increasing risks for each day of antibiotics for selected outcomes. **A**: Severe morbidity or death after first postnatal week (n = 4577). aOR 1.14 (1.05-1.22). Test for nonlinearity $P = .559$. **B**: Severe morbidity at discharge (n = 4404). aOR 1.12 (1.04-1.21). Test for nonlinearity $P = .524$. **C**: Severe bronchopulmonary dysplasia (n = 4577). aOR 1.14 (1.04-1.25). Test for nonlinearity $P = .366$. Nonlinear modelling applying restricted cubic splines with 5 knots. Predicted proportions estimated for region 1, singleton boy delivered by sectio, gestational age 208 days, birth weight *z* score −.72, Apgar 5 = 8, CRIB_2 = 6, no IVH, ANS = yes, 0 days of mechanical ventilation first week, birth year 2018. Linear model fits added for comparison. Complete case analysis with adjustment for clustering on siblings. *P* values from tests of non-linearity in log-odds implied. *ANS*, antenatal steroids; *IVH*, intraventricular hemorrhage.

Table I. Missing values in study data (n = 4932). Data on all other variables used were complete

Confounders	Number missing values (%)
CRIB2	269 (5.5)
Antenatal steroids	110 (2.2)
Outcome	
Late-onset sepsis; after first postnatal wk	2 (0.04)
Severe retinopathy of prematurity	8 (0.2)
Auxiliary (used in MICE)	
Growth velocity (g/kg/d) until 34 wk postmenstrual age	305 (6.2)

CRIB2, clinical risk index for babies 2; *MICE*, Missing Imputation by Chained Equations.

Table II. Predictive performance of CRIB2 and the final model with included confounders regarding outcomes and antibiotics

Outcomes	CRIB2 n = 4663	All included confounders n = 4577
Severe morbidity* or death after the first postnatal wk	0.831[n = 4656]	0.882
Severe morbidity (deaths excluded)	0.820[n = 4481]	0.868[n = 4404]
Death†	0.839	0.898
Severe NEC‡	0.866	0.891
Severe BPD§	0.806	0.864
Severe ROP¶	0.867	0.890
cPVL	0.691	0.802
LOS after the first postnatal wk**	0.813[n = 4661]	0.845[n = 4575]
Antibiotic exposure		
Any exposure the first postnatal wk	0.788	0.856
Exposure first 3 postnatal days	0.805	0.867
Exposure > 4 d	0.775	0.836
Each additional day of antibiotics[1]	0.565	0.684

cPVL, cystic periventricular leukomalacia.
Predictive performance given as area under receiver operating curves (AUROC) for CRIB2 or for the predicted probabilities for model with more confounders, except each additional day of antibiotics[1] analyzed by Pearson correlation.
*Severe morbidity; any severe BPD, cPVL, severe NEC, or severe ROP in either eye during the hospital stay, but after the first postnatal week.
†Death after first postnatal week.
‡Severe NEC; necrotizing enterocolitis, defined as Bells stage 2 or 3 and diagnosed after the first postnatal week requiring surgical intervention.
§Severe BPD; severe bronchopulmonary dysplasia, defined as receiving any respiratory support (not solely oxygen) at 36 weeks postmenstrual age.
¶ROP: severe retinopathy of prematurity, defined as stage 3-5 and/or any treated ROP in either eye.
**Late-onset sepsis: Culture-proven sepsis after the first postnatal week.

