Antibiotic Use in Term and Near-Term Newborns

Håkon Stangeland Mundal MD[a], Arild Rønnestad MD PhD[b,f,g], Claus Klingenberg MD PhD[c,e], Hans Jørgen Stensvold MD PhD[b,g], Ketil Størdal MD PhD[b] on behalf of the Norwegian Neonatal Network*

[a] Paediatric Department, Ostfold Hospital Trust, Grålum, Norway
[b] Department of Neonatal Intensive Care Unit, Clinic of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[c] Paediatric Research Group, Faculty of Health Sciences, UiT-The Arctic University of Norway, Tromsø, Norway
[d] Department of Neonatal Intensive Care Unit, Clinic of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[e] Department of Paediatrics, University Hospital of North Norway, Tromsø, Norway
[f] University of Oslo, Institute of Clinical Medicine, Oslo, Norway
[g] Neonatal clinical and epidemiological research group, Oslo University Hospital, Norway
*A complete list of group members appears in the Acknowledgments

Address correspondence to: Håkon S. Mundal, Department of Pediatrics, Ostfold Hospital Trust, Kalnesveien 300, 1714 Grålum, Norway. E-mail: hakon.mundal@gmail.com, 004747254229.

Short title: Antibiotic Use in Newborns

Conflict of Interest Disclosures (includes financial disclosures): The other authors have no conflicts of interest to disclose.

Funding/Support: No funding was secured for this study

Abbreviations: GBS: Group B streptococcus, **NNN**: Norwegian Neonatal Network, **GA**: Gestational age, **ICD-10**: International Classification of Diseases, 10th Revision, **NPR**: Norwegian Patient Registry, **CoNS**: Coagulase negative staphylococci, **NNT**: Number needed to treat, **CI**: Confidence interval, **CRP**: C-reactive protein, **SD**: Standard deviation; **QI:** Quality improvement, **ANOVA**: Analysis of variance, **NICE**: National Institute for Health and Care Excellence, **AAP**: American Academy of Pediatrics.

Article summary

This nationwide population-based study including all infants from 34 weeks gestation in Norway suggests that antibiotic use can safely be reduced without increasing adverse outcomes.

What's Known on This Subject

Antibiotic treatment in newborns may be associated with long-term adverse outcomes and increase in antibiotic resistance, but adequate and timely antibiotic treatment is needed to prevent sepsis related morbidity and mortality.

What This Study Adds

Our findings suggest that in a high-resource setting with low newborn mortality, a stricter policy than previously practiced regarding antibiotics is safe without increased risk for

adverse outcomes. Hospitals with antibiotic stewardship projects saw the largest reduction in antibiotic use.

Contributors' Statement:

Dr Mundal carried out the analyses, drafted the initial manuscript and revised the manuscript. Dr Stensvold was responsible for data retrieval and processing, contributed to data analyses and reviewed the manuscript. Dr Rønnestad helped conceptualize the study and ensured complete data collection and reviewed the manuscript. Dr Klingenberg conceptualized and designed the study, contributed during data analysis and reviewed the manuscript. Dr Størdal conceptualized and designed the study and contributed considerably to data analyses and in the writing process. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objectives

We aimed to study whether national and local antibiotic stewardship projects have reduced the antibiotic use in newborns, and to monitor potential changes in adverse outcomes.

Methods

In a nationwide, population-based study from Norway we included all hospital live births from 34 weeks gestation (n=282 046) during 2015 to 2019. The primary outcome was the proportion of newborns treated with antibiotics from 0 to 28 days after birth. Secondary outcomes were overall duration of antibiotic treatment and by categories; culture-positive sepsis, clinical sepsis, and no sepsis.

Results

A total of 7365 (2.6%) newborns received intravenous antibiotics during the period, with a reduction from 3.1% in 2015 to 2.2% in 2019 (30% decrease, $p<0.001$). Hospitals with antibiotic stewardship projects experienced the largest reduction (48% vs 23%, $p<0.001$). We found a small decrease in the median duration of antibiotic treatment in newborns without sepsis from 2.93 to 2.66 days ($p=0.011$), and geographical variation was reduced during the study period. The overall number of days with antibiotic treatments was reduced by 37% from 2015 to 2019 (119.1/1 000 versus 75.6/1 000, $p<0.001$). Sepsis was confirmed by blood culture in 206 newborns (incidence rate 0.73 cases per 1000 live births). We found no increase in sepsis with treatment onset >72 hours of life, and sepsis-attributable deaths remained at a very low level.

Conclusions

During the study period, a substantial decrease in the proportion of newborns treated with antibiotics was observed together with a decline in treatment duration for newborns without culture-positive sepsis.

Introduction

Newborns are at risk of sepsis, and suspected sepsis is a major reason for admission to the neonatal intensive care unit.[1] Clinical signs of sepsis in the newborn are nonspecific and biomarkers are insufficient to make a certain diagnosis.[2] Intravenous antibiotics early in life affect the developing microbiota, [3] may be associated with long-term adverse outcomes,[4-6] increasing antimicrobial resistance[3,7] and impaired growth up to school age.[8]

In recent years there has been a push internationally to decrease the use of antibiotics.[9] The Norwegian Ministry of Health published a national strategy in 2015 against antibiotic overuse aiming to reduce the use by 30% from 2012 to the end of 2020.[10]

There is a large variation between countries in the use of antibiotics in neonatal care.[11-13] During 2009-2014 there was also a geographical variation within Norway, with a twofold difference between hospitals in proportion of newborns treated with antibiotics.[14] This is an unwanted variation not explained by differences in incidence of sepsis.

In this study we describe changes in the use of intravenous antibiotics in all term and near-term newborns in Norway between 2015 and 2019, and geographical variations. Moreover, we present epidemiological data on culture-positive and clinical sepsis. Our hypothesis was that during this five-year period national and local initiatives had led to a decrease in antibiotic consumption without increased incidence of readmissions, sepsis-attributable mortality or delayed diagnosis of sepsis in the newborn period.

Material and methods

Study population, data sources and setting

In an observational study we included all liveborn newborns with a gestational age (GA) ≥34 weeks born in Norway during the five-year period between January 1, 2015, to December 31, 2019, Fig 1. The Regional Ethical Committee for Medical and Health Research Ethics approved the study.

Data on the total number of live births were obtained from the Medical Birth Registry of Norway.[15] Prospectively collected clinical data were obtained from the Norwegian Neonatal Network (NNN), a web-based nationwide registry governed by the Norwegian Institute of Public Health.[16] In the NNN, data on investigations, treatments and diagnoses are entered on a daily basis by the attending physician on all infants admitted to each participating neonatal unit. There are 21 neonatal units across Norway, all of which included all admissions during the study period. Virtually all neonates receiving intravenous antibiotics are admitted to one of these neonatal units. Lastly, we analyzed data from the Norwegian Patient Registry (NPR) on diagnosis of sepsis in all newborns up to four weeks of age during the study period. NPR provides data on patients treated at all hospitals including diagnosis labeled with International Classification of Diseases, 10th Revision (ICD-10) codes.[17] Reimbursement for hospital stays is linked to the NPR, providing high completeness of discharge data. At some of the hospitals in Norway newborns may be admitted to regular pediatric wards for complications arising after discharge from the maternity ward. In order to capture all newborns with sepsis after discharge from the maternity ward, the NPR was used as a supplementary data source to identify all cases admitted to any department >72 hours of life with a discharge code of sepsis.

Norway has 5.4 million inhabitants and consists of 11 counties which are grouped into four regional health care trusts (South-East, West, Central and North). The neonatal death rate in 2019 was 1.3/1000 live births,[18] and health services during pregnancy and childhood are universal and free of charge. Most of the deliveries are conducted at hospitals with specialized obstetric departments. Due to large geographical distances there are also some smaller delivery units for low-risk deliveries with a limited number of annual births. Newborns from such facilities who need antibiotic treatment are transferred to the nearest neonatal unit. Less than 0.3% of the deliveries are conducted as planned home deliveries. We excluded home deliveries due to missing information in regard to which region the children were born.

During the study period, the following antibiotic stewardship strategies were implemented:

- Standardized criteria for neonatal sepsis diagnosis published in October 2015.[19]
- A reminder message given to the physician during daily registration in the NNN suggesting to reconsider antibiotics after three days therapy, introduced in 2015.
- The national Choosing Wisely campaign launched in 2018 included a recommendation of early discontinuation of antibiotics.[20]
- In 2017 neonatal units in three large hospitals performed a quality improvement (QI) project including automatic 48-hour stop order on antibiotic use and implementing procalcitonin as a biomarker to reduce antibiotic treatment duration.[21]
- During 2017-2018 another large hospital implemented serial physical examinations for suspected sepsis as a QI project.[22]

Study definitions

Diagnoses registered in NNN were defined according to the ICD-10 codes. Bacterial sepsis in the newborn (P36.0–P36.8) is defined as growth of bacteria in blood cultures together with clinical signs and symptoms compatible with infection. Growth of coagulase negative