Table V. Distribution of outcomes according to gestational age groups

Outcomes	Infants < 28 wk n = 1403	Infants 28-31 wk n = 3529	All infants < 32 wk n = 4932
Severe NEC*, N (%)	60 (4.3)	11 (0.3)	71 (1.4)
Death after first postnatal wk, N (%)	153 (10.9)	34 (1.0)	187 (3.8)
Severe morbidity† or death after first postnatal wk, N (%)	703 (50.1)	348 (9.9)	1051 (21.3)
Severe morbidity† at discharge, N (%)	624 (44.5)	332 (9.4)	956 (19.4)
LOS after first postnatal wk‡, N (%)	352 (25.1)	123 (3.5)	475 (9.6)
Severe BPD§, N (%)	457 (32.6)	229 (6.5)	686 (13.9)
Severe ROP¶, N (%)	176 (12.5)	42 (1.2)	218 (4.4)
Cystic periventricular leukomalacia, N (%)	81 (5.8)	58 (1.6)	139 (2.8)

Data are presented as No. (%).
*Severe NEC: necrotizing enterocolitis, defined as Bells stage 2 or 3 and diagnosed after the first postnatal week requiring severe intervention/review.
†Severe morbidity is any severe BPD, cystic PVL, severe NEC after the first postnatal week, or severe ROP in either eye during the hospital stay, or death after 7 d of life.
‡LOS: late-onset sepsis, culture-proven after the first postnatal week.
§Severe BPD: Severe bronchopulmonary dysplasia, defined as receiving any respiratory support (not solely oxygen) at 36 wk postmenstrual age.
¶ROP: severe retinopathy of prematurity, defined as stage 3-5 and/or any treated ROP (laser or antivascular endothelial growth factor therapy) at any stage in either eye.

Table VI. Mortality and morbidities among very preterm infants (n = 4932) and early antibiotics, ORs adjusted for CRIB2 scores only

	aOR for adverse outcomes in relation to antibiotic (AB) exposure					
	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)	aOR* (95% CI)
Outcomes	**Any AB vs no AB first 7 d†**	**1-3 d vs no AB†**	**4-7 d vs no AB†**	**4-7 d vs 1-3 d AB‡**	**≥5 d vs 0-4 d AB§**	**Each additional d of AB**
Severe NEC¶	4.51 (0.59-34.8); *P* = .148	3.35 (0.38-29.3); *P* = .275	4.89 (0.63-37.8); *P* = .129	1.46 (0.58-3.64); *P* = .418	**2.85 (1.29-6.30); *P* = .010**	**1.24 (1.04-1.49); *P* = .017**
Death after first postnatal wk	**13.5 (1.84-98); *P* = .010**	**10.0 (1.31-77); *P* = .027**	**14.7 (2.01-108); *P* = .008**	1.47 (0.84-2.57); *P* = .173	**2.17 (1.35-3.48); *P* = .001**	**1.30 (1.15-1.47); *P* < .001**
Severe morbidity** or death after first postnatal wk	**2.92 (1.89-4.50); *P* < .001**	**1.94 (1.20-3.14); *P* = .007**	**3.51 (2.22-5.55); *P* < .001**	**1.81 (1.28-2.55); *P* = .001**	**2.49 (1.85-3.35); *P* < .001**	**1.25 (1.17-1.34); *P* < .001**
Severe morbidity at discharge**,††	**2.53 (1.62-3.95); *P* < .001**	**1.72 (1.04-2.84); *P* = .034**	**3.01 (1.88-4.82); *P* < .001**	**1.75 (1.21-2.52); *P* = .003**	**2.30 (1.68-3.14); *P* < .001**	**1.22 (1.14-1.31); *P* < .001**
LOS after first postnatal wk‡‡	1.46 (0.92-2.34); *P* = .112	1.09 (0.62-1.89); *P* = .771	**1.65 (1.02-2.68); *P* = .043**	**1.52 (1.02-2.28); *P* = .042**	**1.51 (1.11-2.06); *P* = .010**	**1.08 (1.01-1.15); *P* = .033**
Severe BPD (36 wk)§§	**3.54 (2.01-6.23); *P* < .001**	**2.12 (1.14-3.96); *P* = .018**	**4.40 (2.43-7.97); *P* < .001**	**2.07 (1.34-3.21); *P* = .001**	**2.60 (1.81-3.72); *P* < .001**	**1.28 (1.18, 1.39); *P* < .001**
Severe ROP (treated)¶¶	1.07 (0.40-2.85); *P* = .895	0.56 (0.16-1.96); *P* = .368	1.26 (0.47-3.43); *P* = .647	2.24 (0.92-5.47); *P* = .077	**2.02 (1.11, 3.67); *P* = .022**	**1.16 (1.02, 1.33); *P* = .028**
cPVL	1.97 (0.97-4.02); *P* = .062	2.19 (1.00-4.80); *P* = .051	1.86 (0.89-3.89); *P* = .101	0.85 (0.50-1.45); *P* = .547	1.11 (0.70-1.76); *P* = .668	1.04 (0.94, 1.15); *P* = .426