156 staphylococci (CoNS) in blood culture in this age group was considered as a contamination.[1]
157 Unspecified bacterial sepsis (P36.9) or "clinical sepsis" is applied when there are clinical and
158 biochemical signs of sepsis, without growth of bacteria in blood cultures or when blood
159 cultures were not obtained. In 2006 (reviewed 2014-2015), neonatologists within the
160 Norwegian Pediatric Association suggested the following four criteria for the use of P36.9:
161 (1) clinical signs of infection, (2) maximum C-reactive protein level (CRP) > 30 mg/L, (3)
162 minimum duration of five days antibiotic treatment and (4) other explanations for the clinical
163 picture excluded.[19] The CRP cut-off value was chosen to find a balance between sensitivity
164 and specificity for sepsis, and observational studies show that most healthy newborn have
165 CRP values well below 30 mg/L.[23,24]

166 We classified children treated with antibiotics in three groups: culture-positive sepsis (P36.0-
167 P36.8), clinical sepsis (P36.9), and no sepsis (antibiotics, but no P36.0-P36.9 code at
168 discharge).

169 ***Main outcome***

170 The main outcome of the study was any exposure to systemic intravenous antibiotics during
171 first 28 days of life. The secondary outcome was duration of antibiotics in days, counted as
172 calendar days from the first to the last dose. The secondary outcome was analyzed for all
173 newborns who were commenced on antibiotics, and thereafter separately for those with
174 culture-positive sepsis, clinical sepsis and no sepsis.

175 ***Additional variables***

176 We included GA, type of blood culture pathogen and diagnosis in the analysis. Our data do
177 not include information on maternal risk factors for neonatal sepsis such as fever during
178 delivery or clinical signs of chorioamnionitis.

Statistical analysis

Data was analyzed using IBM-SPSS version 25 statistical software (IBM, Armonk NY, USA) and Stata version 16.0 (StataCorp 2019, Stata Statistical Software, College Station, TX, USA). Results are expressed as percentage with 95% confidence interval (CI) or as means with standard deviations (SD), as appropriate. To test the significance of our findings, we used chi-square test for categorical analyses, ANOVA with logarithmic transformation for continuous data and a p-value of <0.05 as significance level.

Results

Between 2015 and 2019, a total of 288 623 children were born in Norway. After excluding children with missing data on GA, missing health region of birth, and GA <34 weeks we were left with a cohort of 282 046 children (Fig 1), of whom 7 365 (2.6%) were treated with antibiotics. Near-term infants (GA 34.0-36.6 weeks) contributed with 12 917 (4.5%) of the cohort, and proportions did not vary by birth year or region (data not shown).

During the study period we found a 30% reduction in the proportion of children started on antibiotics at a national level (from 3.1% in 2015 to 2.2% in 2019 during day 0-28 after birth, $p<0.001$). Data on antibiotic exposure only during day 0-7 after birth are presented in Table 1.

The difference between the region with the highest versus lowest proportion of babies commenced on antibiotics did not change appreciably over time (1.0% in 2015 vs 0.9% in 2019, Table 1). Four hospitals covering approximately 1/4 of all deliveries in Norway had local antibiotic stewardship QI-projects during the study period.[21,22] Collectively, there was a 48% reduction in children started on antibiotics in these four hospitals compared to a 23% reduction in all the other hospitals who did not have such projects, with a similar baseline (Table 1, $p<0.001$).

Antibiotic treatments were mainly started during the first week of life (6706/7365, 91%), and antibiotic initiation during this first week decreased from 2.9 to 2.1% (Table 1).

We found an overall reduction in duration of antibiotic treatment, from a mean of 3.9 days in 2015 to 3.4 days in 2019 (Table 2, $p<0.001$). This decrease was observed in three out of four health regions. In the West region the duration was unchanged, but markedly lower compared to other health regions at the start of our study in 2015. There was no significant change in treatment duration for culture-positive sepsis, but a significant decrease for clinical sepsis and for those with no sepsis diagnosis (Table 2). Differences in duration of treatment between

regions were reduced over time (Table 2). The annual number of days with antibiotics decreased by 37%, from 119.1/1 000 newborn in 2015 to 75.6/1000 in 2019.

A blood culture was obtained in 6 758 (91.8%) of the children receiving antibiotics. Sepsis was confirmed by blood culture in 206 newborns (0.73/1000 live births at GA ≥34 weeks), 181 of these were born at term (incidence 181/269 851, 0.67/1000 live births). Group B streptococcus (GBS) was the predominant pathogen in culture-positive sepsis (n=73/213, 34%), with an incidence of 0.26/1000 live births in near-term and term infants. The other commonly encountered pathogens were *Escherichia coli* and *Staphylococcus aureus* (Table 3). Overall during the five-year period, 2.6% of newborns in Norway with GA ≥ 34 weeks were treated with antibiotics. Only 2.9% of newborns treated with antibiotics had a culture-positive sepsis; the number needed to treat (NNT) was 36 for each culture-positive sepsis episode.

We found a non-significant decrease in incidence of sepsis with onset at 7-28 days from 62/59 932 (0.10%) in 2015 to 45/55 246 (0.08%) in 2019 (Table 4). The number of repeated courses of antibiotics was stable over time (Table 4). Newborn deaths remained low at around 0.5/1000 with no significant change over time (p=0.54, Table 4). The mortality rate did not change appreciably among those treated with antibiotics or those not treated with antibiotics (Table 4). Death due to sepsis was uncommon, and a significant decrease in both culture-positive and clinical sepsis was observed during the study period. During the five-year period 14 children who died in a neonatal unit had a sepsis-related ICD-10 diagnosis. Ten out of these 14 had other conditions as the primary cause of death (severe congenital anomalies, fulminant viral infections, inborn errors of metabolism). Four children were classified as sepsis-attributable deaths (details in Table 4).

Discussion

In this nationwide, population-based study we found a 30% reduction in the proportion of near-term and term newborns commenced on antibiotics over the 5-year study period. Concomitantly a shorter duration of treatment in newborns without culture-positive sepsis reduced the number of days with systemic antibiotics by 37%. National initiatives and local antibiotic stewardship QI-projects were implemented during this period. The occurrence of sepsis after first week of life and sepsis-attributable mortality remained very low.

The population-based design including virtually all children born in Norway ≥ 34 weeks of gestation is a strength and avoids any selection bias. Another major strength is the sample size allowing for robust estimates. Daily recording in the national registry ensures almost complete data sets including blood cultures, however exact start and end of treatment in hours was not registered.

The main limitation of the study is the reliance on a large number of physicians for the registration into the web-based system. Inaccuracies in the data sets are inevitable in such a registry-based study, though this is unlikely to change systematically over time or vary by geographic region. National initiatives within the Norwegian Pediatric Association for uniform use of the ICD-10 codes on discharge were implemented before start of the study. The diagnosis P36.9 (clinical sepsis) is controversial, and it is likely that the quite steep fall in the number of children discharged with this diagnostic code was at least partly driven by a stricter use of the diagnostic criteria during the study period.[19,25]

Blood culture growth of CoNS was considered to be a likely contaminant, in line with previous studies on this subject.[1,16] However, there is a possibility that some of the blood cultures with growth of such low-grade pathogens represented true sepsis. We did not have information on maternal antibiotics during labor, and therefore we cannot estimate the impact of such antibiotics on incidence of early-onset sepsis in our population.

A previous study from the Norwegian neonatal network during 2009-2011 showed that 2.3 % of term infants were treated with antibiotics the first week of life. [16] At the end of the current study, the corresponding proportion in term infants was 1.9%. Several interventions took place during the study period, including an electronic reminder in the NNN daily registration platform to reconsider antibiotic prescription after three days instituted in 2015. Limited by the observational design, we cannot draw conclusions regarding the effect of the specific interventions. Interestingly, institutions that had antibiotic stewardship QI-projects during the study period saw a substantially larger reduction in antibiotic use compared to other hospitals.[21,22] This suggests that local projects may strengthen the effect of national initiatives. The geographic variation in the proportion of newborns started on antibiotic treatment persisted, but the duration of antibiotics was more uniform at the end of our study period.

A national neonatal sepsis guideline was not available during the study period. However, by tradition most Norwegian neonatal units do not treat asymptomatic infants just based on risk factors. It is well known that screening guidelines based on maternal risk factors for sepsis in newborns may result in extensive use of systemic antibiotics. Using the Centers of Disease Control 2010 guidelines, 7% of infants born at ≥35 weeks gestation received empiric antibiotics for suspected early-onset sepsis.[26] The NICE guidelines,[27] also using a risk-based approach, led to empiric treatment of far more than 10% of near-term and term infants in a UK study.[28] Implementation of an electronic neonatal sepsis calculator, which takes into account clinical observations in addition to maternal risk factors, may safely reduce antibiotic use during first three days of life by around 50% compared to traditional risk-based management.[28-31]

The decision to start antibiotics could in principle be made by risk factors or when the newborn presents with symptoms. Most decisions tools utilize a combination of these two in addition to laboratory markers, as is the current clinical practice in Norway. There will always

be a trade-off between treating infants without infections and delaying treatment in those who do have infection. The NNT to cover one culture-positive sepsis in the present study was 36, which is lower than in 2009-2011 (NNT=44).[16] Delayed treatment should be avoided as much as possible, though the clearly adverse events – permanent morbidity or death – are rare. The sensitivity of any guideline or screening algorithm will never reach 100%, and the balance between optimal sensitivity and specificity to detect sepsis will continue to challenge neonatologists.[31,32]