cPVL, cystic periventricular leukomalacia.
P values <.05 are indicated in bold.
*Adjusted for CRIB2.
†Reference is 0 days.
‡Reference is 1-3 days.
§Reference is 0-4 days.
¶Severe NEC; necrotizing enterocolitis, defined as Bells stage 2 or 3 and diagnosed after the first postnatal week requiring severe intervention/review.
**Severe morbidity at discharge; any severe BPD, cPVL, severe NEC after the first postnatal week or severe ROP in either eye during the hospital stay, or death after 7 days of life.
††n = 4745, deaths excluded from analysis.
‡‡LOS: Culture positive sepsis after the first postnatal wk.
§§Severe BPD: severe bronchopulmonary dysplasia, receiving any respiratory support (not solely oxygen) at 36 wk postmenstrual age.
¶¶ROP: severe retinopathy of prematurity, defined as stage 3-5 and/or any treated ROP in either eye.

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Table VII. aOR for mortality and morbidities among very preterm infants (n = 4932) and exposure to antibiotics the first 3 postnatal days

Outcomes	aOR of adverse outcomes in relation to antibiotic (AB) exposure aOR* (95% CI) Start antibiotics within first 3 postnatal ds vs no antibiotic first 3 postnatal d †
Severe NEC‡	3.14 (0.39-25.0); *P* = .280
Death after the first postnatal wk	**7.74 (1.60-37.4); *P* = .011**
Severe morbidity§ or death after the first postnatal wk	**2.63 (1.71-4.06); *P* < .001**
Severe morbidity at discharge§,¶	**2.30 (1.48-3.58); *P* < .001**
LOS after the first postnatal wk**	1.09 (0.68-1.75); *P* = .708
Severe BPD (36 wk)††	**3.22 (1.82-5.69); *P* < .001**
Severe ROP (treated)‡‡	0.82 (0.29-2.28); *P* = .702
cPVL	0.96 (0.45-2.02); *P* = .913

cPVL, cystic periventricular leukomalacia.
P values <.05 are indicated in bold.
*Adjusted for gestational age (nonlinear), sex, multiple births, mode of delivery, CRIB2, Apgar score at 5 min, antenatal steroids, birth weight Z score (nonlinear), intraventricular hemorrhage grade 3-4, year of birth (nonlinear) and birth region. Days of mechanical ventilation within the first postnatal week is not included as a confounder when analyzing antibiotic exposure within first 3 postnatal days.
†Reference is no antibiotics in the first 3 postnatal days.
‡Severe NEC; necrotizing enterocolitis, defined as Bells stage 2 or 3 and diagnosed after the first postnatal week requiring laparotomy.
§Severe morbidity is any severe BPD, cPVL, severe NEC after the first postnatal week, or severe ROP.
¶n = 4745, deaths excluded from analysis.
**LOS; Culture-positive sepsis after first postnatal week.
††Severe BPD: severe bronchopulmonary dysplasia, receiving any respiratory support (not solely oxygen) at 36 weeks postmenstrual age.
‡‡ROP: severe retinopathy of prematurity, defined as stage 3-5 and/or any treated ROP at any stage in either eye.