Algorithms and guidelines need to consider the setting, including the incidence of sepsis in the population, recommendations for GBS screening and for intrapartum antibiotics. Similar to the UK guidelines[33], the Norwegian national policy does not recommend a systematic screening for GBS during pregnancy in healthy females. Intrapartum antibiotics are recommended if a previous child has had GBS sepsis, if a urinary tract infection with GBS has been diagnosed in pregnancy and in the case of maternal fever or prolonged rupture of membranes more than 18 hours.[34] The usual standard of care in Norway is observation of newborns 48 hours post-delivery, which allows for recognition of signs occurring before discharge. Early signs of infection are subtle, and serial monitoring of vital signs in newborns with risk factors should capture symptoms as soon as they appear and lead to therapy.[22] Serial monitoring is currently also one of the possible strategies to identify infants with suspected sepsis, suggested by AAP.[35] Early hospital discharge may increase the risk of missing symptoms and signs, and careful selection of low-risk newborns should be implemented before any change in discharge policy.

In the current study, the decreased duration of antibiotic treatment in non-infected newborns was minor, especially with regard to the reduction in the proportion of newborns started on antibiotics. However, due to the large reduction in newborns commenced on antibiotics, the newborns treated in 2019 had a higher likelihood of true sepsis as indicated by a lower NNT.

They are therefore not directly comparable to those started on antibiotics in 2015. In the SCOUT study the decision to start treatment was deemed inappropriate in only 4% of the cases, but continuation inappropriate in 39% of cases.[13] The ultimate goal to discontinue antibiotics in non-septic infants within 36-48 hours remains, and future initiatives should be aimed towards early discontinuation. In one of the two antibiotic stewardship projects conducted in Norway an automatic stop order was part of the interventions, as also described from other institutions.[21,36,37] Similar to our study, the SCOUT study saw a 27% reduction in overall antibiotic use in newborns in an antibiotic stewardship program, without changes in any safety outcomes.[13]

Our findings suggest that in a high-resource setting with low newborn mortality, a stricter policy than previous practice regarding antibiotics is safe without increased risk for adverse outcomes. The number of sepsis-attributable deaths should however be interpreted with caution given the low frequency of this event. With a limited accuracy of decision tools and biomarkers to identify sepsis, clinical vigilance is paramount and a sufficiently low threshold to start antibiotics is necessary to avoid unnecessary deaths due to missed sepsis diagnoses.

Conclusions

In this nationwide study, we found a reduction in the proportion of term and near-term newborns who were treated with antibiotics over a five-year period. We found no increased incidence of readmissions, sepsis-attributable mortality or delayed diagnosis of sepsis during the same period. The duration of antibiotic therapy in non-septic newborns was reduced and better aligned across the country, but needs further efforts to reduce unnecessary prolonged treatment.

Acknowledgments

We thank the neonatal units from the following hospital in Norway for contributing with data to the Norwegian Neonatal Network and thus making this study possible: Oslo University Hospital-Rikshospitalet, Oslo; Oslo University Hospital-Ullevål, Oslo; Akershus University Hospital, Lørenskog; Drammen Hospital, Drammen; Østfold Hospital Trust,Fredrikstad; Innlandet Hospital Trust, Lillehammer; Innlandet Hospital Trust, Elverum; Telemark Health Trust, Skien; Hospital of Southern Norway, Kristiansand; Hospital of Southern Norway, Arendal; Stavanger University Hospital, Stavanger; Haukeland University Hospital, Bergen; Fonna Health Trust, Haugesund; Health Sunnmøre Trust, Ålesund; Førde Health Trust, Førde; St. Olav University Hospital, Trondheim; Nord-Trøndelag Health Trust, Levanger; Nordland Central Hospital, Bodø; University Hospital of North Norway, Tromsø and Finnmark Health Trust, Hammerfest.

References

1. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics*. 2011;127(5):817-826.
2. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. *Lancet*. 2017;390(10104):1770-1780.
3. Fjalstad JW, Esaiassen E, Juvet LK, van den Anker JN, Klingenberg C. Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. *J Antimicrob Chemother*. 2018;73(3):569-580.
4. Wan S, Guo M, Zhang T, et al. Impact of Exposure to Antibiotics During Pregnancy and Infancy on Childhood Obesity: A Systematic Review and Meta-Analysis. *Obesity (Silver Spring)*. 2020;28(4):793-802.
5. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. *Pediatrics*. 2011;127(6):1125-1138.
6. Esaiassen E, Fjalstad JW, Juvet LK, van den Anker JN, Klingenberg C. Antibiotic exposure in neonates and early adverse outcomes: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2017;72(7):1858-1870.
7. Aslam B, Wang W, Arshad MI, et al. Antibiotic resistance: a rundown of a global crisis. *Infect Drug Resist*. 2018;11:1645-1658.
8. Uzan-Yulzari A, Turta O, Belogolovski A, et al. Neonatal antibiotic exposure impairs child growth during the first six years of life by perturbing intestinal microbial colonization. *Nat Commun*. 2021;12(1):443.
9. World Health Organization. Global action plan on antimicrobial resistance. https://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/policy/global-action-plan-2015. Published 2015. Accessed June 22, 2021.
10. National Strategy against antibiotic resistance 2015–2020. https://www.regjeringen.no/contentassets/5eaf66ac392143b3b2054aed90b85210/antibiotic-resistance-engelsk-lavopploslig-versjon-for-nett-10-09-15.pdf. Published 2015. Accessed June 22, 2021.
11. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379(9832):2151-2161.
12. Cantey JB, Wozniak PS, Sanchez PJ. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. *Pediatr Infect Dis J*. 2015;34(3):267-272.
13. Patel SJ, Oshodi A, Prasad P, et al. Antibiotic use in neonatal intensive care units and adherence with Centers for Disease Control and Prevention 12 Step Campaign to Prevent Antimicrobial Resistance. *Pediatr Infect Dis J*. 2009;28(12):1047-1051.
14. Moen A, Ronnestad AE, Stensvold HJ, Uleberg B, Olsen F, Byhring HS. The Norwegian Neonatal Healthcare Atlas, 2009-2014. https://helseatlas.no/sites/default/files/norwegian-neonatal-healthcare.pdf. Published 2016. Updated September 6, 2017. Accessed June 22, 2021.
15. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand*. 2000;79(6):435-439.
16. Fjalstad JW, Stensvold HJ, Bergseng H, et al. Early-onset Sepsis and Antibiotic Exposure in Term Infants: A Nationwide Population-based Study in Norway. *Pediatr Infect Dis J*. 2016;35(1):1-6.
17. Bakken IJ, Ariansen AMS, Knudsen GP, Johansen KI, Vollset SE. The Norwegian Patient Registry and the Norwegian Registry for Primary Health Care: Research potential of two nationwide health-care registries. *Scand J Public Health*. 2020;48(1):49-55.

18. Macsali F, Engjom H, Stangenes K, Klungsøyr K, Júlíusson P, Askeland O. 2020-numbers from the Medical Birth Registry https://www.fhi.no/hn/helseregistre-og-registre/mfr/2020-tallene-fra-medisinsk-fodselsregister/. Published 2021. Accessed June 22, 2021.
19. Nakstad B, Lang A, Solevag A, Klingenberg C. Neonatale diagnosekoder i ICD-10. https://www.helsebiblioteket.no/retningslinjer/nyfodtmedisin/neonatale-diagnosekoder-i-icd-10. Published 2019. Accessed June 22, 2021.
20. Norwegian Society of Pediatricians. Choosing Wisely, early discontinuation of antibiotics. https://www.legeforeningen.no/kloke-valg/anbefalinger/fagmedisinske-anbefalinger/norsk-barnelegeforening/1.antibiotika-til-nyfodte-bor-avsluttes-etter-36-48-timer-dersom-ingen-vekst-i-blodkultur-og-fredelig-klinikk/. Published 2018. Updated July 3, 2018. Accessed June 22, 2021.
21. Dretvik T, Solevag AL, Finvag A, Stordal EH, Stordal K, Klingenberg C. Active antibiotic discontinuation in suspected but not confirmed early-onset neonatal sepsis-A quality improvement initiative. *Acta Paediatr*. 2020;109(6):1125-1130.
22. Vatne A, Klingenberg C, Oymar K, Ronnestad AE, Manzoni P, Rettedal S. Reduced Antibiotic Exposure by Serial Physical Examinations in Term Neonates at Risk of Early-onset Sepsis. *Pediatr Infect Dis J*. 2020;39(5):438-443.
23. Mjelle AB, Guthe HJT, Reigstad H, Bjorke-Monsen AL, Markestad T. Serum concentrations of C-reactive protein in healthy term-born Norwegian infants 48-72 hours after birth. *Acta Paediatr*. 2019;108(5):849-854.
24. Perrone S, Lotti F, Longini M, et al. C reactive protein in healthy term newborns during the first 48 hours of life. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(2):F163-F166.
25. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-Negative Early-Onset Neonatal Sepsis - At the Crossroad Between Efficient Sepsis Care and Antimicrobial Stewardship. *Front Pediatr*. 2018;6:285.
26. Mukhopadhyay S, Eichenwald EC, Puopolo KM. Neonatal early-onset sepsis evaluations among well-appearing infants: projected impact of changes in CDC GBS guidelines. *J Perinatol*. 2013;33(3):198-205.
27. NICE guideline: Neonatal infection (early onset): antibiotics for prevention and treatment. https://www.nice.org.uk/guidance/cg149. Published 2012. Updated January 1, 2017. Accessed June 22, 2021.
28. Goel N, Shrestha S, Smith R, et al. Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(2):118-122.
29. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis. *JAMA Pediatr*. 2017;171(4):365-371.
30. Achten NB, Klingenberg C, Benitz WE, et al. Association of Use of the Neonatal Early-Onset Sepsis Calculator With Reduction in Antibiotic Therapy and Safety: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2019.
31. Pettinger KJ, Mayers K, McKechnie L, Phillips B. Sensitivity of the Kaiser Permanente early-onset sepsis calculator: A systematic review and meta-analysis. *EClinicalMedicine*. 2020;19:100227.
32. Achten NB, Plotz FB, Klingenberg C, et al. Stratification of Culture-Proven Early-Onset Sepsis Cases by the Neonatal Early-Onset Sepsis Calculator: An Individual Patient Data Meta-Analysis. *J Pediatr*. 2021.

33. Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. *BJOG*. 2017;124(12):e280-e305.
34. Brigtsen A, Oian P, Sanda B, Findal G, Rolfsen A. Guidelines from the Norwegian Society for Gynecology and Obstetrics. Group B Streptococci in Pregnancy and Labour https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/veileder-i-fodselshjelp/gruppe-b-streptokokker-hos-gravide-og-fodende/. Published 2020. Updated September 6, 2020. Accessed June 22, 2021.
35. Puopolo KM, Benitz WE, Zaoutis TE, Committee On F, Newborn, Committee On Infectious D. Management of Neonates Born at >/=35 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. *Pediatrics*. 2018;142(6).
36. Tolia VN, Desai S, Qin H, et al. Implementation of an Automatic Stop Order and Initial Antibiotic Exposure in Very Low Birth Weight Infants. *Am J Perinatol*. 2017;34(2):105-110.
37. Astorga MC, Piscitello KJ, Menda N, et al. Antibiotic Stewardship in the Neonatal Intensive Care Unit: Effects of an Automatic 48-Hour Antibiotic Stop Order on Antibiotic Use. *J Pediatric Infect Dis Soc*. 2019;8(4):310-316.

Table 1: Use of antibiotics the first week of life in newborns born ≥ 34 gestational week by year and health region.

Year/ live births with GA ≥ 34 weeks	2015 n=58 644	2016 n=58 744	2017 n=56 297	2018 n=54 916	2019 n=54 167	p-value*
Antibiotics started day 0-3 of life, n (%)	1693 (2.9)	1479 (2.5)	1282 (2.3)	1129 (2.1)	1104 (2.0)	<0.001
Antibiotics started day 4-7 of life, n (%)	55 (0.10)	63 (0.11)	58 (0.11)	54 (0.10)	39 (0.07)	0.35
Region						
South-East, n (%)	1052 (3.3)	920 (2.8)	798 (2.6)	724 (2.4)	714 (2.3)	<0.001
West, n (%)	379 (2.8)	302 (2.3)	252 (2.0)	189 (1.6)	170 (1.4)	<0.001
Central, n (%)	185 (2.3)	186 (2.3)	180 (2.4)	175 (2.4)	170 (2.3)	1.00
North, n (%)	132 (2.9)	134 (3.0)	111 (2.6)	95 (2.2)	89 (2.2)	0.06
By gestational age						
GA ≥ 34 w, n (%)	1748 (3.0)	1542 (2.6)	1341 (2.4)	1183 (2.2)	1143 (2.1)	<0.001
GA ≥ 37 w, n (%)	1485 (2.7)	1321 (2.4)	1152 (2.1)	1029 (2.0)	1008 (1.9)	<0.001
GA 34-36 w, n (%)	263 (9.7)	221 (8.1)	189 (7.6)	154 (6.4)	135 (5.5)	<0.001
Local quality improvement project [a]						
Yes, n (%)	413 (2.9)	380 (2.7)	262 (1.9)	238 (1.8)	200 (1.5)	<0.001
No, n (%)	1335 (3.0)	1162 (2.6)	1079 (2.5)	945 (2.3)	943 (2.3)	<0.001

[a] Four large neonatal units conducted antibiotic stewardship quality improvement projects during the study period as explained in the Methods section. The n (%) of newborns started on antibiotics in these units is compared to hospitals without such local initiatives.

Table 2: Duration of antibiotic treatment in days (mean/SD) and numbers with a diagnosis (%).

	2015	2016	2017	2018	2019	p-value [a,b]
Overall	3.9 (3.0)	3.9 (3.1)	3.5 (2.6)	3.6 (2.9)	3.4 (2.6)	<0.001
Duration by region						
-South-East	4.0 (2.9)	4.0 (3.1)	3.6 (2.6)	3.8 (3.0)	3.5 (2.3)	<0.001
-West	3.1 (2.4)	3.5 (3.3)	3.0 (2.3)	3.2 (2.8)	3.4 (3.5)	0.54
-Central	4.3 (3.6)	4.0 (3.2)	3.8 (3.1)	3.6 (2.8)	3.4 (2.6)	0.09
-North	4.3 (4.0)	3.3 (2.4)	3.3 (2.8)	3.1 (1.9)	3.2 (2.2)	0.006
Duration by diagnosis						
Culture-positive sepsis	8.9 (5.9)	8.8 (5.5)	8.9 (5.2)	9.5 (5.8)	9.1 (5.0)	0.98
Clinical sepsis	5.3 (2.9)	5.4 (2.9)	5.0 (2.6)	5.0 (2.5)	5.0 (2.3)	0.01
No sepsis	2.9 (2.3)	2.8 (2.3)	2.6 (1.9)	2.8 (2.3)	2.7 (1.9)	0.02
Numbers with diagnosis						
Culture-positive sepsis	47 (0.08)	52 (0.09)	34 (0.06)	38 (0.07)	34 (0.06)	0.34
Clinical sepsis	609 (1.0)	523 (0.9)	413 (0.7)	364 (0.7)	325 (0.6)	<0.001
No sepsis	1159 (1.9)	1044 (1.7)	957 (1.7)	885 (1.6)	859 (1.6)	<0.001

[a] one-way ANOVA with logarithmic transformation for trend for duration during the period 2015-2019

[b] Chi-square test for change in numbers with diagnosis during the period 2015-2019

Table 3: Growth of pathogens in blood cultures from newborns in Norway during 2015 - 2019 (n=213 [a]).

	2015	2016	2017	2018	2019	Total
Group B streptococcus	15	20	14	13	11	**73**
Other streptococci	4	7	2	5	4	**22**
S. aureus	7	8	5	6	5	**31**
E. coli	9	10	9	7	7	**42**
Other specified bacteria [b]	11	8	5	5	7	**36**
Unspecified growth	2	2	0	2	3	**9**
Total (excluding CoNS [c], fungi and viruses)	48	55	35	38	37	**213**

[a] if the culture had growth of two virulent organisms both were included (n=2). Five children had two separate blood cultures with growth of different pathogens, thus the total number of infants with positive blood cultures is 206.

[b] Other specified bacteria (descending frequency): Enterococcus, other Gram-positive cocci, other Gram-positive rods, *Bacillus spp, Bacillus cereus, Enterobacter cloaca, Klebsiella oxytoca, Acinetobacter spp*, other Gram-negative cocci and one anaerobe.

[c] CoNS; Coagulase negative staphylococci: 133 blood cultures showed growth of CoNS and 83/133 (62%) received ≥ 5 days of antibiotics.

Table 4: Admissions from day 4-28 of life, repeated antibiotic treatments and deaths by year.

	2015	2016	2017	2018	2019	p-value[c]
Admission from day 4-28 (from NPR[a]).						
Age at admission 4-6 days	20	11	18	<5	10	0.008
Age at admission 7-28 days	62	62	58	42	45	0.35
Repeated treatments with antibiotics (from NNN[b]).						
1 course	1781	1587	1377	1246	1182	0.56
≥2 courses	51	33	37	37	35	
Deaths (from NNN[b]).						
Total, n (%)	33 (0.06)	33 (0.05)	41 (0.07)	27 (0.05)	29 (0.05)	0.54
With any antibiotic treatment, n (%)	25 (0.04)	23 (0.04)	26 (0.05)	19 (0.03)	14 (0.03)	0.46
With diagnosis P36.9 [d]	5	1	1	0	0	0.03
With culture-positive sepsis[e]	0	4	3	0	0	0.02

[a] recorded in the Norwegian Patient Registry (NPR): Data are complementary to NNN because all newborns are captured regardless of admitting unit (neonatal or other).

[b] reported to the Norwegian Neonatal Network (NNN). P-value calculated for repeated courses relative to the total number of treatments.

[c] chi-squared test or Fishers exact test (lower two rows).

[d] one without severe other morbidity; started antibiotics the first day of life, but died the same day. Autopsy concluded with sepsis as probable cause of death.

[e] three without severe other morbidity: two infants with GBS sepsis (one started antibiotics day ten, died on day 14. The other started antibiotics on day 12, died on day 34). One infant with *E. coli* sepsis (started antibiotics on day one and died on day four).

513 Fig 1: Flowchart of children born in Norway with gestational age ≥ 34 weeks, during 2015-
514 2019.